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MINI REVIEW

# Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol

Reinhold Vieth[1]

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## Abstract

The specific compound that is meant for use in the context of vitamin D supplementation is often ambiguous. The term "supplementation" has been used in the context of cholecalciferol, ergocalciferol, calcidiol, and calcitriol. In nature, by far the major form of vitamin D that nurtures the body is cholecalciferol. In contrast, ergocalciferol is primarily a synthetic and less stable product which is less potent per microgram dose than is cholecalciferol. Calcidol is the major circulating metabolite of cholecalciferol, while calcitriol is the hormone that upregulates the active transport of calcium from the gut, and which suppresses parathyroid hormone secretion. Nutrition policy papers and guidelines leave unstated the obvious fact that calcidiol and calcitriol are not nutrients, and that those metabolites are not pertinent to food fortification or dietary supplementation. Recent evidence shows that ergocalciferol is not stable with storage, and it is far more susceptible to breakdown with cooking and baking than is cholecalciferol. Therefore, it must be concluded that cholecalciferol is the only form of vitamin D that should be considered in the context of the nutritional functions of fortification and supplementation.

The purpose of this short review is to consider cholecalciferol, calcidiol and calcitriol in the context of nutrition, and to present the case that cholecalciferol is the only form of vitamin D that is relevant to dietary supplementation or to food fortification.

The term "vitamin D" is commonly used in the generic sense, as a substitute for 25-hydroxyvitamin D (calcidiol), or for 1,25-dihydroxyvitamin D (calcitriol) and even for any other molecule based upon vitamin D's secosteroid (disrupted steroid-ring) structure—that kind of usage is wrong, because it is ambiguous and misleading [1]. Reference to formal definitions makes it clear that cholecalciferol (vitamin D) is suitably referred to as a vitamin. Calcidiol is an inactive, circulating immediate precursor to the active hormone; hence, calcidiol matches the definition of a "prehormone" (Table 1).

The term, "vitamin" was coined by Funk [2]. The requirement of a true vitamin is that it is an organic micronutrient whose lack in the diet may result in deficiency disease [2, 3]. Before 1970, the term "vitamin D" referred only to either ergocalciferol or cholecalciferol; vitamin D2 or vitamin D3, respectively. Because vitamin D2 (ergocalciferol) and its metabolites are not normally detectable in the circulation, and because ergocalciferol has not been demonstrated as showing the same benefits as cholecalciferol [4–7] it is appropriate to only use cholecalciferol for supplementation or fortification.

In the early 1970's, experiments involving cholecalciferol-based molecules that were labeled with tritium or carbon-14 showed that most of the cholecalciferol in the circulation was hydroxylated at the carbon 25 position, forming 25-hydroxyvitamin D (calcidiol), and if the experimental animals were deficient in calcium and cholecalciferol, then a 1-hydroxylated form could be detected, namely 1,25-dihydroxyvitamin D (calcitriol) [8]. It soon became clear, that the calcitriol was the hormonally active metabolite of cholecalciferol, and that by itself, cholecalciferol was an inactive structural precursor, analogous to the way that cholesterol serves as an inactive precursor to the steroid hormones. It may seem attractive to draw a simplistic analogy between cholecalciferol and cholesterol. However, for the steroid hormones, the concentration of cholesterol does not determine the production of any steroid hormones, such as cortisol, estrogen, or testosterone. The steroid-hormone-producing reactions are "zero-order" in terms of the effect of substrate on the reaction rates of the enzymes generating steroid hormones. What makes the

✉ Reinhold Vieth
reinhold.vieth@utoronto.ca

[1] Department of Laboratory Medicine and Pathobiology, and Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Medical Sciences Building, 5th Floor, Room 5253A 1 King's College Circle, M5S 1A8 Toronto, ON, Canada

**Table 1** Definitions pertinent to the vitamin D system[a].

| |
|---|
| Vitamin: One of a group of organic substances, present in minute amounts in natural foodstuffs, that are essential to normal metabolism; insufficient amounts in the diet may cause deficiency diseases. [L. Vita, life, + amine] |
| Hormone: A chemical substance, formed in one organ or part of the body and carried in the blood to another organ or part; depending on the specificity of their effects, hormones can alter the functional activity, and sometimes the structure, of just one organ or tissue or various numbers of them. [G. Hormon, pres. Part. Of hormao, to rouse or set in motion] |
| Prohormone: An intraglandular precursor of a hormone. e.g., Pro-PTH, pro-insulin, pro-opiocortin |
| Prehormone: A glandular secretory product, having little or no inherent biologic potency, that is converted peripherally to an active hormone. e.g., dehydroepiandrosterone, T4 |

Note that the characteristics of calcidiol match the definition of prehormone, and calcitriol matches the definition of hormone. Vitamin D is indeed a vitamin because "insufficient amounts in the diet may cause deficiency diseases".

[a]These definitions taken from Stedman's Medical Dictionary—27th Ed. (2000).

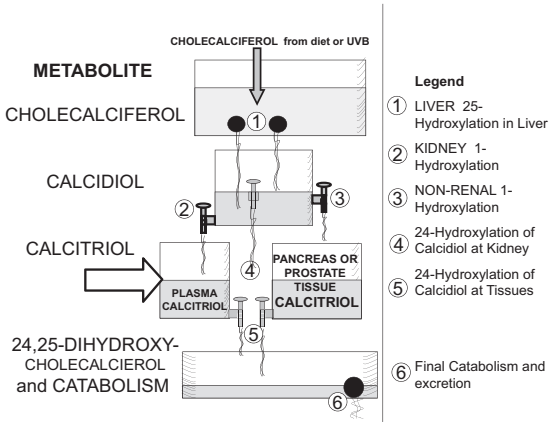


**Fig. 1 The compartments of cholecalciferol metabolism and points of its regulation through the system.** The vessels represent metabolic compartments, stages in the metabolism of cholecalciferol. The height of the shaded portion of each vessel represents the relative concentration of each metabolite indicated in the figure. This figure illustrates the concept that vitamin D metabolism in vivo functions below its enzymatic Michaelis constant (Km), i.e. this system behaves according to the first-order reaction kinetics. This is analogous to the flow of water out of a vessel, where the height of water in a vessel, together with the valve adjustment determines the outflow. The rates of metabolism through the cholecalciferol system are directly related to the concentration of precursor at each step, in conjunction with the corresponding amounts of the enzyme in both the kidney (2 in the figure) and certain peripheral tissues that possess the 1-hydroxylase for paracrine purposes (3 in the figure). When cholecalciferol supplies are low, the flow of calcidiol to the non-endocrine, paracrine pathways is compromised (represented by the higher position of valve at position 3 in the figure) in order to preserve the ability to make the circulating hormone, calcitriol, whose level is the priority, because it is required to sustain calcium homeostasis and life. The heavy bold arrow represents the setpoint required, and circulating calcitriol increases when dietary calcium is low, and it decreases when dietary calcium is abundant. That setpoint concentration is regulated at the level of the calcdiol-1-hydroxylase enzyme present in the kidney (represented by the valves drawn with heavy lines), and passively, by the calcitriol-24-hydroxylase that is upregulated by increased calcitriol to balance the level of the hormone.

cholecalciferol system unique, is that the substrates of the system drive their metabolism rates in a "first-order" manner [9]. In other words, at least in the acute sense, doubling the concentration of precursor in the cholecalciferol system doubles the yield of product.

The cholecalciferol metabolizing system is illustrated in Fig. 1, where it is represented as a series of buckets with valves or holes in them. I use this analogy because it highlights the concept of first-order kinetics: if the level of liquid in the bucket increases, then so too does the outflow from the bucket. That is, as the concentration of cholecalciferol, or calcidiol or calcitriol increases, then the rate of its metabolism also increases, at least until the amount of the enzyme in the tissue can be adjusted (as represented by the valves in Fig. 1).

It is important to note that the circulating concentration of calcitriol is the only metabolite of cholecalciferol that is known to be actively regulated. Within the kidney, regulation to produce the setpoint concentration of calcitriol (represented by the large block arrow) is achieved by adjustments to renal mitochondrial levels of calcidiol 1-hydroxylase to produce it (represented by the valves drawn with bold lines), and balanced by catabolism, as determined by levels of calcitriol-24-hydroxylase in calcitriol-responsive target tissues throughout the body. Induction of the catabolic pathway for calcidiol and calcitriol is the classic sign that a tissue possesses biologically active vitamin D receptor [8].

This is a unique system metabolically, because of the first-order reaction kinetics, which affect the dosing considerations with cholecalciferol, calcidiol, and the hormone, calcitriol. The system requires time to adapt to large doses of vitamin D, or to unstable seasonal cycling of serum 25 (OH)D [9–11] In the most severe sense of inappropriate dosing regimes, annual or monthly pulse dosing with cholecalciferol has been related to more harm in the sense of increased falls than in the placebo or lower-dose control groups [12, 13]. My contention is, that fluctuations in serum calcidiol should be avoided, to sustain its levels at whichever target level is preferred, be it greater than 50 or greater than 75 nmol/L.

Calcidiol (25(OH)D) has been used in clinical trials since the 1970's [14, 15]. Several manufacturers have produced calcidiol in large amounts since the original patent expired for the compound. Much has been made about the approximately fourfold greater serum 25(OH)D response per microgram of calcidiol versus per microgram of cholecalciferol [16]. That potency difference is an obvious one,

given the inherent inefficiencies of metabolism through multiple stages, from oral consumption of cholecalciferol, to tissue storage and retrieval of it, to liver metabolism to produce calcidiol. And there is no evidence that the greater potency of calcidiol is in any superior to simply using more cholecalciferol. In recent years, there has been a resurgence of research into the clinical use of calcidiol [13, 17], Based on the research done, there has been no clinical advantage reported for the use of calcidiol, compared with cholecalciferol or ergocalciferol, once the potency of each to increase serum calcidiol is taken into account [13, 14]. Calcidiol is a minor dietary component that is acquired incidentally along with cholecalciferol from pork, beef, chicken, and fish, but the amount is highly variable, and less than cholecalciferol content of the tissues [18]. Given that by far the major supply of humans' cholecalciferol comes from exposure of skin to sunshine, the use of calcidiol as a dietary source of vitamin D seems unnecessarily artificial. Moreover, given that the natural way the body handles cholecalciferol through storage in tissues, and since some tissues possess the 25-hydroxylase to utilize cholecalciferol [19], there seems to be no logical purpose to deprive the body of the potential benefit of the non-liver 25-hydroxylation of cholecalciferol.

Calcitriol was first used to treat patients with vitamin D resistant rickets type 1 (genetic defect in the renal 1-hydroxylase) [20]. In general, calcitriol is most commonly used as a hormone replacement for patients who have kidney failure to such a degree that their capacity to produce calcitriol is severely limited [21]. The use of calcitriol requires very careful monitoring because it carries a great risk of causing hypercalcemia. In the present nutritional context, use of the therapeutic hormone replacement drug, calcitriol, does not belong in any discussion of fortification or supplementation. It makes no more sense to include calcitriol among things suitable for fortification or supplementation, than it would to include steroid hormones like cortisol, testosterone, or estrogen in the context of nutrition.

Table 2 summarizes the pharmacology of cholecalciferol and its major metabolites. As commentary on the pharmacology, it is interesting to note that of the roughly 250 mcg of cholecalciferol that can be acquired per day through exposure of skin to sunshine, a mere 1–2 mcg will eventually become calcitriol. Most cholecalciferol is excreted through metabolism by the liver and by cleavage of the steroid sidechain to produce calcitroic acid. If vitamin D nutrition is abruptly stopped, such as happened during submarine missions that failed to provide adequate vitamin D supplement, the serum calcidiol declines with a half-life of about 2 months [22]. The long half-life is sustained by cholecalciferol released from stores in muscle and adipose, which reenter the circulation and become 25-hydroxylated [23]. The long half-life of the vitamin D system is also

**Table 2** Pharmacokinetic features of cholecalciferol, ergocalciferol, calcidiol, and calcitriol.

| | Cholecalciferol | Ergocalciferol | Calcidiol | Calcitriol |
|---|---|---|---|---|
| Volume of distribution | Larger than body size | Larger than body size | Larger than plasma volume | Plasma compartment |
| Tissue distribution for longer-term | Adipose and muscle | Adipose and muscle | Blood, adipose, and muscle | Blood and tissues |
| Circulating half-life | 2 days | 2 days | 2 weeks | 12 h |
| Functional half-life | 2–3 months | 2 months or less | 2–3 months if generated from tissue cholecalciferol stores | 12 h |
| Physiologic dose rate per day | 5–250 mcg/day | N/A | 5–60 mcg/day | 1–2 mcg/day |
| Pharmacologic dose rate per day | >250 mcg/day | >250 mcg/day | >60 mcg/day | >2 mcg/day |
| Minimal toxic dose per day | >1000 mcg/day | >1000 mcg/day | Not tested, likely 400 mcg/day | >2 mcg/day |

1 mcg = 40 IU of cholecalciferol or ergocalciferol; dosages for other metabolites are properly considered in mass units [16].

evident by the relatively small, 20% decline in serum calcidiol through the "vitamin D winter", when solar-derived ultraviolet B radiation is minimal through half the year, to the point of not making it impossible to produce vitamin D in the skin (or to sustain or acquire a tan). It is clear from the summary of vitamin D pharmacology, that cholecalciferol is a long-term nutrient that distributes widely into muscle and adipose, from which it is released gradually to permit continued production of calcidiol, which is a laboratory marker of long-term vitamin D nutritional status.

## Conclusion

There are many excellent reviews and policy papers dealing with vitamin D supplementation and fortification. None of them involves any consideration of the use of calcidiol or calcitriol in the nutritional context [24–28]. It is not the purpose of the present review to detail dosage recommendations further. Instead, the aim is to make it clear that calcidiol and calcitriol are not suitable for nutritional fortification or supplementation. The strong recommendation of this review is consistent with an unstated feature of the policy papers just cited, which is that cholecalciferol is the only form of vitamin D that should be considered in the context of the nutritional functions of fortification or supplementation. Cholecalciferol is very stable and bioavailable when baked into bread [29]. It is also stable as a component of cooked food, and is suitable for fortification and fully bioavailable in cheese that is baked onto pizza [30]. The Institutes of Medicine formally considers ergocalciferol as equivalent to cholecalciferol; however, ergocalciferol is comparatively unstable, and recent evidence shows that its instability makes it unsuitable with cooking or fortification of flour for production of bread [4, 6, 7].

### Compliance with ethical standards

**Conflict of interest** The author declares that he has no conflict of interest.

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