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Pharmacology of Vitamins and Trace Elements

Vitamin D: Physiology, Pharmacology and Clinical Evidence for Supplementation—A Narrative Review

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ABSTRACT

Vitamin D is a nutrient and prohormone obtained from diet and supplements and synthesized in the skin. It is essential for calcium and phosphate homeostasis and skeletal health and influences multiple extra-skeletal processes, yet deficiency remains common worldwide. This narrative review summarizes vitamin D sources, physiology, metabolism, pharmacokinetics, clinical relevance and safety and outlines the distinct pharmacokinetic profiles and clinical roles of vitamin D, calcidiol and calcitriol and its analogues. Evidence consistently supports vitamin D, combined with calcium, for preventing and treating deficiency-related skeletal disorders in high-risk populations, and in specific conditions such as malabsorption, chronic kidney disease, hypoparathyroidism and frailty. In vitamin D-replete populations, large trials show limited extra-skeletal benefits, apart from modest effects on cancer mortality and progression from prediabetes to Type 2 diabetes. Untargeted screening is not recommended. Future research should prioritize targeted supplementation, standardized assays and identification of populations most likely to benefit from supplementation.

1 | Introduction

Vitamin D is a fat-soluble secosteroid that plays a central role in calcium and phosphate homeostasis, bone mineralization and overall skeletal health. Its discovery in the early 20th century marked a major advance in the prevention of rickets, a disease that at that time was widespread among children in industrialized nations. Beyond its classical role in bone health, vitamin D has been implicated in a wide range of physiological processes, including immune regulation, cardiovascular function and cellular differentiation.

Vitamin D has unique biological features that distinguish it from other vitamins. It can be obtained from diet or supplements but is also synthesized endogenously in the skin upon exposure to ultraviolet-B (UVB) radiation. After ingestion or cutaneous synthesis, vitamin D undergoes sequential hydroxylation to form its biologically active metabolite, 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$, calcitriol], which exerts its effects through the

vitamin D receptor (VDR) by regulating gene transcription. Thus, vitamin D is both a nutrient and a prohormone, and at pharmacological doses or when administered as synthetic analogues, it can also be considered a drug.

Despite its biological importance, vitamin D deficiency remains common worldwide. The main drivers are limited sun exposure and low dietary intake due to the scarcity of natural vitamin D sources. Observational studies have associated vitamin D deficiency with increased risk of many chronic diseases and all-cause mortality. These observations have stimulated interest in vitamin D supplementation for chronic disease prevention, but evidence from randomized controlled trials (RCT) remains mixed.

This review provides an overview of vitamin D, from basic physiology and pharmacology—including its absorption, distribution, metabolism, excretion and pharmacokinetic and pharmacodynamic properties—to clinical implications.

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atmospheric absorption of UVB at higher altitudes), air pollution, time of day (most effective production at solar noon), weather conditions such as thick clouds, clothing and skin pigmentation [1].

Ageing has been implicated as a factor that would reduce cutaneous vitamin D production, because the concentration of the 7-dehydrocholesterol in the skin decreases with ageing [4]. However, the skin retains the capability to produce significant amounts of vitamin D₃ even in older people [5].

In laboratory settings, sunscreens with sun protection factor (SPF) as low as 8 have markedly reduced vitamin D production in the skin exposed to UV lamps [6], but in real world RCTs this has not been observed [7]. However, these studies used sunscreens with rather low SPF (about 16), and more recent evidence suggests that the now commonly recommended SPF 50 may more effectively reduce cutaneous synthesis [8].

2.2 | Vitamin D in Diet

Natural dietary sources of vitamin D are limited. Fish is a major source for vitamin D₃, but there are large differences in vitamin D₃ content between different fish species [9]. As a rule of thumb, fatty fish, such as salmon, mackerel and trout, contain higher amounts and lean fish, such as tuna, contain lower amounts [9]. However, the vitamin D₃ content can also vary between farmed and wild-caught fish, with, for example, farmed salmon containing less than wild salmon [10]. Other foods that naturally contain small amounts of vitamin D₃ include egg yolks and liver [9]. Vitamin D₂ is present only in some wild mushrooms or in UVB-exposed cultivated mushrooms [11] and typically contributes little to total intake.

Some countries have implemented voluntary or mandatory policies for fortification of foods such as milk, fat spreads and cereals with vitamin D to prevent deficiency. In Finland, fortification of liquid dairy products and margarines with vitamin D₃ since 2003 has substantially improved population vitamin D status [12]. Some foods, such as egg yolk, milk, fish and meat, also contain small amounts of calcidiol [13], the main intermediate metabolite between vitamin D and the biologically active vitamin D metabolite calcitriol. Some estimates suggest that calcidiol can account for over a quarter of the total vitamin D intake from diet [13].

2.3 | Vitamin D Supplements

Non-prescription vitamin D supplements are available as D₂ or D₃, but vitamin D₃ is the predominant or even the only available supplemental form in most countries. The most common source for vitamin D₃ in supplements is lanolin in sheep's wool, and therefore, most vitamin D₃ supplements are not suitable for individuals avoiding animal products. However, some lichens, such as reindeer lichen, are rich sources of vitamin D₃ [9], and recently, lichen-derived vitamin D₃ supplements have become available. Fish liver oil is also a rich source of vitamin D₃ [9].

Because adequate intake from diet alone is often difficult to achieve, many organizations provide recommendations for supplemental vitamin D. For example, in Finland, recommended supplemental doses range between 300 and 800 IU/day (7.5–20 µg/day), depending on age and dietary intake of vitamin D [14]. The US Endocrine Society guideline recommends supplementation for children and adolescents, adults over 75 years, pregnant women and individuals at high risk of diabetes [15]. The supplementation recommendations are empiric, meaning that testing for serum 25(OH)D concentration is not needed to determine the dose. Doses used in RCTs have varied widely, from modest daily doses of about 400 IU (10 µg) to very large annual bolus doses of several hundreds of thousands of IUs.

2.4 | Other Vitamin D Sources

Prescription vitamin D metabolites or analogues are used in clinical situations where standard vitamin D supplements are ineffective in treating or preventing vitamin D deficiency. Such cases include different malabsorption syndromes, defects in vitamin D metabolism and obesity [16, 17]. For example, oral calcidiol corrects vitamin D deficiency more rapidly (approximately 2–6 times higher potency) and more effectively than vitamin D [18, 19]. European Union and some other countries have approved calcidiol also for use in over-the-counter food supplements [13]. Calcitriol has been used in specific clinical cases, but because its use is frequently associated with hypercalcaemia, it is commonly replaced with analogues with lower calcaemic activity, such as paricalcitol and alfacalcidol [16].

Although oral administration is the standard route, parenteral vitamin D may be used in specific situations. These include severe intestinal malabsorptive diseases [20], critically ill patients [21] and following bariatric surgery [22].

3 | Physiology of Vitamin D

3.1 | Absorption and Distribution

Vitamin D is a highly lipophilic compound and follows the absorption pathway typical of dietary fats. After oral intake, vitamin D enters the small intestine where it requires bile salts and pancreatic enzymes to form micelles that enable passive diffusion of vitamin D into the enterocytes. Some evidence suggests that active transport via cholesterol transporters may also contribute, especially at dietary doses [23]. Absorbed vitamin D is incorporated into chylomicrons and enters the lymphatic system before reaching the systemic circulation. In contrast, calcidiol is more hydrophilic, is absorbed via the venous portal route and does not require bile salts for absorption, resulting in faster and more efficient increases in vitamin D status [18].

A critical component of vitamin D transport is the vitamin D binding protein (DBP), a glycoprotein synthesized in the liver, with a half-life of about 1.7–2.5 days [24, 25]. DBP binds with high affinity approximately 85% of circulating vitamin D and its metabolites, with greater affinity for vitamin D₃ and its metabolites than for vitamin D₂ and its metabolites [26]. Albumin

and lipoproteins bind with lower affinity most of the remainder, leaving less than 1% in the free form [16]. According to the 'free hormone hypothesis', the unbound fraction may be most biologically active because the DBP-bound metabolites are not available to most cells [27]. However, this concept remains debated [28]. DBP concentrations in circulation greatly exceed those of the vitamin D metabolites. Thus, DBP is not just a transporter molecule, but it can also act as a stable reserve pool for the vitamin D metabolites. Some peripheral tissues, mainly adipose tissue but also muscle, can uptake and store vitamin D, and the rest is removed from the circulation by the liver [29]. Conditions such as liver disease, acute illness and trauma can significantly reduce DBP (and albumin) concentrations and subsequently the circulating vitamin D metabolite concentrations [30].

3.2 | Metabolism

Vitamin D is biologically inactive and requires sequential hydroxylation for activation [30]. The first step, 25-hydroxylation, occurs mainly in the liver but also in some other tissues, such as the skin (Figure 1). This reaction is primarily catalysed by the microsomal 25-hydroxylase CYP2R1, although other cytochrome P450 enzymes like CYP27A1 can contribute [17]. CYP2R1 preferentially 25-hydroxylates vitamin D₃ over D₂ [31]. The product, 25-hydroxyvitamin D [25(OH)D, calcidiol/calcifediol], is a pro-hormone and the major circulating vitamin D form but does not have significant biological activity. Unlike the highly lipophilic vitamin D that is mainly stored in adipose tissue, the less lipophilic 25(OH)D is more evenly distributed throughout the body, with about 30% in circulation, 35% in adipose tissue, 20% in muscle tissue and the rest in other tissues [29]. In animal models, activity of CYP2R1 has been reduced in obesity and diabetes, and during fasting, resulting in lower serum 25(OH)D concentrations [32, 33].

The next activation step occurs primarily in the kidney where 1 α -hydroxylase CYP27B1 converts 25(OH)D to 1,25(OH)₂D (calcitriol), which is a steroid hormone and the biologically active vitamin D metabolite that is delivered to target tissues in the circulation bound mainly to DBP (Figure 1). Unlike most other tissues where uptake of 25(OH)D is limited to the unbound form, the megalin/cubilin complex in the kidneys (and also in parathyroid gland and placenta) allows for uptake of DBP-bound 25(OH)D by endocytosis [27].

Extra-renal production of 1,25(OH)₂D by CYP27B1 occurs in several tissues, particularly in cells of the immune system [34, 35]. The extra-renal production contributes to local autocrine or paracrine effects but not significantly to circulating 1,25(OH)₂D concentrations, except for in some conditions (e.g., pregnancy and sarcoidosis) [30]. Among all cell types, the expression of CYP27B1 is the highest in the skin keratinocytes, and keratinocytes are the only known type of cells that contain the entire pathway of vitamin D metabolism [36].

Unlike the less controlled hepatic synthesis of 25(OH)D from vitamin D, the conversion of 25(OH)D to 1,25(OH)₂D in the kidney is tightly regulated. When calcium or phosphate levels are low, parathyroid hormone (PTH) stimulates CYP27B1 activity,

increasing 1,25(OH)₂D production to enhance intestinal calcium absorption. Conversely, high calcium or phosphate levels or elevated fibroblast growth factor 23 (FGF23) or 1,25(OH)₂D itself inhibit this enzyme. In contrast, in extra-renal tissues like macrophages, monocytes and keratinocytes, production of 1,25(OH)₂D is activated primarily by inflammatory cytokines [30].

Some estimates suggest that about 1 out of 3–10 molecules of vitamin D and 25(OH)D are converted to 25(OH)D or 1,25(OH)₂D, respectively [37]. Calcidiol can also be converted to 24,25(OH)₂D and other metabolites, such as epimers (Figure 1), but the ultimate fate of the unconverted molecules is not completely understood. Some of these molecules may be esterified for degradation via bile and potentially recovered by de-esterification in hepatobiliary-intestinal recycling [30].

3.3 | Physiological Effects

The physiological effects of vitamin D are mediated primarily through the VDR, a nuclear receptor expressed in most cells. Upon binding 1,25(OH)₂D, VDR forms a heterodimer with the retinoid X receptor (RXR) and binds to vitamin D response elements (VDREs) in target genes (Figure 1) [16]. This genomic mechanism leads to changes in transcriptome and proteome that, for example, regulates the transcription of proteins critical for calcium and phosphate homeostasis, which ensures proper bone mineralization. Vitamin D influences the expression of hundreds of genes, also outside of bone metabolism [38]. The widespread distribution of VDR suggests potential pleiotropic effects beyond bone health, such as immune regulation and cell proliferation and differentiation [39]. There is some evidence that 1,25(OH)₂D₂ formed from ergocalciferol would be less effective or have different functions than the 1,25(OH)₂D₃ formed from cholecalciferol, but current data are limited and inconclusive [26].

In addition to the slow genomic actions, 1,25(OH)₂D can exert non-genomic effects through rapid signalling pathways, without involving VDR and changes in gene expression [38, 40]. These include activation of signalling molecules, second messengers, protein kinases and opening of ion channels [40].

3.4 | Excretion

Catabolism of vitamin D metabolites is mediated by the 24-hydroxylase CYP24A1, which is expressed in most cells, and by CYP3A4, which is primarily expressed in the liver and intestines [30]. Both enzymes initiate degradation of 25(OH)D to 24,25(OH)₂D and 1,25(OH)₂D to 1,24,25(OH)₃D and ultimately to an inactive metabolite calcitroic acid for excretion via the biliary route (Figure 1). In addition to the 24-hydroxylation, both enzymes also catalyse the 23-hydroxylase pathway, which leads to formation of lactone products (Figure 1). Renal CYP24A1 is tightly regulated by the concentrations of 1,25(OH)₂D, FGF23, PTH and calcium and phosphate but in the direct opposite fashion to the control of CYP27B1 in the synthesis of 1,25(OH)₂D. For example, renal CYP24A1 (and also CYP3A4) is induced by increased concentrations of 1,25(OH)₂D, which serves as a

negative feedback mechanism to prevent systemic vitamin D toxicity and hypercalcaemia. Such regulation does not occur in extra-renal tissues where, for example, elevated $1,25(\text{OH})_2\text{D}$ or calcium concentrations do not stimulate CYP24A1. Therefore, elevated $1,25(\text{OH})_2\text{D}$ concentrations and hypercalcaemia are often seen in inflammatory granulomatous diseases, such as sarcoidosis, where macrophages produce $1,25(\text{OH})_2\text{D}$ without the normal feedback regulation [41]. Inactivating mutations in CYP24A1 can lead to impaired degradation of $1,25(\text{OH})_2\text{D}$ and to hypercalcaemia, illustrating the importance of this pathway in maintaining homeostasis and preventing excess accumulation of $1,25(\text{OH})_2\text{D}$. In contrast, mutations in CYP3A4 can lead to accelerated degradation of $1,25(\text{OH})_2\text{D}$, leading to vitamin D-dependent rickets type 3 [42].

4 | Pharmacokinetics of Vitamin D

After ingestion of vitamin D_2 or D_3 , their plasma concentrations peak within about 24 h. The half-life of vitamin D_3 in circulation is about 1 day and for D_2 about 2 days [17]. Calcidiol has a much longer half-life of about 2–3 weeks [17], with slightly lower for $25(\text{OH})\text{D}_2$ than for $25(\text{OH})\text{D}_3$ [43]. The half-life of $1,25(\text{OH})_2\text{D}$ is only 5–8 h [17]. However, in contrast to its short half-life in circulation, due to its lipophilicity and slow release from adipose tissue, the functional half-life of vitamin D in the body is about 2 months [44].

On average, about 80% of ingested vitamin D is absorbed, although absorption varies widely between individuals, ranging from about a half to almost 100% [45, 46]. Factors influencing absorption include dietary fat intake, bile secretion, and gastrointestinal health [45–48]. A meal containing a little fat may improve vitamin D absorption compared to intake without a meal, but a meal high in fat, especially polyunsaturated fatty acids, may impair absorption [48]. Intestinal malabsorption conditions such as celiac disease, Crohn's disease or pancreatic insufficiency can impair absorption [20, 46]. However, ageing or obesity [47] or the form of vitamin D (D_2 or D_3) [26] appears to have little effect on absorption. In contrast to absorption of vitamin D, intestinal fat malabsorption does not significantly affect absorption of calcidiol [20].

Vitamin D supplements are available in various formulations, such as hard powder tablets, oil-containing capsules, oil-based drops, buccal sprays and even gummies. More recently, nanotechnology-based vehicles have been developed to increase the bioavailability [49]. Although some differences in bioavailability between formulations have been reported [50–54], their clinical relevance remains uncertain. Vitamin D_3 supplements are generally preferred over vitamin D_2 supplements due to their higher potency in increasing serum $25(\text{OH})\text{D}$ concentrations, possibly due to the stronger binding of vitamin D_3 metabolites to DBP, hepatic 25-hydroxylase and VDR [26].

In RCTs, supplementation regimens have varied widely, ranging from smaller daily doses to larger doses once per week, once per month, once every few months or once per year. Although equivalent average doses can achieve similar increases in serum $25(\text{OH})\text{D}$ over time [55], dosing frequency appears to influence biological effects and safety. Large bolus doses induce CYP24A1

activity, which not only catabolizes $1,25(\text{OH})_2\text{D}$ more rapidly but also alters the metabolic ratio to favour the production of inactive catabolites like $24,25(\text{OH})_2\text{D}$, an effect that can persist for weeks and potentially limit the biological efficacy of the dose [56].

Some estimates suggest that in healthy adults 100 IU (2.5 μg) of vitamin D increases the serum $25(\text{OH})\text{D}$ concentrations, on average, by 1 ng/mL (2.5 nmol/L) [57]. However, serum $25(\text{OH})\text{D}$ response to supplementation is highly variable [37]. The reasons for these differences are not completely known, but genetic factors in vitamin D metabolism or racial differences seem to explain only a small fraction [37, 58]. The serum $25(\text{OH})\text{D}$ concentrations increase more rapidly when the concentrations are low, but the conversion rate from vitamin D to $25(\text{OH})\text{D}$ decreases as the dose of vitamin D and serum $25(\text{OH})\text{D}$ concentrations increase [37, 59, 60]. Obesity is associated with lower baseline levels and attenuated response to supplementation [18]. This can be a consequence of several potential factors, such as less exposure to sunlight, increased volumetric dilution and sequestration of vitamin D in the larger mass of adipose tissue or lower conversion of vitamin D to $25(\text{OH})\text{D}$ due to lower hepatic CYP2R1 activity [18]. Some evidence suggests that age may affect the response, with greater response among older than younger people [61].

Besides calcium and phosphate, other nutrients may also play a role in determining the concentrations of vitamin D metabolites. Magnesium is needed as a cofactor for binding of vitamin D metabolites to DBP [62], for the cytochrome P450 enzymes responsible for synthesis and catabolism of vitamin D metabolites [63–65], and in synthesis and metabolism of PTH [66]. In some studies, co-supplementation of magnesium with vitamin D has resulted in larger increase in serum $25(\text{OH})\text{D}$ concentrations than supplementing only with vitamin D [67], and magnesium supplementation alone without vitamin D has increased serum $25(\text{OH})\text{D}$ concentrations [68–70]. Riboflavin (vitamin B_2) is a precursor for flavoenzymes, which are essential cofactors for cytochrome P450 enzymes, including those involved in vitamin D metabolism [71]. In animal models, riboflavin deficiency has resulted in marked decline in serum $25(\text{OH})\text{D}$ concentrations, but human data are lacking [71].

Certain medications can affect vitamin D metabolism or reduce intestinal absorption. The hepatic enzyme CYP3A4 that contributes to the catabolism of vitamin D is also the major drug-metabolizing enzyme [72]. The drug-induced excess activity of the CYP3A4 results in an accelerated inactivation of vitamin D metabolites and lower serum $25(\text{OH})\text{D}$ concentrations, whereas some drugs can reduce the activity of the enzyme [73, 74]. In theory, statins could decrease $25(\text{OH})\text{D}$ concentrations by reducing concentrations of 7-dehydrocholesterol, the precursor for vitamin D_3 in the skin. However, statin use has not been shown to decrease circulating $25(\text{OH})\text{D}$ concentrations, and some statins, such as rosuvastatin and atorvastatin, may rather modestly increase the concentrations [75]. This may be a result of statin-induced inhibition of CYP3A4 and enhanced intestinal vitamin D absorption due to upregulated cholesterol transporters [75]. Because vitamin D is a fat-soluble vitamin, its absorption is linked to lipid absorption. Consequently, medications that reduce intestinal fat absorption, such as orlistat and olestra,

can concurrently reduce vitamin D absorption [46]. In contrast, drugs such as ezetimibe or plant sterols that reduce absorption of cholesterol do not seem to significantly affect vitamin D absorption [47, 76]. Currently, there is little direct information from RCTs about the effects of medication use on the response in circulating 25(OH)D concentrations to vitamin D supplementation and whether medications could modify the effects of supplementation on disease risk. However, the risk of medication induced changes in vitamin D metabolism requires consideration especially in elderly populations where polypharmacy is prevalent.

Finally, there is increasing interest in assessing vitamin D responses using molecular endpoints rather than serum 25(OH)D alone. One proposed approach, the 'personal vitamin D response index', categorizes individuals into high, mid and low responders based on transcriptomic and epigenetic responses to supplementation [77]. The low responders (who may account for 25% of the population) may require significantly higher doses of vitamin D to achieve the same physiological effects and health benefits as high responders [77]. However, this concept remains experimental and has not been applied in clinical trials.

4.1 | Pharmacokinetic Differences Between Vitamin D, Calcidiol and Calcitriol

Vitamin D and calcidiol supplements are both used to correct deficiency, but they differ in their metabolism and pharmacokinetic properties [17–19]. Vitamin D must be converted to 25(OH)D, whereas calcidiol bypasses this step. Consequently, oral calcidiol produces a faster and generally more predictable increase in serum 25(OH)D concentrations, whereas vitamin D has a longer lipophilic storage phase and remains the established choice for routine supplementation. Calcitriol is the active hormonal form, directly activates the VDR and does not serve as a nutritional replacement for low 25(OH)D. Table 1 summarizes the main pharmacokinetic differences between vitamin D, calcidiol and calcitriol.

5 | Clinical Relevance and Health Effects

Serum total 25(OH)D concentration is the accepted biomarker for vitamin D status. The biologically active 1,25(OH)₂D is not a reliable biomarker because it has a very short half-life, it exists in picomolar concentrations in circulation and its levels are tightly regulated, so its measurement is justified only in some rare clinical cases [28]. The time of day for clinical measurement of circulating 25(OH)D is not relevant, as there is very little diurnal variation in the concentrations [78]. Although free 25(OH)D may theoretically better reflect biological activity, current evidence does not support its routine use. The free 25(OH)D concentrations are highly correlated with the total 25(OH)D concentrations in healthy people [79], there is currently no reliable evidence for its superiority as a biomarker of status in various medical conditions, and the technical challenges in measuring the free 25(OH)D concentrations add uncertainty in the applicability of free 25(OH)D in assessing vitamin D status [28]. Overall, a persistent challenge in vitamin D research is the lack of standardization for assays measuring serum 25(OH)D

concentrations [80]. This variability complicates comparison and pooling of results and data across different studies and defining thresholds.

There is currently no universal consensus on optimal circulating 25(OH)D concentrations. Most population-level national and international guidelines usually define severe vitamin D deficiency as serum/plasma 25(OH)D concentration of <10–12 ng/mL (<25–30 nmol/L) and sufficiency as ≥20 ng/mL (≥50 nmol/L) [81–85], mainly based on skeletal health outcomes (Figure 2). Higher thresholds for sufficiency have also been suggested, based on observational studies that have indicated that the lowest risk of several skeletal and extra-skeletal outcomes is observed when the 25(OH)D concentrations are at least 30 ng/mL (75 nmol/L) [86]. Several guidelines for various diseases and conditions also recommend concentrations of at least 30 ng/mL (75 nmol/L) (see Section 5.4). Concentrations exceeding 50–60 ng/mL (125–150 nmol/L) are generally not recommended.

Dietary intake recommendations for vitamin D typically range from 400 to 800 IU/day (10–20 µg) for adults, with the higher intakes for older adults [87]. These recommendations are typically designed to achieve serum 25(OH)D concentrations ≥20 ng/mL (≥50 nmol/L) in the majority of the population. The tolerable upper intake level for long-term use is generally set at 4000 IU/day (100 µg/day) for adults, with lower levels for children [88, 89].

Vitamin D insufficiency remains highly prevalent globally [90–92], driven by the limited number of dietary sources of vitamin D and, due to environmental or behavioural reasons, by limited cutaneous vitamin D synthesis. A recent estimation among almost eight million participants from 81 countries concluded that, on average, 53% of females and 45% of males were vitamin D insufficient (serum 25(OH)D <20 ng/mL [50 nmol/L]) [91]. The prevalence was the highest in the Eastern Mediterranean region and in lower-middle-income countries. There can also be within-country differences in the prevalence of insufficiency between population groups. For example, in Finland, non-White immigrants had a significantly higher prevalence of vitamin D insufficiency than White immigrants or the general White Finnish population, and significant differences were also observed among the non-White immigrant groups [93]. Similar findings have been reported in other countries [92]. Differences are also apparent across life stages, with a lower prevalence of insufficiency observed in childhood and older adulthood than in adolescence and adulthood [90–92].

Despite the high prevalence of vitamin D insufficiency and deficiency, untargeted, population-level screening for vitamin D status is currently not recommended [15, 17, 94, 95]. One reason is the lack of standardized serum 25(OH)D assay method. Screening asymptomatic populations also increases the economic burden of healthcare, without strong evidence for health benefits of screening [15, 94, 96, 97]. However, testing for vitamin D status in clinical settings in individuals at high risk for deficiency is still relevant. Such individuals include institutionalized people, people with chronic diseases, people using medications that increase vitamin D metabolism, people with obesity, dark-skinned people and patients after bariatric surgery [17].

TABLE 1 | Pharmacokinetic differences between vitamin D, calcidiol and calcitriol.

Feature	Vitamin D	Calcidiol	Calcitriol	Clinical relevance
Absorption and transport	Lipophilic; absorption depends more on bile acids, micelle formation, dietary fat, and lymphatic/chylomicron transport	More hydrophilic; absorbed with less dependence on micelles and transported mainly through portal circulation	Administered in microgram doses; exposure produces direct hormonal effects rather than replenishing vitamin D pool	Calcidiol may be better absorbed in fat malabsorption states. Calcitriol is not used to improve nutritional vitamin D status
Metabolic pathway	Requires hepatic 25-hydroxylation	Already 25-hydroxylated	Already 1 α -hydroxylated; directly activates the VDR	Calcidiol may be useful when hepatic 25-hydroxylation is impaired. Calcitriol is reserved for selected disorders in which endogenous production of 1,25(OH) ₂ D is inadequate
Distribution	Greater adipose tissue sequestration and prolonged storage due to its lipophilicity	Less adipose tissue sequestration	Does not provide an equivalent 25(OH)D depot	Vitamin D provides more sustained coverage, whereas calcidiol increases serum 25(OH)D concentrations faster and response is less affected by adiposity. Calcitriol is not interchangeable with vitamin D and calcidiol in building a circulating 25(OH)D reservoir
Increase in serum 25(OH)D	Slower and more variable, affected by, for example, baseline status, obesity, malabsorption, and hepatic metabolism	Rapid and generally more linear and predictable	Does not reliably correct low 25(OH)D and may suppress PTH without restoring the nutritional vitamin D pool	Calcidiol is useful when rapid or reliable repletion is needed. A normal or improved PTH response to calcitriol does not demonstrate correction of vitamin D deficiency
Half-life	Circulating half-life about 1–2 days, longer functional half-life of about 2 months due to lipophilicity	Circulating half-life about 2–3 weeks	Circulating half-life about 5–8 h	Vitamin D may provide more sustained source of vitamin D, whereas calcidiol permits faster adjustment after dose changes. Calcitriol requires close calcium and phosphate monitoring
Relative potency	Reference compound	Commonly 2–6 times more potent by weight	Pharmacologically active in microgram doses; no reliable direct conversion into vitamin D or calcidiol doses	Product-specific dosing should be followed. Universal microgram-to-microgram conversion should not be assumed

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; VDR, vitamin D receptor.
Source: Based on references [17–19].

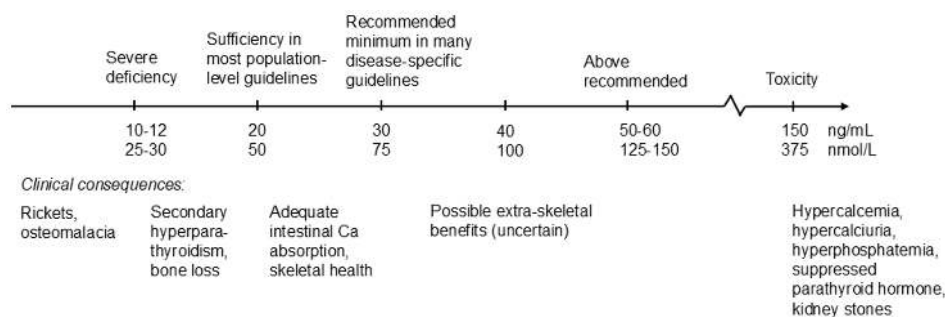


FIGURE 2 | Serum 25-hydroxyvitamin D concentration zones, corresponding clinical consequences, and selected guideline thresholds. Sufficiency is most commonly defined as ≥ 50 nmol/L (20 ng/mL) based on skeletal outcomes, although some guidelines suggest ≥ 75 nmol/L (30 ng/mL). Toxicity is biochemically defined as concentrations ≥ 375 nmol/L (150 ng/mL) accompanied by hypercalcaemia.

Observational studies consistently associate low serum 25(OH)D concentrations with increased risk of practically all major chronic diseases and mortality [39], but confounding and reverse causation complicate the interpretation of causality from these studies. Low serum 25(OH)D concentrations often associate with lower physical activity, adiposity, smoking and several chronic diseases [98–101], which may explain at least a part of the observed associations between low serum 25(OH)D concentration and increased disease risk.

Several large RCTs, some including thousands or even over 20000 participants, have investigated whether increasing serum 25(OH)D concentrations with high-dose vitamin D₃ supplementation could reduce risk of a wide array of especially non-skeletal health outcomes (Table 2). In addition to these so-called ‘mega-trials’, hundreds of smaller RCTs have been performed, and the findings contribute to the wealth of knowledge about the clinical relevance of vitamin D. This section briefly summarizes the recent findings from meta-analyses of RCTs across several skeletal and extra-skeletal domains and discusses potential reasons for the rather disappointing results from the large RCTs.

5.1 | Skeletal Health, Muscle Function and Fall Risk

Vitamin D is essential for skeletal health by facilitating intestinal calcium and phosphate absorption. The skeletal consequences of vitamin D deficiency are well established and exist on a spectrum of severity. In milder forms, vitamin D deficiency impairs intestinal calcium absorption, leading to a compensatory increase in PTH and to secondary hyperparathyroidism. This increases the conversion of 25(OH)D to 1,25(OH)₂D, which increases calcium absorption but also increases bone turnover [110]. This, over time, leads to progressive bone loss, increasing the risk of osteopenia, osteoporosis and fragility fractures in older adults. When vitamin D deficiency is severe (serum 25(OH)D < 12 ng/mL or < 30 nmol/L) and long-lasting, the body cannot adequately mineralize newly formed bone matrix (osteoid), which results in the classic metabolic bone diseases osteomalacia in adults and rickets in children [111].

Meta-analyses consistently show that the combination of vitamin D and calcium effectively reduces the risk of hip and other fractures in high-risk populations, that is, frail,

institutionalized older adults or in those with severe vitamin D deficiency [112, 113]. Supplementation of vitamin D without calcium has not been shown to be effective in preventing fractures [112, 113].

Falls are the leading cause of fractures, and muscle function can affect the susceptibility of falling. Preclinical evidence strongly suggests a role for vitamin D in muscle health. The VDR is present in muscle cells, where it is involved in regulating myoblast proliferation and differentiation [114]. Furthermore, vitamin D helps modulate T cells involved in muscle repair, influences mitochondrial function to support energy metabolism and synergizes with exercise to promote muscle regeneration [114]. However, despite this strong biological rationale, clinical evidence is inconsistent. A meta-analysis did not find benefits of vitamin D supplementation on muscle strength, function or mass and rather suggested adverse effects on muscle health [115].

The relationship between vitamin D and fall risk is particularly complex, with evidence from observational studies pointing to a U-shaped association. Some studies suggest that the optimal 25(OH)D range for minimizing fall risk may be between 20 ng/mL (50 nmol/L) and 40–60 ng/mL (100–150 nmol/L) [114], although there is no clear biological mechanism that could explain the increased fall risk with higher concentrations. The results in vitamin D supplementation RCTs have been variable. Some studies suggest lower fall risk, but only with daily doses of 800–1000 IU (20–25 μ g) and among vitamin D-deficient participants [116]. In contrast, large intermittent doses have increased falls [117].

5.2 | Non-Skeletal Health Effects

5.2.1 | Cardiovascular Health

Several biological mechanisms have been proposed through which vitamin D could influence cardiovascular health, including modulation of inflammation, improvement of endothelial function and regulation of the renin-angiotensin-aldosterone system [114].

However, evidence from RCTs has been largely inconsistent. Meta-analyses have generally not shown significant effects of vitamin D supplementation on blood pressure [118]. Similarly, recent

TABLE 2 | Large randomized controlled trials of the effects of vitamin D supplementation on disease incidence in generally healthy populations.

Study acronym, location	Sample size (n), age (y)	Duration (y)	Vitamin D ₃ dose and frequency	Primary endpoints	Baseline 25(OH)D (nmol/L/ ng/mL)	Baseline 25(OH)D <50 nmol/L (%)	Follow-up 25(OH)D (nmol/L/ ng/mL)	Maximum allowed amount of extra-trial supplemental vitamin D
VIDA, New Zealand [102]	5110, 50–84	3.3 y (median)	200000 IU (5000 µg) once, 100000 IU (2500 µg) once per month thereafter (~3320 IU/d/83 µg/d)	CVD, respiratory disease, fractures, cancer	63/25	30	135/54	≤ 600 IU/d (15 µg/d) if aged 50–70 y; ≤ 800 IU/d (20 µg/d) if older
VIDAL, UK [103]	1615, 65–84	2	100000 IU (2500 µg) once per month (~3320 IU/d/83 µg/d)	Feasibility study for a larger trial	52/21	54	110/44	≤ 500 IU/d (12.5 µg/d)
DO-HEALTH, Europe [104]	2159, 70+	3	2000 IU (50 µg) daily with or without fish oil and with strength or flexibility home exercises (2 × 2 × 2 design)	Non-vertebral fractures, functional decline, blood pressure increase, cognitive decline, any infection	58/23	28	95/38	≤ 800 IU/d (20 µg/d)
VITAL, USA [105]	25 874, 50+ (men), 55+ (women)	5	2000 IU (50 µg) daily with or without fish oil (2 × 2 design)	CVD, cancer	78/31	14	105/42	≤ 800 IU/d (20 µg/d)
FIND, Finland [106]	2495, 60+ (men), 65+ (women)	5	1600 IU (40 µg) daily or 3200 IU (80 µg) daily	CVD, cancer	75/30	9	100/40 (40 µg/day arm), 120/48 (80 µg/day arm)	≤ 800 IU/d (20 µg/d)
D2d, USA [107]	2382, 30+	3	4000 IU (100 µg) daily	Type 2 diabetes	70/28	22	135/54	≤ 1000 IU/d (25 µg/d)
TIPS-3, multinational [108]	5713, 55+ (men), 60+ (women)	5	60000 IU (1500 µg) once per month (~2000 IU/d/50 µg/d) (2 × 2 × 2 design with either Polycap, aspirin, vitamin D or placebo)	Fractures in the vitamin D arm	N/A	N/A	N/A	≤ 400 IU/d (10 µg/d)
D-Health, Australia [109]	21 315, 60–84	5	60000 IU (1500 µg) once per month (~2000 IU/d/50 µg/d)	Total mortality, cancer	77/31	24	115/46	≤ 500 IU/d (12.5 µg/d)

Abbreviations: D2d, The Vitamin D and Type 2 Diabetes Study; DO-HEALTH, Vitamin D3—Omega3—Home Exercise—Healthy Ageing and Longevity Trial; FIND, Finnish Vitamin D Trial; TIPS-3, The International Polycap Study 3; VIDA, The Vitamin D Assessment Study; VIDAL, Vitamin D and Longevity Trial; VITAL, Vitamin D & Omega-3 Trial.

large RCTs conducted mostly in vitamin D-replete populations have not demonstrated clear benefits in preventing major cardiovascular events [119, 120]. Despite these null primary findings, results from RCTs like D-Health, FIND and VINDICATE have reported some potential benefits, including modest reductions in the risk of myocardial infarction [121] and atrial fibrillation [122] and improvement of cardiac function and left ventricular structure and function in patients with chronic heart failure [123].

5.2.2 | The Immune System, Infections and Autoimmunity

Vitamin D modulates both adaptive and innate immune systems, generally enhancing innate immune responses while suppressing adaptive immune activity [124].

5.2.2.1 | Acute Respiratory Infections. Vitamin D induces innate antimicrobial mechanisms that could protect against respiratory infections [124]. However, a meta-analysis of 46 RCTs found no overall protective effect against acute respiratory infections, although modest benefits were observed in RCTs using daily supplementation, with doses of 400–1000 IU/day (10–25 µg) and in RCTs conducted in children and adolescents [125]. In another meta-analysis, maternal vitamin D supplementation during pregnancy did not affect the risk of respiratory tract infections in offspring [126].

5.2.2.2 | COVID-19. Observational studies consistently associate low serum 25(OH)D concentrations with worse COVID-19 outcomes [127]. However, COVID-19 is an outcome where reverse causation may have especially affected the observational findings. Acute inflammation is known to decrease serum 25(OH)D concentrations [128], so the commonly observed low concentrations in the COVID-19 patients would rather be the consequence of than the cause for the infection. In addition, low serum 25(OH)D concentrations are common among individuals at higher risk of severe COVID-19, such as older people and people with obesity, frailty or chronic diseases such as cardiovascular disease (CVD) and diabetes [101]. RCTs evaluating vitamin D supplementation for prevention or treatment of COVID-19 have produced conflicting results and have not demonstrated clear clinical benefits [127, 129].

5.2.2.3 | Autoimmune Diseases. Autoimmune disease prevention is one of the more promising areas of vitamin D research, although the evidence for prevention of autoimmune diseases or for disease progression is still scarce [130]. For example, in the VITAL trial, vitamin D supplementation reduced the incidence of autoimmune diseases by 22%, particularly rheumatoid arthritis and polymyalgia rheumatica [131]. In the D-Lay-MS trial, vitamin D monotherapy for 24 months reduced disease activity in patients with multiple sclerosis [132]. However, confirmation from additional large RCTs is still lacking.

5.2.3 | Glycaemic Control and Diabetes Prevention

Vitamin D may influence glucose metabolism by improving pancreatic beta-cell function, reducing insulin resistance and modulating inflammation [114]. Meta-analyses indicate that vitamin D

supplementation reduces the incidence of Type 2 diabetes among individuals with prediabetes but not among those with normal glucose regulation [133–135]. For example, an individual participant data meta-analysis of three RCTs found that vitamin D supplementation reduced the risk of progression from prediabetes to Type 2 diabetes and increased the likelihood of regression to normoglycaemia [135]. Notably, participants who achieved and maintained intratrial serum 25(OH)D concentrations ≥ 50 ng/mL (≥ 125 nmol/L) experienced the greatest benefit.

5.2.4 | Cancer

Vitamin D has antiproliferative effects, including regulation of cell proliferation, differentiation and survival and suppression of inflammation [16]. Meta-analyses have not demonstrated a reduction in overall cancer incidence with vitamin D supplementation but suggest a modest reduction in total cancer mortality, particularly in studies using daily dosing rather than intermittent bolus administration [136].

5.2.5 | Neurological Disorders and Depression

Vitamin D may influence neurological and psychiatric outcomes through anti-inflammatory and neuroprotective mechanisms, effects on neuronal plasticity and modulation of immune and molecular signalling pathways [137, 138]. Vitamin D supplementation has reduced depressive symptoms in patients with depression and improved some domains of cognition [139, 140]. However, evidence is currently insufficient to conclude whether supplementation could prevent development of dementing diseases [141] or major depressive disorders [142].

5.2.6 | Molecular Biomarkers of Biological Ageing

The VITAL and DO-HEALTH trials investigated molecular markers of biological ageing, including telomere length and epigenetic clocks, which may provide insight into the effects of vitamin D supplementation on the ageing process. However, these studies have yielded variable results. In the VITAL trial, vitamin D₃ supplementation was associated with reduced leukocyte telomere shortening compared with placebo, suggesting slower cellular senescence [143]. In the DO-HEALTH trial, the combination of vitamin D supplementation, omega-3 supplementation and a home exercise programme improved some DNA-methylation-based ageing measures, indicating slower biological ageing [144]. However, vitamin D alone had no significant effect. The clinical significance of these findings is still uncertain.

5.2.7 | Maternal, Neonatal and Infant Health

During pregnancy, circulating 1,25(OH)₂D concentrations from renal production more than double to meet the increased calcium demands and to adapt the mother's innate immune system for pregnancy [145, 146]. Also, the circulating DBP concentrations increase, but concentrations of 25(OH)D remain unchanged [145]. Maternal 25(OH)D crosses the placenta and determines foetal vitamin D supply [145].

Vitamin D deficiency is common during pregnancy [147, 148] and is associated with gestational diabetes, pre-eclampsia, preterm birth, low birth weight and small for gestational age infants [147]. However, RCTs conducted among generally healthy pregnant participants have not shown consistent clinically meaningful benefits of vitamin D supplementation for maternal or neonatal outcomes [147, 148]. Evidence in high-risk populations remains limited [147, 148].

5.3 | Reconciling the Evidence: Why Do Supplementation Trials Yield Mixed Results?

The largely null findings from recent large vitamin D trials contrast with observational associations but likely reflect methodological challenges rather than absence of biological effects. Understanding these factors is key to reconciling the evidence and guiding future research.

Many RCTs enrolled predominantly vitamin D-replete individuals, reducing the potential for benefit. Many RCTs were not adequately powered to evaluate effects in important subgroups, such as individuals with severe deficiency. This 'one-size-fits-all' methodology not only masks potential benefits within specific high-risk populations but potentially confounds the ability to draw meaningful conclusions about true therapeutic potential of supplementation. For example, two recent emulation trials showed that the lack of an effect on mortality and CVD outcomes in the two largest vitamin D supplementation trials, VITAL and D-Health, was expected due to the high baseline serum 25(OH)D concentrations but that substantial benefits would be expected in populations with low vitamin D status [149, 150]. However, ethical constraints limit the ability to recruit vitamin D-deficient participants to RCTs. In contrast to drug trials, in studies with nutrients there is rarely if ever a true placebo group because it would be unethical to create or maintain a deficiency in essential nutrients. With vitamin D, the situation is even more complex because vitamin D is also produced by the skin. The recent trials also allowed off-study supplementation due to ethical reasons (Table 2). Therefore, in RCTs even in the placebo group, the vitamin D exposure (through diet, extra-trial supplements and/or UVB light) may be sufficient for avoiding severe deficiency. This reduces the contrast in the exposure between the placebo group and the vitamin D group(s). If the health effects of vitamin D supplementation are mainly small or at best modest (at least in participants with sufficient vitamin D status), this creates a requirement for a very large, long-term (and thus extremely expensive) RCT to be able to see any significant differences in incidence of diseases between the placebo and vitamin D supplementation groups.

Dosing regimen also appears to be important. Benefits for some extra-skeletal outcomes, such as reduced cancer mortality and fewer respiratory infections, have been observed primarily in trials using daily dosing rather than intermittent high-dose boluses [125, 136]. However, the optimal vitamin D dose for maximizing benefit remains uncertain, as doses across trials have varied widely.

All large trials (Table 2) have used a fixed-dose vitamin D supplementation regimen that does not account for baseline concentrations or interindividual variability in the serum 25(OH)D response to supplementation. This may have resulted in serum 25(OH)D concentrations that were too low in some participants to achieve potential benefits. This limitation was addressed in the recent TARGET-D trial where vitamin D doses were titrated every 3 months to achieve and maintain a targeted serum 25(OH)D concentration of 100–200 nmol/L (40–80 ng/mL) in all participants in the vitamin D arm [151]. Although the trial was underpowered and did not detect statistically significant effect on its primary outcome (major adverse cardiovascular events), it suggested a significantly lower risk of recurrent myocardial infarction among these participants with a recent myocardial infarction at baseline [151]. Such individualized treat-to-target trials, when adequately powered, could provide more relevant information on the optimal serum 25(OH)D concentrations for disease prevention, although defining 'optimal' for various outcomes might be challenging.

One possibility for the lack of benefit in RCTs is that the effects of vitamin D supplementation depend on interactions with other nutrients involved in metabolism or biological actions of vitamin D, including magnesium [63–65, 67, 68], riboflavin [71], zinc, vitamin A, and vitamin K. Zinc, as zinc fingers, acts as an important cofactor for activity of vitamin D-dependent genes by contributing to structural conformational changes in the VDR that lead to transcriptional activation of genes [152]. High vitamin A intake may reduce the effects of vitamin D because both vitamins require the same RXR to bind to DNA [153]. This antagonizing effect has been observed in animal models [154]. Vitamin D and vitamin K can have synergistic effects because of their complementary roles. For example, 1,25(OH)₂D upregulates the expression of key proteins such as osteocalcin for bones and matrix glutamate protein (MGP) for blood vessels, whereas vitamin K is essential for activating these proteins through carboxylation [155]. Vitamin K deficiency could thus reduce the activity of these proteins and increase the risk of osteoporosis and vascular calcification (a situation known as 'calcium paradox', where calcium content is reduced in bone and increased in arterial walls), the latter because MPG acts as an inhibitor of soft tissue calcification [155]. There is indeed evidence from small RCTs that co-supplementation with vitamins D and K may have benefits on bone and cardiovascular health over supplementing with vitamin D alone [155, 156]. Whether all or some of these interactions mentioned above contribute meaningfully to the null findings of the large vitamin D RCTs remains uncertain.

5.4 | Disease-Specific or Condition-Specific Guidelines for Vitamin D Supplementation

Although vitamin D supplementation has not shown strong benefits in disease prevention, it is warranted in some cases. Various diseases and conditions can affect the absorption, metabolism or requirements for vitamin D, creating a need for higher vitamin D intakes than in the general population. The appropriate regimen depends on whether the goal is nutritional repletion of vitamin D, correction of metabolic defect, prevention of treatment-related hypocalcaemia or management of a broader skeletal disorder.

As with vitamin D recommendations for the general population, no international consensus exists regarding the vitamin D doses and target serum 25(OH)D concentrations for many conditions and diseases [95]. This also underscores the need for individualized treatment in many cases. Such individualization requires screening of serum 25(OH)D concentrations, and measurement is also appropriate when the result will influence the diagnosis, treatment, safety monitoring or follow-up of the disease or condition. Several, although not all, clinical vitamin D guidelines recommend serum 25(OH)D screening before initiation of supplementation and reassessment at various intervals thereafter [17, 95]. Often, correcting vitamin D status is only one component of disease management.

Examples of vitamin D supplementation recommendations are presented in Table S1 and summarized below and in Figure 3.

5.4.1 | Chronic Kidney Disease and Liver Disease

Recommendations for chronic kidney disease and liver disease are based on altered vitamin D metabolism, impaired absorption, cholestasis, comorbidity and bone disease. Vitamin D supplements are generally used to correct deficiency, whereas active analogues are reserved for selected disorders in which endogenous vitamin D activation is inadequate or hormonal regulation is substantially altered.

5.4.2 | Malabsorptive Conditions

These conditions, including those following bariatric surgery, require higher vitamin D doses and more prolonged treatment

than general nutritional deficiency. Vitamin D₃ is commonly preferred, but calcidiol or parenteral administration may be used when oral absorption is unreliable.

5.4.3 | Osteoporosis

Osteoporosis guidelines generally recommend vitamin D supplementation for individuals with osteoporosis for fracture prevention. In these guidelines, vitamin D (combined with calcium) is regarded as a supportive therapy rather than a substitute for osteoporosis medication. The recommendations aim to ensure adequate intestinal absorption of calcium and phosphorus in these individuals with high risk of fracture and to reduce the risk of hypocalcaemia during treatment with anti-resorptive or anabolic osteoporosis medications.

5.4.4 | Hypoparathyroidism

Hypoparathyroidism is characterized by hypocalcaemia and hyperphosphataemia due to PTH deficiency. In this disorder, active vitamin D analogues combined with calcium supplements are needed to correct low serum 25(OH)D concentrations and hypocalcaemia, whereas vitamin D₂ or D₃ is used for maintenance of vitamin D status.

5.4.5 | Disorders of Vitamin D Metabolism

These disorders commonly lead to rickets when untreated and require treatment matched to the specific defect. A normal or high serum 25(OH)D concentration does not necessarily reflect

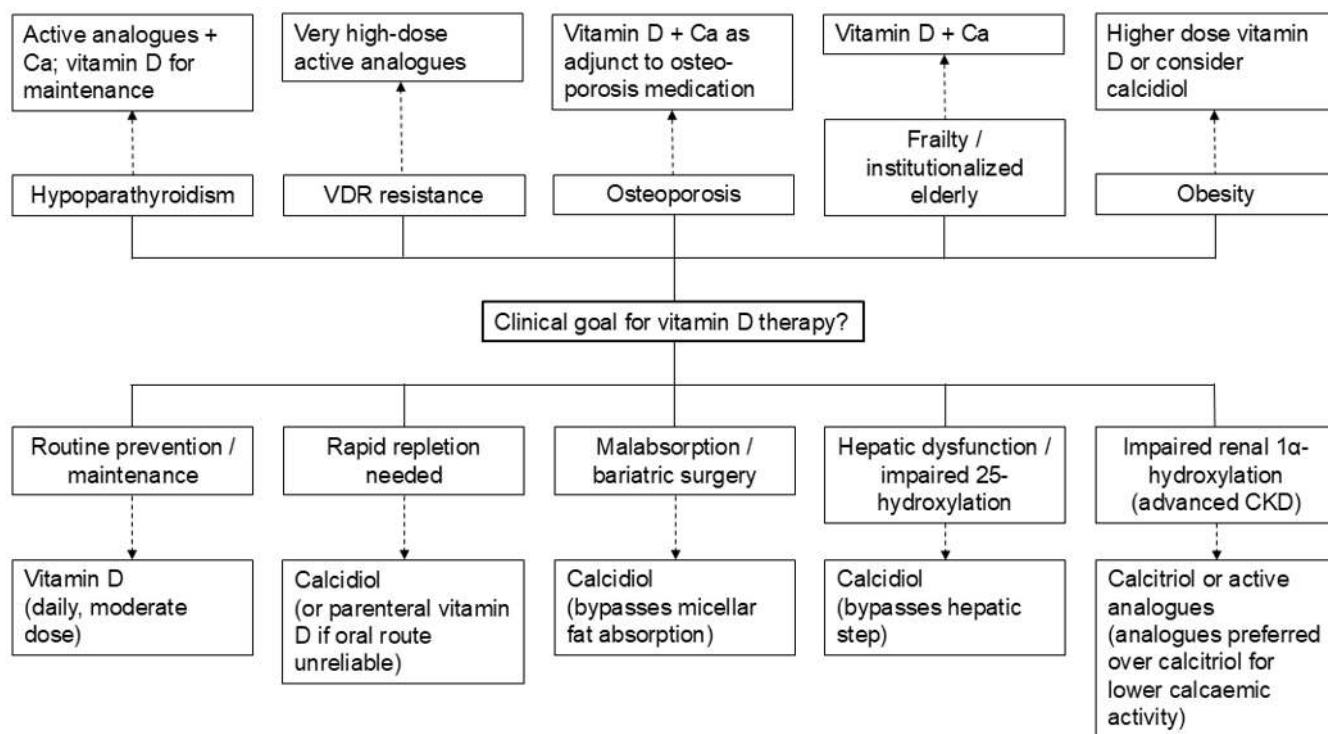


FIGURE 3 | Clinical decision tree for selecting vitamin D, calcidiol or calcitriol and its synthetic analogues based on the clinical goal and the presence of conditions affecting absorption, metabolism or activation of vitamin D. CKD, chronic kidney disease.

TABLE 3 | Potential clinical indications for use of vitamin D, calcitriol and calcitriol and its synthetic analogues.

Clinical situation	Vitamin D	Calcitriol	Calcitriol and its synthetic analogues
Routine prevention, maintenance, or uncomplicated deficiency	Standardized dosing, broad availability, long clinical experience, and a larger evidence-base for disease outcomes	Raises 25(OH)D rapidly and predictably	Not a routine nutritional replacement; does not reliably restore 25(OH)D and has a narrowed safety margin
Need for rapid correction of deficiency	Slower onset and more variable response	Faster onset and greater potency; may be useful when fast repletion is needed	Not a substitute for repletion; can act rapidly on PTH but does not correct the 25(OH)D deficiency
Obesity	May require higher or repeated doses because of sequestration in adipose tissue	May be advantageous because exposure is less affected by adiposity	Not indicated solely because of obesity
Fat malabsorption or bariatric surgery	Absorption may be impaired and response may be variable	May be advantageous because absorption is less dependent on micellar fat transport	Does not correct nutritional deficiency
Severe hepatic dysfunction or impaired 25-hydroxylation	May be less reliable because hepatic 25-hydroxylation is required	Bypasses the hepatic 25-hydroxylation step required for vitamin D	Calcitriol and paricalcitol bypass hepatic 25-hydroxylation, for example, alfacalcidol requires it
Hypoparathyroidism or disorder requiring direct calcium regulation	May provide nutritional substrate but may not control calcium adequately by itself	Provides substrate but still depends on renal or tissue activation	Calcitriol or synthetic analogues may be used to maintain calcium, but require careful monitoring for hypercalcaemia and hypercalciuria
Selected chronic kidney disease or persistent failure of vitamin D therapy	Corrects low 25(OH)D but may have limited PTH effects in advanced CKD	Can increase 25(OH)D efficiently and may improve control of vitamin D deficiency	Calcitriol and its synthetic analogues may be used to suppress PTH when CKD-related secondary hyperparathyroidism or impaired renal activation requires pharmacological VDR stimulation
Osteoporosis and fracture prevention	Remains the better-established vitamin D component of skeletal care	Has mainly demonstrated superior 25(OH)D correction	Not a general substitute for nutritional supplementation; may be used in selected calcium-metabolism disorders

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; PTH, parathyroid hormone; VDR, vitamin D receptor.
Source: Based on references [17–19].

adequate vitamin D status in these conditions. Impaired renal conversion of 25(OH)D to 1,25(OH)₂D may require the use of active analogues; defective 25-hydroxylation of vitamin D to 25(OH)D may be treated with calcidiol; and VDR resistance may require very high doses of active analogues.

5.4.6 | Frailty

Frail older adults often have several risk factors for vitamin D deficiency, such as being housebound or institutionalized or having malnutrition or multimorbidity. This frequently creates a need for supplemental vitamin D and calcium to correct the deficiency. However, recommendations for frail older adults should be distinguished from guidelines for healthy older adults [15, 87].

5.4.7 | Administration of Vitamin D Versus Calcidiol Versus Calcitriol and Its Synthetic Analogues

Vitamin D remains an appropriate choice for routine supplementation and maintenance in most cases, because its dosing is familiar and it is supported by a stronger evidence base for health benefits. Some guidelines recommend supplementing with calcidiol instead of vitamin D. The main advantage of using calcidiol is pharmacokinetic rather than a demonstrated superiority in disease prevention or treatment. Calcidiol is particularly useful when rapid repletion, a predictable dose–response, obesity, fat malabsorption or severe hepatic dysfunction is clinically relevant [17]. Calcitriol and its synthetic analogues are used, for example, in cases of limited or absent hepatic 1 α -hydroxylase activity, which results in absent or impaired hepatic formation of 1,25(OH)₂D [17]. Table 3 and Figure 3 present examples of clinical indications for the preferential use of the different forms.

6 | Safety

Vitamin D is generally considered safe due to a wide therapeutic window. Vitamin D toxicity is biochemically defined by markedly elevated serum 25(OH)D concentrations (> 150 ng/mL/> 375 nmol/L), accompanied by severe hypercalcaemia, hypercalciuria and hyperphosphataemia, and suppressed PTH levels [157, 158]. Clinical symptoms include vomiting, constipation, dehydration, polyuria and kidney stones [157]. Prolonged hypercalcaemia can lead to irreversible kidney damage, cardiac arrhythmias and soft tissue calcification [157]. Vitamin D toxicity is rare and usually results from mega-doses due to prescription errors, supplement misuse, use of unlicensed pharmaceutical products or manufacturing or labelling errors [157, 159]. Doses up to 10000 IU/day (250 μ g) have generally not been associated with severe toxicity [160], not even in children [161], although a recent meta-analysis reported a small increase in hypercalcaemia risk with long-term daily doses of 3200–4000 IU (80–100 μ g) in a small proportion of the participants in RCTs [162]. However, no increase in the incidence of hypercalciuria, kidney stones or mortality was observed [162]. Finally, as already mentioned, high intermittent bolus dosing has been associated with increased fall risk [117] and is discouraged [56].

Although calcidiol is generally well tolerated, the greater potency and the rapid increase in serum 25(OH)D concentrations following calcidiol supplementation necessitate monitoring for excessive 25(OH)D concentrations, hypercalcaemia or hypercalciuria. Similarly, the use of the active form calcitriol and its synthetic analogues requires careful monitoring because their direct pharmacological action confers a higher risk of hypercalcaemia, hypercalciuria and hyperphosphataemia [17]. Synthetic analogues of calcitriol, such as paricalcitol and alfacalcidol, have lower calcaemic activity, and their use is therefore recommended over calcitriol [17].

7 | Conclusions and Future Perspectives

Vitamin D plays a critical role in skeletal health, and supplementation—often combined with calcium—is effective for preventing and treating deficiency-related skeletal disorders in at-risk populations. For extra-skeletal outcomes, current evidence does not support untargeted supplementation in vitamin D–replete populations, although modest benefits have been observed in specific contexts, such as reduced cancer mortality and prevention of progression from prediabetes to Type 2 diabetes.

Future research must move beyond broad population studies and focus on identifying specific population groups that would benefit most from vitamin D supplementation, utilizing appropriate dosing strategies to clarify and harness the full therapeutic potential of vitamin D. The current evidence suggests that more frequent (daily) dosing with moderate amounts of vitamin D₃ would be the preferred approach and especially large infrequent bolus doses should be avoided. The new approach should prioritize subjects with lower baseline serum 25(OH)D concentrations, adopt treat-to-target approaches to establish definitive thresholds and standardize protocols to facilitate individual patient data meta-analyses capable of detecting modest effects [163]. Standardization of 25(OH)D assays is essential to improve comparability across studies and advance guideline development. At the same time, given the continued global prevalence of vitamin D insufficiency, public health strategies, such as food fortification [164], should continue to ensure that at least the current intake recommendations would be met at the population level.

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Examples of guidelines for vitamin D supplementation in various diseases and conditions.