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REVIEW

Is calcifediol better than cholecalciferol for vitamin D supplementation?

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Abstract

Modest and even severe vitamin D deficiency is widely prevalent around the world. There is consensus that a good vitamin D status is necessary for bone and general health. Similarly, a better vitamin D status is essential for optimal efficacy of antiresorptive treatments. Supplementation of food with vitamin D or using vitamin D supplements is the most widely used strategy to improve the vitamin status. Cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2) are the most widely used compounds and the relative use of both products depends on historical or practical reasons. Oral intake of calcifediol ($25OHD_3$) rather than vitamin D itself should also be considered for oral supplementation. We reviewed all publications dealing with a comparison of oral cholecalciferol with oral calcifediol as to define the relative efficacy of both compounds for improving the vitamin D status. First, oral calcifediol results in a more rapid increase in serum 25OHD compared to oral cholecalciferol. Second, oral calcifediol is more potent than cholecalciferol, so that lower dosages are needed. Based on the results of nine RCTs comparing physiologic doses of oral cholecalciferol with oral calcifediol, calcifediol was 3.2-fold more potent than oral cholecalciferol. Indeed, when using dosages ≤ 25 μg/day, serum 25OHD increased by 1.5 ± 0.9 nmol/l for each 1 μg cholecalciferol, whereas this was 4.8 ± 1.2 nmol/l for oral calcifediol. Third, oral calcifediol has a higher rate of intestinal absorption and this may have important advantages in case of decreased intestinal absorption capacity due to a variety of diseases. A potential additional advantage of oral calcifediol is a linear dose-response curve, irrespective of baseline serum 25OHD, whereas the rise in serum 25OHD is lower after oral cholecalciferol, when baseline serum 25OHD is higher. Finally, intermittent intake of calcifediol results in fairly stable serum 25OHD compared with greater fluctuations after intermittent oral cholecalciferol.

Keywords Absorption of vitamin D (metabolites) · Calcifediol or 25-hydroxyvitamin D_3 or 25OHD oral supplementation · Cholecalciferol or vitamin D_3 oral supplementation · Conversion efficacy of vitamin D into 25OHD · Ergocalciferol or vitamin D_2 oral supplementation · Metabolism of vitamin D · Vitamin D deficiency · Vitamin D supplementation

Abbreviations

Calcifediol	25-Hydroxyvitamin D_3
25OHD	25-Hydroxyvitamin D_3 and 25-hydroxyvitamin D_2 combined in plasma
Vitamin D	Vitamin D_3 or D_2
RCT	Randomized controlled trial

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Introduction

The majority of vitamin D comes from endogenous production in the skin during exposure to sunlight (UVB 290–315 nm), whereas dietary vitamin D intake is low in most areas of the world. In a large European study, the median oral intake was well below 5 μg/day in most countries apart for the Scandinavian countries (due to the habitual high consumption of oily fish and/or cod liver oil) [1]. In North America, the mean intake of vitamin D is slightly higher than in Europe because of large-scale supplementation of a variety of food items with ergocalciferol or cholecalciferol [2]. The UVB light responsible for the production of vitamin D is also oncogenic due to DNA damage. Cumulative DNA damage of the epidermal layers of the skin is ultimately a risk factor for all

types of skin cancer and photoaging of the skin [3, 4]. Therefore, there is a difficult trade-off between sufficient exposure to UVB to produce the minimal amount of vitamin D necessary for bone and global health, and the cumulative risks of skin damage. Many dermatologists recommend an absolute minimal exposure to sunlight for high-risk groups such as infants and young children and only occasional short exposure for adults with a fair skin (Fitzgerald score 1–3). In addition, several groups avoid sunlight because of religious or cultural reasons or because of personal preference. This leads to a high frequency of vitamin D deficiency in several risk groups such as most Muslims and in the large majority of elderly subjects around the world. Finally, migration of people with a dark skin to areas with a much more limited sunshine are prone to vitamin D deficiency due to the mismatch between their darker skin color (and consequently higher needs for UVB light to produce vitamin D) and sunlight exposure [5].

For all these reasons, modest and even severe vitamin D deficiency is widely prevalent around the world. Based on extensive literature overviews of vitamin D status around the world [6], about 7% of the world population is severely vitamin D deficient (serum 25OHD below 25/30 nmol/l (10/12 ng/ml)) and 37% has serum 25OHD concentrations below 50 nmol/l (20 ng/ml) and thus suffers from mild vitamin D deficiency (Table 1). Severe vitamin D deficiency is very rare in Africa but high in the Middle East and Gulf states as well as in Northern China and Mongolia. However, also about 13% of adults in Europe have severe vitamin D deficiency [7–15] (Table 1). Others consider that the optimal vitamin D status requires 25OHD concentrations above 75 nmol/l (30 ng/ml), implying that more than half (88%) of the world population [6] would be vitamin D deficient. In any case, there is now a general consensus that a better vitamin D status is necessary to improve both bone and general health [16, 17]. Similarly, a good vitamin D status is essential for optimal efficacy of antiresorptive treatments [18, 19]. Governmental and scientific societies' recommendations and/or clinical guidelines also endorse such policy [20].

There are not a large number of strategies to correct vitamin D deficiency. First, one could recommend a higher regular exposure to sunlight or artificial UVB light as this was the natural solution during the evolution of mammals and humans. However, due to much longer life expectancy of modern humans (over the last two centuries) and the well-documented oncogenic character of UVB light, such strategy may well create more problems than solutions and cannot be recommended. Moreover, safe exposure to sunlight, such as only short (5–30 min depending on season, latitude, and skin type) exposure of sufficient skin areas, is difficult to explain and to implement in real-life situations. Increasing the dietary intake of vitamin D by higher consumption of food items with high natural vitamin D content is not a real option either as there is no sufficient oily fish in the oceans of the world to cover the needs of the world population. Increasing the food content of specific food items by special strategies (such as increasing vitamin D or 25OHD content of eggs or meat, UVB irradiation of mushrooms) is still in an early phase of exploration and thus not proven to be feasible, practical, and economically viable on a very large scale.

Table 1 Selective overview of mean serum 25OHD concentrations in adults around the world

Serum 25OHD (nmol/l)	< 25/30	< 50
World overview [6]	6.7%	37%
USA: NHANES 2010 data [7] (> 12 years)	6.7%	26%
EU countries (adults) [8]	13%	40%
Middle East/N Africa [9]		
Iran and Jordan	~ 50%	90%
US elderly men (MrOs) [10]	2.9%	26%
European adult men (EMAS) [11]	7.9%	41%
Postmenopausal osteoporotic women [12]	4.1%	28%
5 continents—25 countries		
Australia [13]		
Adult women (< 60 years) in wintertime		
Queensland (27° S)	7.1%	41%
Geelong (38° S)	7.9%	37%
Tasmania (67° S)	13%	67%
African countries [14]	< 0.1%	7.0%
China [15]	~ 72%	~ 37%
Mongolia [9]	~ 50%	

Supplementation of food with vitamin D or using vitamin D supplements is therefore the most widely used strategy to improve the vitamin status. Cholecalciferol and ergocalciferol are the most widely used compounds and the relative use of both products depends on historical or practical reasons (ergocalciferol being the most widely used product in North America and cholecalciferol most frequently used in Europe). There is extensive discussion about the relative potency of both compounds whereby there is growing consensus that daily use of ergocalciferol is largely equipotent to daily use of cholecalciferol but intermittent use of ergocalciferol is much less efficient than intermittent cholecalciferol [21, 22]. Nevertheless, some well-performed comparative studies reveal that even daily supplementation with ergocalciferol added to either biscuits or juice is only about 70% as potent as cholecalciferol in raising serum 25OHD in vitamin D-deficient adults [23].

25-Hydroxyvitamin D (25OHD) is present in low concentrations in some natural food products and the use of modern assay technology has led to a reappraisal that 25OHD may be present in some foods and thereby (slightly) increase the overall biological "vitamin D-like" activity of several food items such an egg or meat [24].

25-Hydroxyvitamin D (calcifediol), however, should also be considered for oral supplementation, either added to food or prescribed as supplement. We will first review the differences between the fate of oral ergocalciferol/cholecalciferol and calcifediol, from intestinal absorption to further metabolism into the biologically active or inactive metabolites. Then, we will summarize the existing literature comparing the relative biological properties of cholecalciferol with calcifediol. Indeed, as we aim to compare the fate of oral cholecalciferol/ergocalciferol with that of calcifediol, it is essential to compare the intestinal absorption and secondly to discuss the fate of vitamin D before it is converted to 25OHD (or other metabolites). Once vitamin D is 25-hydroxylated into 25OHD, its fate (metabolism) becomes indistinguishable whether it is derived from direct intake or from 25-hydroxylation of vitamin D.

Intestinal absorption of vitamin D (metabolites)

Vitamin D produced in the skin is transported directly by the blood stream while being mostly bound to the serum-binding protein, vitamin D-binding protein (DBP), or GC [25]. Dietary vitamin D is absorbed by intestinal cells and transported by chylomicrons into the lymph before being delivered to the blood stream [26].

Mechanism and efficacy of intestinal absorption of vitamin D or 25OHD

The absorption efficacy of cholecalciferol/ergocalciferol is good but not complete, as the mean absorption is about 79% (62–91%) in normal subjects as determined from recovery of labelled cholecalciferol in feces [27]. The intestinal absorption of radiolabelled calcifediol is 93% in normal subjects and (nearly) equally efficient in patients with severe fat malabsorption due to celiac disease or pancreatectomy and only slightly decreased in patients with short bowel disease [28]. Cholecalciferol/ergocalciferol is poorly absorbed in patients with intestinal fat malabsorption. The malabsorption of cholecalciferol/ergocalciferol was first demonstrated in patients with celiac disease, pancreatic insufficiency, or biliary cirrhosis [27, 28] as the absorption of labelled cholecalciferol/ergocalciferol varied between nil and 48%. A similar difference in intestinal absorption of cholecalciferol/ergocalciferol was observed in patients with severe biliary cirrhosis (absorption nearly nil) whereas their absorption of 25OHD was substantially better [29]. Absorption of calcifediol from the gut is largely achieved by the vena porta [30]. This is also in line with the observation that the intestinal absorption of calcifediol is not dependent on the presence of bile acids and micelle formation [31]. Intestinal fat malabsorption for whatever reason is therefore frequently associated with malabsorption and deficiency of fat-soluble vitamins such as vitamins A, D, E, and K, and such deficiencies should be routinely explored and treated accordingly in such situations. Patients with bariatric surgery are at increased risk for a large number of nutritional deficiencies including fat-soluble vitamins [32]. Deficiency of vitamin D is quite common and can cause in first instance calcium malabsorption, osteomalacia, and osteoporosis after weight loss surgery. Vitamin D deficiency in this patient group can progress to severe secondary or tertiary hyperparathyroidism and even brown tumors [33].

The intestinal absorption of cholecalciferol/ergocalciferol has long been considered to be due to simple diffusion by the proximal jejunum and distal ileum as based on gut perfusion studies in anesthetized rats [34]. However, more recent data dispute this hypothesis. Indeed, both in vitro and in vivo animal data suggest that several proteins involved in the intestinal absorption of cholesterol are also involved in the uptake of cholecalciferol/ergocalciferol. This should not be a surprise as both compounds are closely related lipophilic (seco)steroids with the same long side chain structure. In CaCo2 cells (intestinal epithelial-like cells), cholecalciferol/ergocalciferol uptake is concentration-, temperature-, and direction-dependent and can be significantly impaired by co-incubation with cholesterol or tocopherol [35]. Synthetic inhibitors of the cholesterol transporter proteins also inhibit cholecalciferol/ergocalciferol uptake in vitro and ex vivo (intestinal explants). Mice with overexpression of one of the cholesterol transporters (scavenger receptor class B type 1) have a 60% higher intestinal absorption of cholecalciferol/ergocalciferol [35]. Whether a similar mechanism is also operational in humans or whether the intestinal absorption of cholecalciferol/ergocalciferol is dependent on genetic variations in these transporters is so far unexplored. As calcifediol is much more polar and absorbed via the blood stream (vena porta), it is unlikely to use the same cholesterol transport system.

Profile of vitamin D concentration and 25OHD concentration after oral intake

When serum concentrations of vitamin D_3 or $25OHD_3$ are measured repeatedly after a single high (140 μg) dose, the maximal concentration of each vitamin D metabolite (thus independent from further conversion) or the area under the curve during the first 24 h is about 2-fold higher for calcifediol compared with cholecalciferol [36]. Whether meal composition has an effect on the efficacy of the intestinal uptake of cholecalciferol is unclear but several studies suggest that a low-fat meal may facilitate the uptake of cholecalciferol compared with intake of cholecalciferol without a meal [37, 38]. A high-fat meal however may also impair the absorption of cholecalciferol from the intestine in rodents and humans [37, 38].

Moreover, poly-unsaturated fats were particularly effective in decreasing cholecalciferol absorption [39].

In summary, the intestinal absorption of cholecalciferol is probably carrier-mediated and has a good efficacy (about 70%) in normal subjects. Its intestinal absorption can however be severely impaired in case of intestinal fat malabsorption (including after bariatric surgery). Oral cholecalciferol is transported by chylomicrons and reaches the general circulation after transport via the lymph pathway. Oral calcifediol is absorbed with very high efficacy (close to 100%), and after intestinal absorption, it is transported directly to the general blood stream via the vena porta. These differences explain the more rapid and higher peak of plasmatic levels of calcifediol compared with cholecalciferol after acute oral intake.

Metabolism of vitamin D and its metabolites

Metabolism of vitamin D

Pre-vitamin D_3 or vitamin D_3, produced in the skin, can be photochemically transformed into a number of mainly inactive steroids such as tachysterol, lumisterol, and suprasterol I and II-5,6-transvitamin D. Vitamin D, either synthesized in the skin or absorbed from the gut, is rapidly taken up by the liver (about 50% of an oral dose is taken up within 2–6 h), or other tissues such as fat and muscle. The liver rapidly metabolizes vitamin D into 25OHD mainly by the microsomal enzyme CYP2R1 [40, 41]. Indeed, this enzyme is clearly capable of 25-hydroxylation of vitamin D_3 to the same extend as vitamin D_2 and its characteristics are fully in line with the characteristics of 25-hydroxylase activity of liver homogenates [40, 42]. However, mice with bi-allelic null mutations of Cyp2R1 still have some circulating 25OHD and can produce $1,25(OH)_2D$, thereby demonstrating that some other enzyme must be present and capable of 25-hydroxylation of vitamin D_3/D_2. There are several candidates as reviewed by De Luca's group [43]. The initially most likely running-up candidate, CYP27A1, is however not the physiologic back-up candidate as Cyp27A1 KO mice did have higher (not lower) circulating 25OHD and the same was to some extend even true in mice with double Cyp2R1/Cyp27a1 KO [40]. Moreover, the high Km of CYP27A1 makes it more likely to be involved in metabolism of pharmacological amounts of vitamin D. Four other microsomal candidates are Cyp2J2/3, cyp3A4, Cyp2D25, and Cyp2C11, as reviewed by Zhu et al. [40]. The crystal structure of human CYP2R1-vitamin D_3 complex has been published, and gene mutations thus can be modeled to evaluate their consequences [44]. Several bi-allelic mutations of CYP2R1 can cause clinical rickets clinically indistinguishable from vitamin D deficiency rickets. The patients, however, do not respond to normal repletion with cholecalciferol, but rapidly normalize after calcifediol therapy [45–47]. In such patients with bi-allelic mutations of CYP2R1, some very low 25OHD concentrations remain detectable as well as low-normal $1,25(OH)_2D$ concentrations, clearly indicating some (alternative) 25-hydroxylase activity. The conversion of vitamin D into 25OHD is thus undoubtedly complex, not fully understood and its regulation (if any) is also not fully explored. Whatever mechanisms are involved, vitamin D is cleared from the circulation within several hours and then reappears as 25OHD in serum bound to the liver-produced vitamin D-binding protein (DBP) [25].

A number of studies have addressed the conversion efficacy of vitamin D into 25OHD in vivo based on serum 25OHD concentrations. In chickens, calcifediol is about 2 to 4 times more potent than cholecalciferol to increase calcium absorption or bone resorption [48]. Divergent results were obtained in rats (conversion factors of 1.4 to 5) and pigs (equipotent effects of cholecalciferol and calcifediol on serum levels of 25OHD) [49]. In a recent study in pigs, the authors concluded that feeding sows with calcifediol were considered to improve maternal supply with cholecalciferol and thereby maintain calcium homeostasis during gestation and lactation [50]. The conversion efficacy in humans will be summarized and discussed below.

The liver is undoubtedly the major tissue capable of 25-hydroxylation but the enzyme is also expressed in many other tissues at low concentration (including the skin). The regulation of the "25-hydroxylase activity" is not fully explored but most data indicate that the increase in serum 25OHD does not linearly increase with increasing vitamin D dosages, with steeper increase when vitamin D-deficient subjects are exposed to low dosages of vitamin D and much lower slope when vitamin D-replete subjects receive higher dosages. In some studies, even a real plateau level was observed. There are no hard data to interpret these results as being due to feedback inhibition of the enzyme activity, but they fit with the Km and Vmax of the major enzyme Cyp2R1.

Vitamin D may also be metabolized into 20S- and 22-hydroxymetabolites rather than 25OHD by CYP11A1 resulting in 20SOHD; 22OHD; $20S,22(OH)_2D$; and $20S,23(OH)_2D$ but the regulation of this metabolism and above all the functional implications are largely unknown [51, 52]. 3-Epi-25OHD is also found in serum but it is presently unclear which enzyme is responsible for the generation of this metabolite [53]. About 5% of serum 25OHD is present as 3-epi-25OHD in adults, but in infants and young children, the absolute and relative concentration of this epimer can be much higher, up to 50% [54]. The enzyme responsible for the generation of this epimer is unknown and not even whether this is the product of vitamin D conversion or the result of transformation of 25OHD into 3-epi-25OHD [55, 56].

Metabolism of 25OHD

25OHD is converted into $1\alpha,25(OH)_2D$ by a single P450 enzyme, CYP27B1. This is the only enzyme capable to

perform this reaction as clearly shown by the total absence of 1α,25(OH)$_2$D in mice or humans with bi-allelic deletion of the gene for CYP27B1 [45, 57, 58]. This enzyme is mainly expressed in the renal proximal tubuli where it catalyzes the production of the vitamin D hormone, 1α,25(OH)$_2$D. Several other cells and tissues (such as keratinocytes, monocytes, brain glia cells, and parathyroid cells) also express this enzyme at mRNA and protein level. The kidney is however the only tissue that exports the production of this hormone, whereas other cells and tissues are producing 1α,25(OH)$_2$D only in an auto/paracrine fashion, except in some pathological conditions (monocytic excess production of 1α,25(OH)$_2$D in case of inflammatory diseases such as sarcoidosis) [16, 17]. Whether the parathyroid glands are also able to secrete 1α,25(OH)$_2$D into the circulation is unclear but one publication (in abstract form only) suggests this to be possible in mice [59].

The uptake of 25OHD into its target tissues is supposed to be largely limited to free 25OHD (not protein bound). The kidney has access to free 25OHD at the serosal (blood) site and also to DBP-bound 25OHD filtered in the glomeruli whereby a cargo receptor complex (megalin, cubulin) can mediate the uptake of "total" 25OHD from the luminal site. A few other cells/tissues also express megalin but at a much lower level and their capability for uptake of DBP-bound 25OHD is unclear [60].

25OHD and 1α,25(OH)$_2$D can be further metabolized into 24-hydroxylated metabolites [24R,25(OH)$_2$D and 1α,24R,25(OH)$_3$D] by another P450 enzyme, CYP24A1 [61]. The enzyme is responsible for multiple further enzymatic transformations of their end product, finally resulting in the production of calcitroic acid and lactones [62]. Alternatively, 25OHD can be hydroxylated at the 23 position. The expression of CYP24A1 in many tissues is strongly upregulated by 1,25(OH)$_2$D and helps to maintain a strict feedback regulation of this active hormone and calcium homeostasis. This tight feedback control is clearly demonstrated by the clinical picture of infantile hypercalcemia or adult-onset renal calcification in case of inactivating CYP24A1 mutations [63]. Whether 24R,25(OH)$_2$D itself has biological activity on cartilage and fracture healing by activating a G-protein-coupled receptors (GPCRs) is still controversial [64].

Cyp3A4 is not only capable of metabolizing vitamin D into 25OHD but also capable of metabolizing 25OHD into 4β,25(OH)$_2$D. This enzyme can be induced by many drugs, including a number of anti-epileptic or anti-tuberculosis drugs, and thereby cause severe vitamin D deficiency up to clinical rickets or osteomalacia [65, 66]. A few cases of activating mutations of this gene resulted in accelerated 25OHD degradation and clinical rickets, labelled as vitamin D-dependent type rickets III [67].

There are in general about 50 metabolites of vitamin D identified from either in vitro or in vivo experiments [68]. Most of these compounds are believed to be degradation products, whereas only 1α,25(OH)$_2$D is believed to be the active hormone able to bind with high affinity to vitamin D receptor (VDR). 25OHD itself is considered to be the precursor for the active hormone and most of the other metabolites. Due to its lower affinity to VDR and higher affinity to DBP, in comparison with 1α,25(OH)$_2$D, one may reasonably assume that 25OHD is a poor agonist. 25OHD is therefore only able to activate VDR when serum concentrations are > 150 ng/ml and thus far exceeds normal concentrations as found in adults even when living in equatorial areas of the world with plenty of sun exposure [69].

Recently, 1β,25(OH)$_2$D has been found in serum of normal adults in picogram per milliliter concentrations and at about 15% of the concentrations of total 1α,25(OH)$_2$D [70]. The origin (tissue and enzyme) of this compound is unknown but as its concentration is strongly correlated with total 25OHD and much less with 1α,25(OH)$_2$D, it is likely to be the product of an alternative hydroxylation of 25OHD in the 1β instead of the 1α position. 1β,25(OH)$_2$D is a poor agonist of VDR but a strong antagonist of non-genomic actions of VDR [71].

Most of the enzymes involved described so far in the metabolism of vitamin D belong to the large ($n = 59$) group of CYP 450 enzymes [72] except for the enzymes involved in epimerization of vitamin D metabolites. However, vitamin D and its major metabolites can also be glucuronidated or sulphatated and such metabolites can be found in serum [73] but are mainly eliminated by hepatocytes into bile [74]. Whether these products can be converted back into vitamin D or 25OHD and be recirculated via the intestine (as is the case for bile acids) is not finally settled but most (older) data suggest this is not a major source of vitamin D [74].

Bile acids are structurally related to cholesterol and vitamin D and some bile acids and especially some metabolites of these bile acids, as produced in the intestine (lithocholic acid), are able to bind to VDR [75]. The functional implications of this phenomenon for calcium homeostasis are unknown but unlikely to be of major physiologic importance as these bile acid metabolites do not activate the intestinal VDR in case of the absence of vitamin D or its major metabolites. Whether this bile acid-VDR interaction would play a role in detoxification of some toxic bile acid metabolites requires further studies but is plausible in view of a series of enzymatic reactions induced by VDR activation in the intestine [76].

In summary, vitamin D produced in the skin is sensitive to photochemical conversion into inactive compounds. Circulating vitamin D (from endogenous synthesis or from dietary origin) is mainly metabolized in the liver into 25OHD. Among the different 25-hydroxylases, CYP2R1 is the main enzyme, with high affinity and low capacity and similar efficacy for conversion of vitamin D$_2$ and D$_3$. The efficacy of this metabolic step in humans is discussed in detail in the next paragraph. Alternative metabolic pathways include

the hydroxylation of vitamin D into 20S- and 22-OHD and some further metabolites mediated by CYP11A. Moreover, vitamin D can be inactivated by either sulphation or glucuronidation as start of their excretion in the bile and intestine [73, 74].

Conversion efficacy of vitamin D into 25OHD in humans

Only a limited number of studies have evaluated the conversion efficacy of vitamin D into 25OHD. As mentioned above, the conversion in experimental animals varies from 1:1 to 1:10, or a conversion efficacy of 10–100%. Most in vivo studies are based on the relative potency of oral cholecalciferol and calcifediol to increase serum 25OHD concentrations.

The seminal study by Stamp et al. [77] in the early 1970s concluded that, in humans, 25OHD was found initially to be about 10-fold more potent than cholecalciferol/ergocalciferol itself for increasing serum 25OHD concentrations into the 100–200 ng/ml range. This study dealt with a variety of patients, mostly with metabolic bone diseases [77]. These patients were, however, not randomized, the vitamin D arm received either cholecalciferol or ergocalciferol without further sub-analysis, the treatment duration was not the same for cholecalciferol/ergocalciferol (> 4 months) and calcifediol (> 6 weeks), and the groups were not matched for the etiology of the disease. Above all, few patients received physiological dosages of calcifediol so that the 1:10 ratio is largely based on comparison of high dosages of cholecalciferol/ergocalciferol (45–1000 μg/day) with more physiologic dosages of calcifediol (15–80 μg/day) [77].

Several other studies evaluated, in a randomized controlled trial (RCT) design, a comparison of a single dose of cholecalciferol with a single oral dose of calcifediol (Table 2).

1) Rossini et al. [86] compared the efficacy of cholecalciferol (mean intake of about 21 μg/day) with that of calcifediol (100 μg/week or about the equivalent of 14 μg/day) in 271 postmenopausal vitamin D-deficient women, followed over 1 year. The calculated relative potency of calcifediol versus cholecalciferol was 1.66. The baseline serum 25OHD was very low (mean 22 nmol/l or 8.8 ng/ml).
2) Jetter et al. [36] compared the evolution of serum calcifediol after daily intake of 20 μg of cholecalciferol with daily intake of 20 μg of calcifediol and in addition compared the equivalent dose of 140 μg of cholecalciferol or $25OHD_3$ given weekly, for a total observation period of 15 weeks. The treated group ($n = 35$) consisted of healthy postmenopausal women with a mean baseline serum 25OHD of about 13 ng/ml. Based on the delta 25OHD [serum 25OHD on the last day of treatment versus baseline 25OHD], the conversion ratio was 2.82 for the daily dosages and 5.6 when weekly dosages were compared. The authors, however, also measured the kinetics of serum 25OHD during the last day so that they could calculate the area under the curve. Based on these data, the relative potency was 2.23 and 2.78 for daily versus weekly supplementation with cholecalciferol or calcifediol. The authors concluded, based on all data in this extensive study, that oral calcifediol was 2–3-fold more potent than cholecalciferol to increase serum 25OHD in these elderly women with modest vitamin D deficiency at baseline [36].
3) Bischoff-Ferrari [80] compared 20 μg of either cholecalciferol with 20 μg of calcifediol per day for 4 months in postmenopausal Swiss women ($n = 20$) and studied either immune/inflammatory parameters or muscle function. These subjects were mildly vitamin D deficient at baseline (mean 25OHD of 13 ng/ml) and the relative potency or conversion efficiency as calculated from the change in serum 25OHD above baseline [delta 25OHD] at a single end point after 4 months. The conversion efficacy was found to be 3.4. Serum 25OHD was measured by MS/MS technology. Another important difference between both compounds was the more rapid increase in serum 25OHD in the calcifediol-treated group, when compared to changes in serum concentration 25OHD after oral intake of cholecalciferol [81].
4) Shieh et al. [83] compared a daily dose of 60 μg (2400 IU) of cholecalciferol with 20 μg of calcifediol in 35 healthy adults with a baseline 25OHD below 20 ng/ml with a follow-up of 16 weeks. Based on delta 25OHD between final concentration and baseline, oral calcifediol was 5.5-fold more potent than cholecalciferol in increasing the serum concentration of total 25OHD. They used a chemiluminescent assay for total 25OHD which is claimed to correlate well with MS/MS results. In addition, they also measured by direct ELISA the free 25OHD concentration, and based on the ration of delta free 25OHD, a similar relative potency (5.66) of oral calcifediol versus oral cholecalciferol was found.

Four studies have compared the relative potency of calcifediol versus cholecalciferol using multiple dosages.

1) Barger-Lux et al. [78] compared three dosages of cholecalciferol (25–250–1250 μ/day) with three dosages of calcifediol (10–20–50 μg/day) during 8 weeks using an open-label design. The subjects were healthy adults (mean age 28 years; $n = 116$). 25OHD was measured with a competitive protein-binding assay after extraction and chromatographic separation as to remove dihydroxylated vitamin D metabolites. When a low dosage of

Table 2 Overview of comparative studies of oral calcifediol with oral cholecalciferol. The relative potency was calculated as the ratio of delta serum 25OHD (final minus baseline) in the group treated with oral calcifediol versus delta serum 25OHD in the group treated with oral cholecalciferol and then corrected for the daily (or equivalent daily dose when given intermittently) dose (expressed in μg). No correction was made for the small difference in molecular weight between $25OHD_3$ and vitamin D_3

Author, year [ref]	Subjects	Country	Assay	Design	25OHD (nmol/l)		Calculated relative potency 25OHD:vitamin D	Comments	Delta 25OHD per μg vitamin D (nmol/l)
					Baseline	Delta			
Barger-Lux, 1989 [78]	$n = 116$ Healthy men Age 28 ± 4 years	USA	CPB + chrom	Open-label winter time At 8 weeks: Vitamin D_3 25 μg/day Vitamin D_3 250 μg/day $25OHD_3$ 10 μg/day $25OHD_3$ 20 μg/day $25OHD_3$ 50 μg/day	67 ± 25	 29 146 40 76 206	Low dose c omparison = 3.5 High dose comparison = 7–8	Only study comparing 3 different doses of vitamin D_3 and $25OHD_3$ Non-linear increase in serum 25OHD with increasing doses of vitamin D More linear increase in serum 25OHD with increasing doses of $25OHD_3$	1.16
Stamp, 1997 [77]	$n = 128$ variety of patients	UK	CPB + chrom	Post hoc analysis of clinical data Vitamin D_2 or D_3 45–1000 μg/day for > 4 months $25OHD_3$ 15–80 μg/day for > 6 weeks	< 62	Only shown in figure	Overall = 9–12 Lower doses of vitamin D = 6	Non-randomized clinical data No valid comparison at physiologic doses (< 50 μg/day) Vitamin D_2 and D_3 data are pooled Good study to compare the potency of high doses of vitamin D	
Cashman, 2012 [79]	Adults > 50 years; $n = 56$	IRL	ELISA	RCT for 10 weeks in winter Placebo Vitamin D_3 20 μg/day $25OHD_3$ 7 μg/day $25OHD_3$ 20 μg/day	44	 − 1.5 19.3 28.2 96.4	20 μg D_3 vs 7 μg $25OHD_3$ = 4.2 20 μg D_3 vs 20 μg $25OHD_3$ = 4.99	No plateau concentration after 5 weeks Only one dosage of vitamin D	0.95
Bischoff-Ferrari, 2012 [80, 81]	$n = 20$ Postmenopausal women Age 61.5 years	CH	MS/MS	RCT for 4 m Vitamin D_3 20 μg/day $25OHD_3$ 20 μg/day	35.4 30.7	143 42	Relative potency = 3.4	Single dose and Single end point	2.1
Jetter, 2014 [36]	$n = 35$ females Age 50–70 yrs	CH	MS/MS	RCT for 15 weeks Vitamin D_3 20 μg/day Vitamin D_3 140 μg/week $25OHD_3$ 20 μg/day $25OHD_3$ 140 μg/week	30.2 40.7 32.65 28.75	47.8 30.8 135.1 172.25	Based on last serum 25OHD Daily intake: relative potency = 2.82 Weekly intake: relative potency = 5.59 Based on 24 h area under curve 25OHD	Author's interpretation:oral 25OHD is 2–3-fold more potent than oral vitamin D3	2.39 1.54

Table 2 (continued)

Author, year [ref]	Subjects	Country	Assay	Design	25OHD (nmol/l)		Calculated relative potency 25OHD:vitamin D	Comments	Delta 25OHD per μg vitamin D (nmol/l)
					Baseline	Delta			
							Daily intake: relative potency = 2.23 Weekly intake: relative potency = 2.78		
Vaes, 2017 [82]	$n = 50$ Adults > 65 years With BMI 20–35	NL	MS/MS	RCT for 24 weeks in winter Vitamin D_3 20 μg/day $25OHD_3$ 5 μg/day $25OHD_3$ 10 μg/day $25OHD_3$ 15 μg/day	 37.7 43.4 38.3 38.6	 33.9 8.8 50.4 71.4	 Relative potency = 1.04 Relative potency = 2.97 Relative potency = 2.81	One dosage of vitamin D3 compared with 3 dosages of $25OHD_3$	1.7
Shieh, 2017 [83]	$n = 35$ Adults 35 years Baseline 25OHD < 50 nmol/l	USA	Chemiluminescence	RCT for 16 weeks Vitamin D_3 60 μg/day $25OHD_3$ 20 μg/day	 40.5 42.5	 34.5 63.75	 Relative potency = 5.54	Relative potency for measured free 25OHD = 5.66 Serum 25OHD > 75 nmol/l in all subjects on 20 μg $25OHD_3$/day	0.57
Rossini, 2005 [83]	Vitamin D-deficient postmenopausal	IT	RIA	RCT for 1 year Vitamin D_3 ~21 μg/day $25OHD_3$ 100 μg/week	 21 22	 63 70	 Relative potency = 1.66	Very severe vitamin D deficiency at baseline	3.0
Navarro-Valverde, 2015 [84]	$N = 40$ Postmenopausal osteoporotic women Mean age 67 years	SP	HPLC and UV absorptiometry	RCT Vitamin D_3 20 μg/day $25OHD_3$ 20 μg/day $25OHD_3$ 266 μg/week $25OHD_3$ 266 μg/2 weeks	 40.5 37.2 38.0 39.5	 45.7 150.8 195.0 171.0	 Relative potency = 3.3 Relative potency = 2.25 Relative potency = 1.71		2.28
Minisola, 2018 [85]	$N = 87$ Caucasian postmenopausal women Age > 55 years	IT	Liason XL (VDSP linked)	RCT for 3 month No vitamin D_3 arm $25OHD_3$ 20 μg/day $25OHD_3$ 40 μg/day $25OHD_3$ 125 μg/week	 37.5 42 41	 85.5 145 75	 		
							Mean relative potency for all studies using vitamin D_3 < 25 μg/day (1000 IU) ≈ 3.5–4.2–3.4–3.0–2.8 Mean relative potency for all studies using vitamin D_3 > 50 μg/day (2000 IU) ≈ 5.54–7 to 8		

Chrom, chromatography; *CPB*, competitive protein-binding assay; *RCT*, randomized controlled trial; *CH*, Switzerland; *NL*, The Netherlands; *IT*, Italy; *SP*, Spain; *RIA*, radioimmunoassay; *VDSP*, vitamin D standardization program

cholecalciferol (25 μg) was compared with similar dosages of oral calcifediol, a relative potency calcifediol/cholecalciferol of 3.5, 3.3, and 3.5 was found (10–20–50 μg/day). When pharmaceutical dosages of cholecalciferol (10–50,000 IU/day) were compared with the highest dose of calcifediol (50 μg or 2000 IU/d), oral calcifediol was 7–8-fold more potent than cholecalciferol.

2) Cashman et al. [79] compared, in a RCT design, the relative potency of oral calcifediol (7 or 20 μg/day) versus cholecalciferol (daily dose of 20 μg only). The study subjects were 56 healthy Irish adults (> 50 years), and 25OHD was measured by ELISA. The study lasted 10 weeks and was organized in wintertime as to avoid endogenous vitamin D synthesis. Oral calcifediol was found to be 4.2 to 5 times more potent than oral cholecalciferol in raising serum 25OHD.
3) Navarro-Valverde et al. [84] compared the effects of cholecalciferol (20 μg/day) versus calcifediol (20 μg/day, 266 μg/week, or 266 μg/every 2 weeks) in 4 × 10 postmenopausal osteoporotic women for 1 year. The majority of these women were modestly vitamin D deficient at baseline. The relative potency of calcifediol given at equivalent daily physiologic doses (20 μg) was 3.3 compared to that of cholecalciferol. When cholecalciferol was given at weekly or biweekly intervals, the relative potency varied between 2.25 and 3.93.
4) Vaes et al. [82] compared a single dosage of oral cholecalciferol (20 μg/day) with three dosages of oral calcifediol (5–10–15 μg/day) for 24 weeks in 50 Dutch elderly subjects (> 65 years) during wintertime. Baseline serum 25OHD concentration was 39 nmol/l (~ 16 ng/ml). 25OHD was measured by MS/MS technology. The relative potency of the low dose of oral calcifediol (7 μg) was about 1.04 versus cholecalciferol, whereas for both other dosages (10–15 μg), a relative potency of 3 and 2.8, respectively, was found.

Minisola et al. [85] reported the efficacy of different oral doses (20 or 40 μg/day or 125 μg/week) of calcifediol in Caucasian Italian postmenopausal women with mean baseline serum 25OHD of 41 nmol/l, given for 1 year [85], but did not include a control group using cholecalciferol. Therefore, no conversion efficacy can be calculated but the data allow to calculate the increase in serum 25OHD per daily microgram of oral calcifediol. The mean increase per microgram was about 4 nmol/l, well in line with the mean of all previously described comparative studies (see below).

Table 2 shows an overview of all studies comparing oral cholecalciferol and oral calcifediol. The majority of the studies included subjects with rather low baseline serum 25OHD concentrations (mean below 50 nmol/l). This table summarizes the potency of cholecalciferol versus calcifediol in each study with a mean relative potency of 4.62 when the results of all studies are combined. The relative potency may be dependent on the dosages as the relative potency of calcifediol is lower (about 3.2), when it is compared with low daily doses of cholecalciferol (below 25 μg or 1000 IU/day as evaluated in 7 studies). When only studies using high-dose oral cholecalciferol (≥ 50 μg or 2000 IU/day) are considered, then the relative efficacy of oral calcifediol over cholecalciferol is 8 (3 studies). For each study, we calculated the mean increase in serum 25OHD per microgram oral intake of either cholecalciferol or oral calcifediol (or daily equivalent when the compounds were given intermittently). The mean increase in serum 25OHD (all studies combined) after intake of 1 μg cholecalciferol per day was 1.53 ± 0.89 nmol/l (M ± SD; n = 10), whereas the mean increase was 4.76 ± 1.17 nmol/l per microgram oral intake of calcifediol. Based on this calculation, the overall relative potency of oral calcifediol was 3.11 greater when compared with oral cholecalciferol.

The increase in serum 25OHD after oral intake of cholecalciferol depended (significantly) on baseline serum 25OHD concentrations (Fig. 1a) with higher "delta 25OHD" in case of lower baseline serum 25OHD. By contrast, "delta 25OHD"

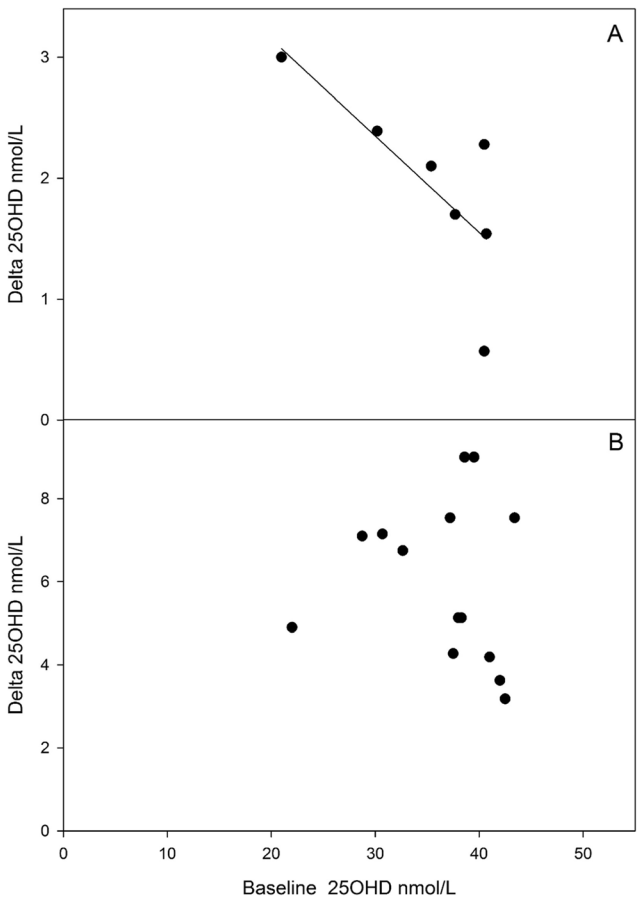

Fig. 1 Mean changes ("delta") in serum 25OHD concentration after oral supplementation with cholecalciferol (**a**) or with calcifediol (**b**) according to baseline serum 25OHD concentration, as reported in RCTs comparing oral both supplementation options

after oral intake of calcifediol was independent from baseline serum 25OHD concentrations (Fig. 1b).

Discussion

Vitamin D is essential for bone health throughout life. Dietary vitamin D intake is low in most countries and dietary intake of 25OHD is very limited as this metabolite is only present in trace amounts in food. Vitamin D supplementation is thus of vital importance if endogenous synthesis is limited for whatever reason. This is especially so for some risks groups, such as infants and small children, the very elderly population around the world and people who for voluntary or other reasons have limited or no access to UVB sunlight. Vitamin D is thus a very widely used therapy around the world either as ergocalciferol, as cholecalciferol, or more recently as calcifediol, and its use increases even rapidly as mild to even severe vitamin D deficiency is being recognized as an important health problem in many countries.

Oral intake of calcifediol rather than cholecalciferol itself may have some advantages but is at present not widely used. The intestinal absorption of calcifediol has a higher efficacy than that of cholecalciferol. Calcifediol is absorbed via the vena porta, whereas cholecalciferol uptake is more complex via the lymph pathway. These differences in intestinal transport can explain part of the greater overall bioavailability of calcifediol. Secondly, vitamin D must be converted into 25OHD and this takes place mostly, but not exclusively, in the liver by CYP2R1. The exact details of the conversion and the conversion efficacy have not received intensive attention. Efficacy could be affected by liver diseases, interactions with inducer/inhibitors, or allelic heterogeneity of cytochrome P450 enzymes involved in the hydroxylation of vitamin D metabolites. Based on all available data published in nine comparative RCTs (Table 2), it seems that oral calcifediol is more potent than oral cholecalciferol. When using only data comparing a daily dose of less than 25 μg/1000 IU of cholecalciferol with similar low dosages of calcifediol, oral calcifediol seems to be 2–5-fold more potent (mean of all studies is about 3.2) than oral cholecalciferol (Table 2). Based on eight studies comparing the efficacy of oral calcifediol supplementation versus oral cholecalciferol in mostly mildly vitamin D-deficient elderly Caucasian women, the increase in serum 25OHD after long-term daily intake of 1 μg of calcifediol is about 4.8 nmol/l. This is substantially greater than the increase of 1.5 nmol/l per 1 μg of cholecalciferol supplement. The increase in serum 25OHD after cholecalciferol supplementation found in the set of comparative RCTs is fully in line with the potency of cholecalciferol as found in numerous studies summarized in the IOM report [87] and summarized by Heaney as 1 ng/ml increase in serum 25OHD by an additional 100 IU of cholecalciferol [88]. These data indicate that, at low dose of cholecalciferol supplementation, about one out three molecules of vitamin D is transformed into 25OHD. When higher cholecalciferol dosages (> 2000 IU/day) are used, only about one in one of eight molecules of vitamin D is ultimately found in serum as 25OHD. Indeed, the potency of calcifediol is much higher in studies using high-dose oral of cholecalciferol, varying from 5.5 [84] to 7–8 [81, 82] and 9–12 times [78] (Table 2). A lower conversion rate of vitamin D into 25OHD at higher oral dosages of cholecalciferol can be explained by a non-linear increase in serum 25OHD with increasing cholecalciferol intake. Indeed, increasing the daily dose of cholecalciferol supplementation does not result in a linear increase in serum 25OHD (Fig. 1b) and dose-response curves indicate a lower efficacy at higher doses of cholecalciferol or even a true plateau level of 25OHD once the daily intake exceeds about 5000 IU cholecalciferol [87, 89, 90]. As oral calcifediol is absorbed in the gut with high efficacy and does not need to be converted in the liver, a more linear relationship between dosage and final concentration can be expected and is in line with several studies in humans [78, 79, 82] (Table 2) and animals [91]. The precise fate of vitamin D not recovered as 25OHD is unclear. The studies reviewed here dealt with generally healthy people and provide data on the relative potency of oral calcifediol versus cholecalciferol but it remains to be explored whether this potency would be different in patients with hepatic or renal diseases or in other situations of abnormal vitamin D transport (pregnancy, trauma, intensive care patients).

There are genetic factors influencing the vitamin D status [92]. Twin studies indicate that genetic factors may explain about 50% of the variation of serum 25OHD. Several GWAS and other studies demonstrated independently a modest effect of polymorphisms of DBP/GC, CYP2R1, 7-dehydrocholesterol reductase (DHCR7), and possibly CYP24A1 on serum 25OHD concentrations in Caucasians and Asians. These polymorphisms combined may explain about 5% of the variation in serum 25OHD. Moreover, these polymorphisms are found in nearly all populations [93–98]. The variation in serum 25OHD found in different areas and populations in the world is thus mainly due to environmental and lifestyle factors, with only minimal contribution of purely racial differences. One genetic variant of DBP, GC2, is associated with a modest (~ 10%) decrease in serum DBP and total 25OHD concentrations for unexplained reasons [92]. However, of these four genes, only CYP2R1 plays a role in the metabolism of oral vitamin D compared with oral 25OHD. Mutations in CYP2R1 are rare in the general population and it seems that only bi-allelic mutations create problems in producing sufficient 25OHD [45, 98]. CYP2R1 is also a polymorphic gene and such polymorphism has a minor influence on vitamin D status. However, the overall effect to CYP2R1 polymorphism on serum 25OHD is minimal, explaining less

than 2% of the overall variation in serum 25OHD. Therefore, whether gene polymorphism has a major influence on the relative potency of cholecalciferol compared to calcifediol is unclear but rather unlikely.

Whether the baseline vitamin D status influences the difference between oral vitamin D and 25OHD is not clear so far. The present overview confirms that the increase in serum 25OHD after oral intake of cholecalciferol is greater in case of more severe vitamin D deficiency [25]. This is in line with the Km of Cyp2R1. The "delta 25OHD" after oral calcifediol however was found to be independent from baseline serum 25OHD and this is in line with the excellent intestinal absorption and the absence of metabolic conversion before appearing in the blood stream. This conclusion is, however, preliminary as most subjects participating in the randomized trials started with mean baseline serum 25OHD concentrations below 50 nmol/l (20 ng/ml), except for the subjects studied by Barger-Lux et al. [78] (mean baseline serum 25OHD of 67 nmol/l) (Table 2). Serum concentrations of 25OHD show very large inter-individual variation for largely unexplained reasons. All known factors related to vitamin D status (skin color, sun exposure, body weight, vitamin D intake…) can explain less than 50% of the variation in serum 25OHD. Supplementation with cholecalciferol does not markedly diminish the inter-individual variations. Supplementation with oral calcifediol could potentially reduce the inter-individual variations as it eliminates a number of steps in the absorption and metabolism of vitamin D into 25OHD. If this would be confirmed, then that would be a great advantage over oral cholecalciferol. However, as we did not have access to individualized data, we cannot reliably answer that question. Indeed, a limitation of the present evaluation is the lack of individual data so that we were unable to perform a true per person meta-analysis. Moreover, the assay methodology used for serum 25OHD concentrations was not standardized. The measurement of serum 25OHD is known to be very assay dependent [99], but recent harmonization efforts have improved the accuracy of the methods [100]. The studies evaluated here used a variety of assay methods. The choice of assay probable did, however, not markedly influence the overall results, as the relative potency is each time calculated based on the delta (final minus baseline) 25OHD concentrations.

In conclusion, severe or mild vitamin D deficiency is highly prevalent around the world, affecting millions or even billions of people [1, 2, 6] (Table 1). Vitamin D supplementation is therefore an essential strategy to improve the vitamin D status and its beneficial effects on bone and maybe on global health [20]. Indeed, a poor vitamin D status is causally linked with increased bone resorption, bone loss, osteoporosis, and fracture risks. It is also likely to increase the risks of falls and associated fractures. Finally, poor vitamin D status may have many other health consequences. Therefore, correction of vitamin D deficiency by either vitamin D or calcifediol supplementation mainly aims to improve musculoskeletal health and may have other health benefits.

Up to now, only ergocalciferol or cholecalciferol has found wide applications. Based on the overall results summarized in this manuscript, we conclude that oral calcifediol may have some advantages for oral supplementation in comparison with the parent vitamin D compound. *First*, oral calcifediol results in a more rapid increase and significant increase in serum 25OHD compared to oral ergocalciferol/cholecalciferol. Therefore, oral calcifediol is able to normalize vitamin D deficiency more rapidly and consistently than oral ergocalciferol/cholecalciferol. *Second*, oral calcifediol is more potent than ergocalciferol/cholecalciferol so that lower dosages are needed. *Third*, oral calcifediol has a higher rate of intestinal absorption and this may have important benefits in case of decreased intestinal absorption capacity due to a variety of diseases. A potential additional advantage of oral calcifediol is a more linear dose-response curve whereas a higher intake of ergocalciferol/cholecalciferol does not result in a linear increase in serum 25OHD concentrations. This is probably, however, only relevant when high 25OHD is needed such as in patients with chronic renal failure as to maximize endogenous production of $1,25(OH)_2D_3$. The kinetics of intermittent cholecalciferol is complex and may give rise to more variable serum 25OHD concentrations and have been associated with increased risks of falls and fractures in case of transient use of megadoses of cholecalciferol [101–103]. Intermittent intake of calcifediol results in fairly stable serum 25OHD [104]. This is not a surprise, as calcifediol is known to have a very long half-life of 2–3 weeks [105].

In the present manuscript, we did not discuss in-depth the potential therapeutic value of oral calcifediol in rare cases of inactivating mutations of genes encoding hepatic 25-hydroxylases (CYP2R1) or in case of specific conditions, where the activity of cytochrome enzymes might be abnormal (e.g., anticonvulsants, corticosteroids, and some antiretroviral and antitubercular drugs), other diseases with abnormal vitamin D handling such as advanced liver insufficiency, obesity, intestinal malabsorption, nephrotic syndrome, or chronic renal failure, as this will be the subject of a separate literature review and analysis.

Based on our review, we suggest that oral calcifediol may be a valid and sometime more favorable alternative compared to oral cholecalciferol for the prevention or treatment of vitamin D deficiency at whatever age or as part of prevention or treatment of osteoporosis.

Compliance with ethical standards

Conflicts of interest MQ has no conflicts of interest to report; RB reports to have received lecture fees from L'Oréal and Abiogen and is co-owner of a university patent on vitamin D analogs licensed to Hybrigenix (France).

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