REVIEW

Calcifediol: a review of its pharmacological characteristics and clinical use in correcting vitamin D deficiency

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Abstract

Background In addition to the role of vitamin D in bone mineralization, calcium and phosphate homeostasis, and skeletal health, evidence suggests an association between vitamin D deficiency and a wide range of chronic conditions. This is of clinical concern given the substantial global prevalence of vitamin D deficiency. Vitamin D deficiency has traditionally been treated with vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol). Calcifediol (25-hydroxyvitamin D_3) has recently become available more widely.

Methods By means of targeted literature searches of PubMed, this narrative review overviews the physiological functions and metabolic pathways of vitamin D, examines the differences between calcifediol and vitamin D_3, and highlights clinical trials conducted with calcifediol in patients with bone disease or other conditions.

Results For supplemental use in the healthy population, calcifediol can be used at doses of up to 10 μg per day for children $\geq$ 11 years and adults and up to 5 μg/day in children 3−10 years. For therapeutic use of calcifediol under medical supervision, the dose, frequency and duration of treatment is determined according to serum 25(OH)D concentrations, condition, type of patient and comorbidities. Calcifediol differs pharmacokinetically from vitamin D_3 in several ways. It is independent of hepatic 25-hydroxylation and thus is one step closer in the metabolic pathway to active vitamin D. At comparable doses to vitamin D_3, calcifediol achieves target serum 25(OH)D concentrations more rapidly and in contrast to vitamin D_3, it has a predictable and linear dose–response curve irrespective of baseline serum 25(OH)D concentrations. The intestinal absorption of calcifediol is relatively preserved in patients with fat malabsorption and it is more hydrophilic than vitamin D_3 and thus is less prone to sequestration in adipose tissue.

Conclusion Calcifediol is suitable for use in all patients with vitamin D deficiency and may be preferable to vitamin D_3 for patients with obesity, liver disease, malabsorption and those who require a rapid increase in 25(OH)D concentrations.

Keywords Vitamin D deficiency · Calcifediol · Cholecalciferol · Immunomodulatory · 25-Hydroxyvitamin D_3 · 1,25-Dihydroxyvitamin D_3

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Introduction

Vitamin D is known to play an important role in bone mineralization, calcium and phosphate homeostasis, and skeletal health. The link between vitamin D deficiency and rickets, osteomalacia and osteoporosis is well established [1–3]. Nowadays, there is growing interest in the potential role of vitamin D in multiple other body functions. Evidence suggests an association between vitamin D deficiency and cardiovascular disease, selected cancers, autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes and rheumatoid arthritis), pulmonary disorders (e.g., asthma and chronic obstructive pulmonary disease), and upper respiratory

infections (e.g., influenza, COVID-19), including potential causal relationships with some of these outcomes [4–8].

The two commonly available forms of vitamin D supplement for maintaining vitamin D status or treating vitamin D deficiency or insufficiency are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) [1]. In Spain, calcifediol (a vitamin D_3 metabolite) has been used for these same purposes for more than 40 years and recently became available in several other European countries (e.g., Poland, The Netherlands, Belgium) and in Latin America (e.g., Chile, Colombia, Ecuador, Peru, Mexico).

This narrative review provides an overview of the physiological functions and metabolic pathways of vitamin D, examines the differences between calcifediol and vitamin D_3, and highlights clinical trials conducted with calcifediol in patients with bone disease or other conditions. To identify relevant published data, targeted literature searches of Pub-Med were conducted using the terms 'vitamin D deficiency' and 'calcifediol' and 'cholecalciferol'; as well as 'calcifediol' and specific disease conditions of interest using the key words 'bone disease', 'Paget's 'osteoporosis', 'osteomalacia', 'osteopenia', 'falls', 'muscle', 'immune system', 'asthma', 'COVID-19' and 'secondary hyperparathyroidism', applying the 'Clinical Trials' filter to individual searches. Additional articles were identified from the reference lists of published articles or were known to the authors. Searches were last updated 24 January 2022.

Physiology of vitamin D

Characterized initially as a vitamin, vitamin D is now also recognized as a prohormone [9]. Vitamin D consists of two forms, vitamin D_2 and vitamin D_3, both of which contribute to overall vitamin D status [10, 11]. Sunlight accounts for more than 90% of the body's daily requirement of vitamin D under normal physiological conditions. Exposure to ultraviolet B radiation converts 7-dehydrocholesterol in the skin to previtamin D_3 which undergoes thermal conversion to form vitamin D_3. Other sources of vitamin D_3 are foods such as oily fish (e.g., wild salmon, mackerel etc.), cod liver oil and egg yolks [1, 2]. Vitamin D_2 is present in UV-exposed mushrooms (e.g., oyster, shiitake mushrooms) [12] and is produced from irradiation of yeast. Vitamins D_2 and D_3 are both used to fortify foods (e.g., milk, margarine, yogurts, breakfast cereals, cooking oil) and as dietary supplements [1, 10, 13–15]. In 2021, calcifediol received a positive evaluation by EFSA for use in the European Union as an additive in food supplements targeting the healthy population at doses of up to 10 μg per day for children ≥ 11 years and adults, including pregnant and lactating women, and up to 5 μg/day in children 3−10 years. European Commission approval is pending [16].

Irrespective of source, vitamin D_2 and vitamin D_3 must undergo a two-step enzymatic process to become biologically active (Fig. 1). First, liver 25-hydroxylases (of the cytochrome P450 group) convert these inert prohormones to 25-hydroxyvitamin D_2 [25(OH)D_2] and 25-hydroxyvitamin D_3 [25(OH)D_3, calcifediol], respectively. The composite of 25(OH)D_2 and 25(OH)D_3 is reported for clinical purposes as the total serum 25-hydroxyvitamin D [25(OH)D] concentration and is the biomarker of vitamin D status. Next, 1α-hydroxylases in the kidneys covert the 25-hydroxylated vitamin D_2 and vitamin D_3 to 1,25-dihydroxyvitamin D_2 [1,25(OH)$_2D_2$] and 1,25-dihydroxyvitamin D_3 [1,25(OH)$_2D_3$, calcitriol], respectively [1, 10, 13–15], which are collectively referred to as 1,25-dihydroxyvitamin D [1,25(OH)$_2$D].

1,25(OH)$_2$D is the biologically active form of vitamin D. 1,25(OH)$_2$D regulates calcium homeostasis by acting on its intestinal absorption, renal reabsorption, and bone mobilization [1, 9]. A reduction in serum calcium concentrations stimulates secretion of parathyroid hormone (PTH), which activates synthesis of 1,25(OH)$_2$D. Conversely, an increase in serum calcium concentrations reduces PTH secretion and decreases the synthesis of 1,25(OH)$_2$D. Phosphate homeostasis is maintained through intestinal phosphate absorption, renal phosphate reabsorption or excretion and/or bone metabolism. The processes are regulated by PTH, 1,25(OH)$_2$D, and bone-derived fibroblast growth factor 23 (FGF23) via several negative feedback loops [17, 18]. In response to hyperphosphatemia, FGF23 suppresses phosphate reabsorption and 1,25(OH)$_2$D synthesis in the kidneys [19]. FGF23 excess is associated with phosphate-wasting disorders (e.g., hypophosphatemic rickets and tumor-induced osteomalacia) and chronic kidney disease, although the hormone also has a role in normal physiological processes in bone and kidney [19].

1,25(OH)$_2$D activity is mediated by the vitamin D specific receptor (VDR), a ligand-dependent transcription regulator molecule belonging to the nuclear receptor superfamily. The presence of VDR in most cells may explain the activity of vitamin D at different tissue sites, including its immunomodulatory effects [1, 4, 6, 9, 20, 21]. In this regard, VDR expression and activity play an important role in T-cell development, differentiation, and function [21]. Acting via the VDR, 1,25(OH)$_2$D suppresses parathyroid gene expression and blocks chief cell proliferation to facilitate the maintenance of optimal serum calcium concentrations [9]. 1,25(OH)$_2$D also increases the intestinal absorption of calcium by interacting with the VDR to enhance expression of the epithelial calcium channel and calcium binding protein [1]. 25(OH)D has also been shown to bind to and activate the VDR, although not as strongly as 1,25(OH)$_2$D [22, 23]. Regulation of renal 1,25(OH)$_2$D production may also directly or indirectly influence the activity of other hormones
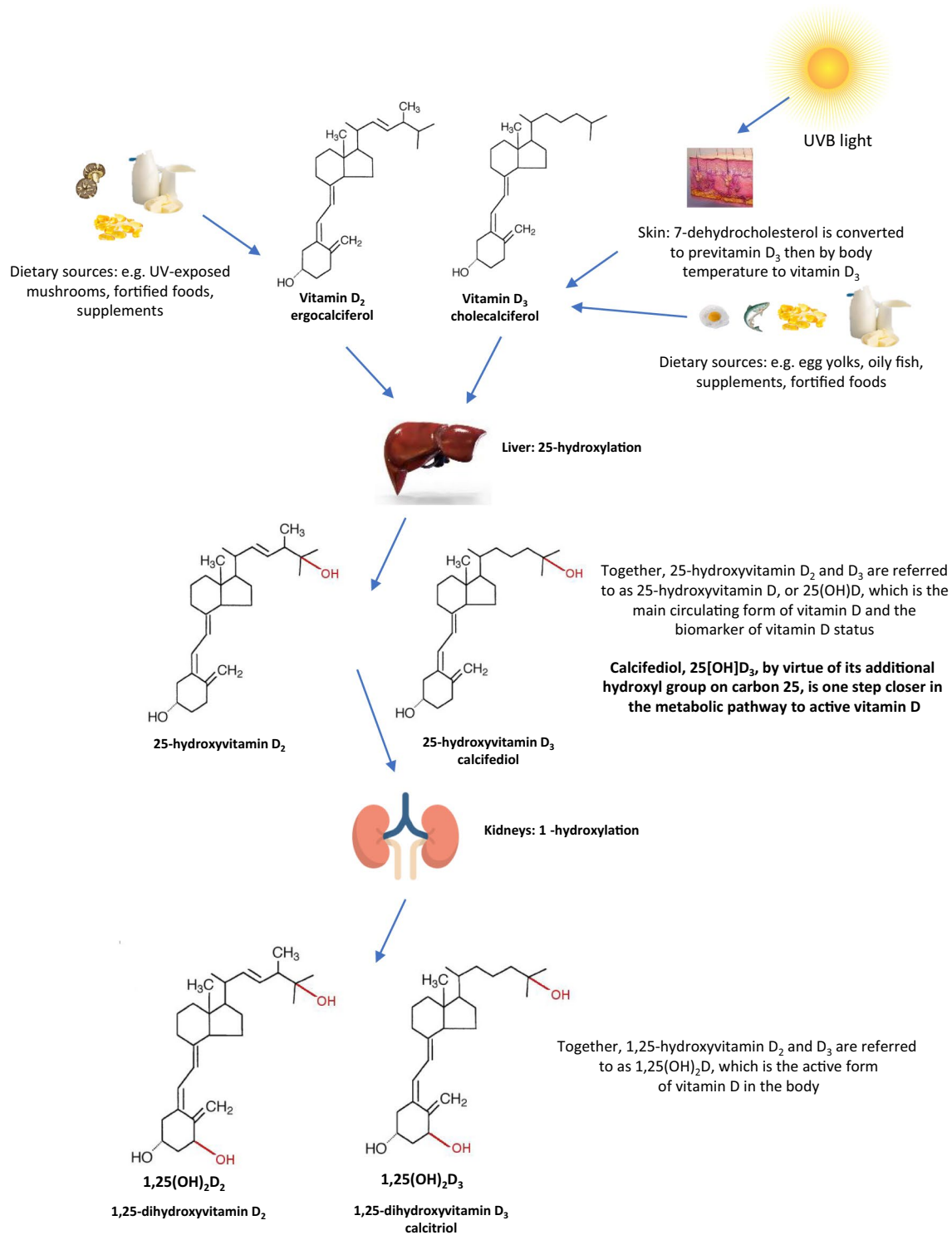
Fig. 1 Vitamin D activation pathway

(PTH, glucocorticoids, growth hormone, estrogens, thyroid hormones, prolactin) on intestinal calcium absorption [24].

Vitamin D deficiency

Although consensus is lacking about an 'optimal' serum 25(OH)D concentration, a 25(OH)D level above 75 nmol/L

(to convert nmol/L to ng/mL, divide by 2.5) can be regarded as the target level based on recommendations by the Endocrine Society Guidelines on vitamin D [25]. Other organizations including the Institute of Medicine [26] regard a 25(OH)D concentration above 50 nmol/L as sufficient, a 25(OH)D concentration between 30−50 nmol/L as insufficient, and a 25(OH)D concentration below 25−30 nmol/L as deficient. It is worth noting that vitamin D thresholds are not always intended to be diagnostic but are indicative of increased risk of disease. Based on these definitions, the prevalence of vitamin D deficiency/insufficiency worldwide is substantial irrespective of geographical region, ethnicity, latitude or altitude [3, 5, 27–35]. Indeed, a large systematic review found that 88% of the worldwide population had serum 25(OH)D concentrations < 75 nmol/L, 37% had concentrations < 50 nmol/L and 7% had concentrations < 25 nmol/L [3].

With some variation, serum 25(OH)D concentrations below 25−30 nmol/L are generally regarded as inadequate and concentrations above 50 nmol/L as adequate for maintaining bone health [36, 37]. A target serum 25(OH)D concentration of > 75 nmol/L may be recommended for individuals with various conditions who are at risk of vitamin D deficiency, or when focusing on the potential multiple/pleiotropic effects of vitamin D [25, 26, 38–41]. In this regard, there is evidence to suggest a role for vitamin D in modulating immune function [6, 42], although clinical data are not yet sufficiently robust to support recommendations for therapeutic vitamin D supplementation in patients with infections or autoimmune diseases [42]. The situation may change, however, as more evidence accumulates. An ancillary study to the randomized, double-blind vitamin D and omega-3 trial (VITAL; $n = 25,871$ participants) showed that improved vitamin D status over 5 years significantly reduced by 22% new incident autoimmune disease [43]. Observational data have suggested that maintaining adequate serum 25(OH)D concentrations may protect against COVID-19 infectivity and severity [44, 45], although a randomized controlled trial has since shown no reduction in the risk of all-cause acute respiratory infection or COVID-19 with vitamin D_3 supplementation in a large group of adults with vitamin D insufficiency [46].

Causes of vitamin D deficiency are myriad and include limited exposure to sunlight, use of sun blockers, dark skin pigmentation, inadequate intake of vitamin D-containing foods, malabsorption, genetic diseases of vitamin D metabolizing enzymes and the VDR, hepatic disease, renal disease, aging, obesity, and drugs that may affect the absorption or metabolism of vitamin D [1, 29, 41]. Depending on dietary preferences and latitude of residence in the general population, natural sources of vitamin D may be inadequate to maintain serum concentrations above 50 nmol/L throughout the year [39]. Strategies to improve vitamin D status include increased sun exposure, although this carries an increased risk of skin cancer; increased dietary intake of vitamin D-containing and vitamin D-fortified foods [47]; and vitamin D supplementation. Options for vitamin D supplementation vary by country. The most widely used supplement for vitamin D deficiency globally is vitamin D_3. Vitamin D_2 is used primarily in the USA and India [1, 10, 48]. Calcifediol is the primary supplement used in Spain and recently has been introduced to other markets.

An important and challenging issue regarding dosage recommendations for vitamin D supplementation is the continued use of international units (IU), which were defined several decades ago. In 1949, the Expert Committee on Biological Standardization defined 1 IU of vitamin D as 0.025 μg of crystalline vitamin D_3. The antirachitic activity of vitamin D was determined by administering various known concentrations of vitamin D to vitamin D deficient rachitic rats for 8 days. The proximal radii and ulnas were harvested and placed in a solution of silver nitrate where the line of new mineralization in the growth plate would turn black. The thickness of the line was determined and related to the amount of vitamin D administered. A higher vitamin D intake resulted in a thicker line and hence a higher visual score as described in the United States Pharmacopeia. This was known as the line test which was used to determine the number of IUs of vitamin D present in food or other substances. Subsequent experiments showed that the effect of 1.5 μg of vitamin D_3 with respect to calcium deposits in the line test was similar to that of approximately 1 μg of calcifediol [49]. As such, it is inappropriate to refer to calcifediol in IU since it is more effective per μg than vitamin D_3 in inducing antirachitic activity in a rat. Calcifediol doses should be expressed in micrograms or milligrams.

Differences between supplemental vitamin D_3 and calcifediol

A key molecular difference between calcifediol and vitamin D_3 is that calcifediol is one step closer in the metabolic pathway to biologically active vitamin D (see Fig. 1) [50]. The additional hydroxyl group on carbon 25 of calcifediol confers pharmacokinetic properties that can be pharmacologically advantageous in certain clinical situations such as malabsorption, liver impairment and obesity (Fig. 2).

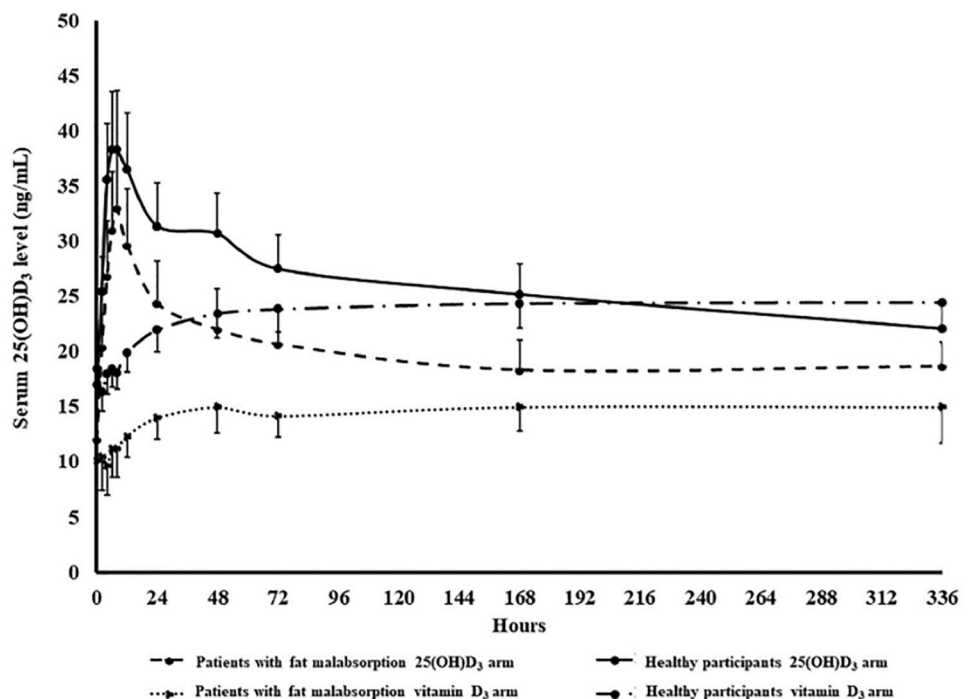### Pharmacokinetic differences and their clinical implications

The intestinal absorption of vitamin D_3, but not calcifediol, depends on the presence of bile acids and micelle formation [51]. In patients with fat malabsorption (e.g., celiac disease, pancreatic insufficiency, biliary cirrhosis), intestinal

Calcifediol increases serum 25(OH)D levels more rapidly than cholecalciferol

Calcifediol has a linear dose-response curve more predictable than that of cholecalciferol

Calcifediol does not require hepatic metabolism for activation making it more suitable for patients with impaired hepatic function

Calcifediol is more hydrophilic than cholecalciferol and less likely to be sequestered in adipose tissue (e.g. in obese patients)

Calcifediol is more likely to be efficacious in patients with malabsorption

Fig. 2 Pharmacological advantages of calcifediol as a vitamin D supplement

absorption of vitamin D_3 is markedly compromised [52–54], whereas that of calcifediol is relatively preserved (Fig. 3) [55]. Some European consensus statements recommend calcifediol as the vitamin D supplement of choice for patients with malabsorption syndromes (e.g., short bowel syndrome), and those undergoing bariatric surgery [56–58]. Calcifediol may also be preferable for use in patients receiving concomitant drugs that interfere with fat absorption, such as orlistat [59].

Calcifediol has a linear dose–response curve irrespective of baseline serum 25(OH)D concentrations [51]. In contrast, with vitamin D_3, the higher the basal 25(OH)D concentration, the smaller the increase during supplementation and vice versa [51]. The less predictable dose response to vitamin D_3 may arise from factors affecting its absorption (as discussed above) and metabolic conversion (e.g., age- and disease-related decreases in hepatic 25-hydroxylase activity). The more linear dose–response curve of calcifediol may be advantageous in situations where higher serum 25(OH)D concentrations are desirable [51]. For example, the requirement for higher doses of vitamin D supplements in patients receiving drugs that interfere with hepatic 25-hydroxylases (e.g., antiepileptic and antiretroviral drugs) [56, 58] suggests a possible advantage for calcifediol over vitamin D_3. Calcifediol is recommended as the preferred vitamin D supplement in patients with advanced liver disease [56].

Numerous comparative clinical trials have demonstrated that, at comparable doses to vitamin D_3, calcifediol induces a more rapid and larger increase in serum 25(OH)D concentrations (Table 1) [55, 60–72]. On a weight basis, calcifediol is considered to be between 3- to sixfold more potent than vitamin D_3, with the range reflecting the non-linear efficacy of vitamin D_3 for vitamin D repletion in comparative studies. The higher potency of calcifediol may be beneficial in clinical situations where a rapid increase in vitamin D status is required, such as patients with symptoms of osteomalacia due to vitamin D deficiency or before initiation of antiresorptive treatment or anabolic bone therapy in patients at risk of fracture [73, 74].

Fig. 3 Mean ± SEM serum 25-hydroxyvitamin D_3 (25(OH)D_3) concentration versus time curve after a single oral 900 µg dose of vitamin D_3 (cholecalciferol) or 25-hydroxyvitamin D_3 (25(OH)D_3, calcifediol) in healthy participants ($n = 10$) and patients with intestinal malabsorption of vitamin D ($n = 6$). The AUC of 25(OH)D_3 was statistically significantly higher with calcifediol than vitamin D_3 in both patient groups (both $p < 0.001$; Wilcoxon signed-rank test). Reproduced with permission from [55]. Copyright Holick 2021. *AUC* area under the curve, *SEM* standard error of the mean

Table 1 Studies comparing calcifediol and vitamin D_3 for improving vitamin D status

Study [reference number] design	Patient population	Treatment (no. of pts)	Results (calcifediol vs vitamin D_3)
Double-blind			
Bischoff-Ferrari et al. 2012 [60] r, db, sc	Healthy Caucasian post-menopausal women 50–70 years of age with serum 25(OH)D concentrations of 20–60 nmol/L	Calcifediol 20 µg/day ($n=5$) or 140 µg/wk ($n=5$) vs vitamin D_3 800 IU/day (20 µg/day) [$n=5$] or 5600 IU/wk (140 µg/wk) [$n=5$]	At 4 months, mean serum 25(OH)D concentrations were 174 nmol/L (69.5 ng/mL) in the calcifediol group and 79 nmol/L (31.0 ng/mL) in the vitamin D_3 group ($p < 0.0001$) Serum 25(OH)D concentrations shifted to > 75 nmol/L in all calcifediol-treated women at 35 days of follow-up, whereas ≈ 50% of those receiving vitamin D_3 had concentrations below the target threshold throughout the 4-month follow-up
Cashman et al. 2012 [61] r, db	Healthy Caucasian men and women ≥ 50 years of age	Calcifediol 7 µg/day ($n=14$) or 20 µg/day ($n=12$) vs vitamin D_3 800 IU/day (20 µg/day) [$n=13$] vs placebo ($n=16$)	Mean increases (per microgram of vitamin D compound) from baseline in serum 25(OH)D concentrations after 10 wks of supplementation were 0.96 ± 0.62 nmol/L with vitamin D_3, 4.02 ± 1.27 nmol/L with calcifediol 7 µg/day, and 4.77 ± 1.04 nmol with calcifediol 20 µg/day
Jetter et al. 2014 [62] r, db, sc	Healthy women 50–75 years of age with serum 25(OH)D concentrations of 20–60 nmol/L	Calcifediol 20 µg/day ($n=5$), 140 µg/wk ($n=5$) or 140 µg single dose ($n=5$) vs vitamin D_3 800 IU/day (20 µg/day) [$n=5$], 5600 IU/wk (140 µg/wk) [$n=5$] or 5600 IU/wk (140 µg/wk) single dose ($n=5$) vs combination of calcifediol 140 µg plus vitamin D_3 5600 IU as single doses	Serum 25(OH)D concentrations of > 75 nmol/L were achieved in 100% of women treated with calcifediol (daily or weekly) after a mean of 16.8 days, versus 70% of women treated with vitamin D_3 (daily or weekly) after a mean of 68.4 days
Catalano et al. 2015 [63] r, sc	Post-menopausal women (mean age 59 years) at low risk of fracture with serum 25(OH)D concentrations < 75 nmol/L	Calcifediol 140 µg/wk ($n=29$) or vitamin D_3 140 µg/wk [$n=28$]	After 24 wks, a significant increase from baseline in mean 25(OH)D levels was observed in both groups ($p < 0.001$), although the level was higher with calcifediol than vitamin D_3 (50.3 ± 15.5 vs 24.3 ± 7.8; $p < 0.001$)
Jakobsen et al. 2018 [64] r, db, co	Healthy male volunteers 20–30 years of age with mean baseline serum 25(OH)D concentration of 56.1 ± 8.5 nmol/L	Run-in with 10 µg/day vitamin D_3 for 4 wks, followed by 3 × 6-wk treatment periods with 10 µg/day of vitamin D_2, 25(OH)D_3 (calcifediol) and vitamin D_3 (cholecalciferol)	Based on the assumption that 1 µg vitamin D_3/day will show an increase in vitamin D status of 1.96 nmol/L, 10 µg vitamin D_3 was similar to 6.8 µg 25(OH)D_3 and 23 µg vitamin D_2
Vaes et al. 2018 [65] r, db	Elderly men and women ≥ 65 years of age with serum 25(OH)D concentrations of 25–50 nmol/L	Calcifediol 5.1 µg/day ($n=14$), 10.3 µg/day ($n=15$) or 15.3 µg/day ($n=16$) vs vitamin D_3 800 IU/day (22.3 µg/day) [$n=14$]	Calcifediol 10 µg/day and 15 µg/day increased serum 25(OH)D concentrations to > 75 nmol/L in 8 and 4 wks, respectively Vitamin D_3 increased serum 25(OH)D concentrations toward 70 nmol/L within 16 wks

Table 1 (continued)

Study [reference number] design	Patient population	Treatment (no. of pts)	Results (calcifediol vs vitamin D_3)
Graeff-Armas et al. 2020 [66] r, db, sc	Healthy Caucasian men and women > 50 years of age	Calcifediol 10 µg/day ($n=22$), 15 µg/day ($n=23$), 20 µg/day ($n=24$) vs vitamin D_3 800 IU/day (20 µg/day) [$n=22$]	At 6 months, mean increases from baseline in serum 25(OH)D concentrations were 50.1, 72.5, and 97.4 nmol/L with calcifediol 10 ($p=0.0173$), 15 ($p<0.0001$), and 20 ($p<0.0001$) µg/day, respectively, versus 38.7 nmol/L with vitamin D_3 Time to reach serum 25(OH)D concentrations of 75 nmol/L were 7 and 10 days with calcifediol 15 and 20 µg/day, versus 40 days with vitamin D_3 (both $p<0.0001$)
Pérez-Castrillón et al. 2021 [67] r, db, mc	Post-menopausal women with serum 25(OH)D concentrations < 50 nmol/L	Calcifediol 266 µg/month ($n=200$) vs vitamin D_3 25,000 IU/month ($n=98$)	At month 4, 35.0% of women treated with calcifediol reached serum 25(OH)D concentrations > 75 nmol/L versus 8.2% treated with vitamin D_3 ($p<0.0001$) [primary end point]; 13.5 vs 0% after 1 month ($p<0.0001$)
Charoenngam et al. 2021 [55] r, db, co, sc	Healthy adults ($n=10$) Patients with intestinal malabsorption of vitamin D ($n=6$)	Vitamin D_3 900 µg (36,000 IU) or calcifediol 900 µg for 14 days, then 14 days' washout and crossover	AUCs of vitamin D_3 were 64% lower in patients with malabsorption than in healthy participants (1177 ± 425 vs. 3258 ± 496 ng•h/mL; $p<0.05$); AUCs of calcifediol were not significantly different between groups ($p=0.540$) In healthy participants, AUCs of vitamin D_3 were 53% lower in the higher vs lower BMI group (2089 ± 490 vs 4427 ± 313 ng•h/mL; $p<0.05$); AUCs of calcifediol were not significantly different between groups ($p=0.500$) C_{max} and T_{max} in the vitamin D_3 arm were 53.5 ± 6.0 vs 24.3 ± 8.4 ng/mL and 10.4 ± 0.7 vs 11.3 ± 0.7 h in healthy participants and malabsorptive patients, respectively C_{max} and T_{max} in the calcifediol arm were 23.1 ± 4.6 vs 23.2 ± 6.8 ng/mL and 11.2 ± 4.1 vs 5.3 ± 0.7 h in healthy participants and malabsorptive patients, respectively
Shieh et al. 2021 [68] r, pg	Healthy adults with serum 25(OH)D concentrations < 50 nmol/L	Calcifediol 20 µg/day vs vitamin D_3 60 µg/day	At 8 wks, there was a significant increase from baseline in serum 25(OH)D concentrations with calcifediol ($p<0.001$) and vitamin D_3 ($p=0.002$), but the increase was greater with calcifediol than vitamin D_3 (127 vs 75 nmol/L)

Non-blinded

Table 1 (continued)

Study [reference number] design	Patient population	Treatment (no. of pts)	Results (calcifediol vs vitamin D_3)
Shieh et al. 2017 [69] r, nb, sc	Adults ≥ 18 years of age with serum 25(OH)D concentrations < 50 nmol/L	Calcifediol 20 μg/day (n = 19) vs vitamin D_3 2400 IU/day (60 μg/day) [n = 16]	At 16-wk follow-up, there was a significant increase in total serum 25(OH)D concentrations with calcifediol versus vitamin D_3 (64 vs 34.5 nmol/L; $p = 0.008$) By 4 wks, 87.5% of calcifediol-treated participants versus 23.1% of vitamin D_3-treated participants had achieved total serum 25(OH)D concentrations ≥ 75 nmol/L ($p = 0.001$)
Ruggiero et al. 2019 [70] r, nb, sc	Elderly men and women > 75 years of age admitted to geriatric acute care ward	Calcifediol 150 μg/wk vs vitamin D_3 6000 IU/wk (150 μg/wk) [n = 67 total for both groups]	After 7 months, serum 25(OH)D increased on average by 47.5 nmol/L (19 ng/mL) in calcifediol-treated participants and by 40.0 nmol/L in vitamin D_3-treated participants ($p = 0.5$) Increase in serum 25(OH)D concentrations was steeper (i.e., more rapid) with calcifediol ($p = 0.01$ for group*time interaction)
Corrado et al. 2021 [71] r, nb, sc	Post-menopausal Caucasian women with serum 25(OH)D concentrations of 20–60 nmol/L	Calcifediol (dose equivalent to 7000 IU/wk (n = 26); vitamin D_3 300,000 IU single dose (n = 28), 100,000 IU/q2mo (n = 26) or 7000 IU/wk (n = 27)	Target serum 25(OH)D concentrations of > 75 nmol/L were reached at 2 months in calcifediol-treated participants versus 3 and 5 months, respectively, in participants treated with vitamin D_3 weekly and q2mo
Non-randomized, non-blinded			
Navarro-Valverde et al. 2016 [72] nr, nb, sc	Post-menopausal osteopenic women with serum 25(OH)D concentrations < 50 nmol/L	Calcifediol 20 μg/day (n = 10), 266 μg/wk (n = 10) or 266 μg q2wk (n = 10) vs vitamin D_3 800 IU/day (20 μg/day) [n = 10]	At 6 and 12 months, serum 25(OH)D concentrations were 161 ± 21.7 and 188.0 ± 24.0 with calcifediol 20 μg/day, 213.5 ± 80.0 and 233.0 ± 81.2 with calcifediol 266 μg/wk, 164.5 ± 41.7 and 210.5 ± 22.2 with calcifediol 266 μg q2wk, and 80.0 ± 2 and 86.2 ± 23.7 with vitamin D_3 20 μg/day Increases with calcifediol were more rapid and significantly greater than with vitamin D_3 ($p < 0.001$)

Conversion factors for serum 25(OH) D concentrations: for ng/mL to nmol/L, × by 2.5; for nmol/L to ng/mL, ÷ by 2.5

AUC area under the curve, *BMI* body mass index, C_{max} maximum concentration, *co* crossover, *db* double-blind, *mc* multicenter, *nb* nonblind, *nr* nonrandomized, *pg* parallel group, *q2mo* every 2 months, *q2wk* every 2 weeks, *r* randomized, *sc* single-center, T_{max} time to maximum serum concentration, *wk* week

Vitamin D_3 is more lipophilic than calcifediol and can be sequestered in adipose tissue [75, 76]. By virtue of its additional hydroxy (OH) group, calcifediol is more hydrophilic, and thus less prone to sequestration [50, 55, 77]. This difference in lipophilicity results in a much-prolonged elimination half-life for vitamin D_3 compared with calcifediol ($\approx$ 2 months versus $\approx$ 10–15 days) [77]. A long and short half-life each may have clinical advantages. A short half-life can be clinically useful as it allows for a more rapid response to dose adjustments [66]. In general, higher doses of any type of vitamin D supplement are required in individuals with obesity to achieve optimal serum concentrations of 25(OH)D [78]. Preclinical data suggesting that hepatic 25-hydroxylation is altered in obesity may account at least in part for the reduction in circulating 25(OH)D concentrations [79, 80]. Some guidelines recommend calcifediol as the vitamin D supplement of choice in patients with obesity [56–58].

Lastly, as discussed above, vitamin D_3 but not calcifediol requires 25-hydroxylation, which has implications for the conversion efficacy of vitamin D_3 to 25(OH)D depending on the functioning of metabolizing enzymes. Studies have shown severe impairment in the expression and activity of hepatic CYP2R1 in obesity [79, 80], during fasting and in type 1 and type 2 diabetes mouse models, with involvement of at least two molecular pathways: the peroxisome proliferator-activated-gamma-coactivator-1α/estrogen-related receptor α axis and the glucocorticoid receptor [81].

Safety and dosage issues

The reference range for vitamin D sufficiency is 50–250 nmol/L. Available data indicate that serum 25(OH)D concentrations associated with vitamin D toxicity (hypervitaminosis D) are in excess of 375 nmol/L [26]. As such, the safety margin is broad irrespective of which supplement is used. Vitamin D toxicity and its associated manifestations (e.g., hypercalcemia, hypercalciuria, nephrocalcinosis) are rare, typically arising from patients self-administering extremely high doses of a vitamin D supplement for prolonged periods of time [25, 39]. Nevertheless, in view of the higher potency of calcifediol relative to vitamin D_3, and greater risk of excessive serum 25(OH)D concentrations in case of overdose, it is important that clinicians are aware of the optimal dosing per condition of each vitamin D supplement and prescribe accordingly. The calcifediol dose, and the frequency and duration of treatment are determined according to the serum 25(OH)D concentration, type of patient, condition being treated and presence of comorbidities such as obesity, malabsorption syndrome, and treatment with corticosteroids [82]. As with all medicines used for therapeutic purposes, patients receiving calcifediol should be advised to adhere to the prescribed dose.

During widespread use of calcifediol for more than 40 years in Spain, there have been few reports to the Spanish Pharmacovigilance System of hypercalcemia and/or hypervitaminosis D [83]. In studies which investigated weekly or biweekly doses of calcifediol 266 µg (i.e., in excess of the recommended dose) for 6–12 months in patients with osteoporosis or asthma, serum 25(OH)D concentrations remained below the 250 nmol/L threshold considered to be a risk for hypercalcemia [84, 85]. In general, monthly administration of calcifediol 266 µg is regarded as adequate to achieve effective vitamin D status and avoid risks associated with excessive concentrations [82, 84]. A pharmacokinetic study in healthy older adults found that calcifediol at doses of 15 and 20 µg/day significantly reduced the time to reach 25(OH)D concentrations of 75 nmol/L compared with vitamin D_3 (20 µg/day); upon discontinuation, calcifediol was eliminated faster than vitamin D_3 [66]. The superior efficacy of calcifediol in repleting serum 25(OH)D concentrations has important implications for clinical practice and should be considered in therapeutic guidelines.

Recommended dosages of vitamin D_3 or calcifediol to correct deficiency may take into account the vitamin D status of the recipient and other factors [86]. As an example, Italian guidelines recommend using different doses of vitamin D_3 or calcifediol depending on basal serum 25(OH)D concentrations [87]. In patients with serum 25(OH)D concentrations below 30 nmol/L, the recommended cumulative dose of vitamin D_3 is 300,000 IU over a maximum period of 12 weeks, divided into daily, weekly, or monthly administration (with no dose to exceed 100,000 IU for safety reasons). The recommended regimen of calcifediol is one capsule (266 µg) twice per month. At serum concentrations of 30–50 nmol/L, vitamin D_3 750–1000 IU/day or corresponding weekly or monthly administration is recommended, or calcifediol can be administered at a dose of one capsule (266 µg) per month. At serum concentrations of > 50 nmol/L, vitamin D supplementation is generally not recommended. Recent guidelines from the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) also recommend different dosage regimens for calcifediol and vitamin D_3 depending on the patient population (general or at-risk populations) [58]. Recommendations for calcifediol are provided in Table 2. Conversely, Dutch guidelines for vitamin D deficiency do not factor baseline serum 25(OH)D concentrations into dosage recommendations for the general population since lower baseline 25(OH)D concentrations result in larger increases during vitamin D_3 supplementation [88].

Table 2 Spanish Society for Bone Research and Mineral Metabolism (SEIOMM)-recommended dosage regimens for calcifediol in different patient populations with vitamin D deficiency [58]

Population	Recommendations
General population with severe deficiency (serum 25(OH)D concentrations < 25 nmol/L)	Calcifediol 266 μg/week for 5 weeks then 266 μg/month
General population with insufficiency (serum 25(OH)D concentrations 25−62.5 nmol/L)	Calcifediol 266 μg/month
Osteoporosis and other populations at risk of deficiency (and with serum 25(OH)D concentrations < 25 nmol/L)	Calcifediol 266 μg/week for 5 weeks then 266 μg every 3–4 weeks
Osteoporosis and other populations at risk of deficiency (and with serum 25(OH)D concentrations of 25−75 nmol/L)	Calcifediol 266 μg every 3–4 weeks

Studies of supplemental calcifediol in disease

Since calcifediol only recently became available outside of Spain, most literature evaluating vitamin D supplementation for bone diseases and other conditions refers to vitamin D_3. Studies of calcifediol have frequently used serum 25(OH)D concentrations as the end point (see Table 1), rather than hard clinical end points such as fracture numbers or hospitalization rates. In recent years, however, several studies conducted with calcifediol have reported non-laboratory clinical end points. The design features and outcomes of these studies are summarized in Table 3 [60, 70, 71, 85, 89–100].

Physical performance and muscle strength parameters in post-menopausal or frail patients

Several studies have examined the effects of calcifediol supplementation on physical performance and muscle strength parameters in post-menopausal women or frail and elderly patients with vitamin D insufficiency [60, 70, 71, 89–91]. Two small comparative RCTs of calcifediol and vitamin D_3 reported modest benefits with calcifediol [60] or no change from baseline with either supplement [89]. In a monocentric open-label randomized trial comparing weekly calcifediol (dosage reported as 7000 IU/week) with vitamin D_3 (at dosages of 7000 IU/week, 100,000 IU every 2 months or 300,000 IU as a single dose) in 107 post-menopausal women, calcifediol achieved target serum 25(OH)D concentrations more rapidly than vitamin D_3 and, at 6 months, was associated with significantly ($p < 0.05$) greater improvement than vitamin D_3 in lower extremity muscle strength/function assessed using the 30-s Sit-to-Stand test and Timed-Up-and-Go test [71]. A prospective, open-label study randomized 50 post-menopausal women with osteopenia/osteoporosis and baseline serum 25(OH)D concentrations of 25−50 nmol/L to receive calcifediol at doses of 20 or 30 μg/day. Serum 25(OH)D concentrations were normalized to above > 75 nmol/L within 30 days in 87% (20 of 23) and 100% (23 of 23) of patients, respectively.

At 6 months, the group treated with calcifediol 30 μg/day showed a modest but statistically significant increase in upper limb (handgrip) strength [90]. In an nonblinded, nonrandomized, uncontrolled, prospective cohort study, calcifediol 20 μg/day was administered to 113 post-menopausal women with osteoporosis and/or serum 25(OH)D concentrations < 75 nmol/L. After 6 months' treatment, statistically significant improvements from baseline were measured in serum 25(OH)D concentrations ($p < 0.001$), as well as in appendicular muscle strength ($p < 0.001$) assessed by Isometric Hand Grip Strength Test and Knee Isometric Extension Strength Test, and physical performance assessed by the Short Physical Performance Battery ($p = 0.002$) and 4-m Gait Speed ($p = 0.01$). There were also statistically significant reductions in the percentage of patients who were recurrent fallers ($p < 0.001$) and in the mean number of falls ($p = 0.020$) [91]. A systematic review and meta-analysis of seven RCTs ($n = 269$ participants), including those reported herein, concluded that, over a median follow-up of 24 weeks, calcifediol may have a positive effect on muscle strength parameters, with less evidence of an effect on physical performance [101].

Asthma control

Calcifediol was associated with improved asthma control in a randomized, placebo-controlled trial involving 112 adults with asthma who had serum 25(OH)D concentrations < 75 nmol/L. In addition to their asthma therapy, patients received calcifediol (dose reported as 16,000 IU/week equivalent to 266 μg/week) or placebo for 6 months. Change/improvement from baseline in Asthma Control Test scores at the end of the study period (primary end point) significantly favored calcifediol over placebo (+3.09 vs −0.57; difference 3.66; 95% confidence interval [CI] 0.89−5.43; $p < 0.001$) [85]. Calcifediol was also associated with a statistically significant improvement compared with placebo in scores on the Mini Asthma Quality of Life Questionnaire [92].

Table 3 Studies of supplemental calcifediol in disease

Study [reference number] design	Patient population	Treatment (no. of pts)	Results
Physical performance and muscle strength parameters			
Bischoff-Ferrari et al. 2012 [60] *r, db, sc*	Healthy Caucasian post-menopausal women 50–70 years of age with serum 25(OH)D concentrations of 20–60 nmol/L	Calcifediol 20 µg/day ($n=5$) or 140 µg/wk ($n=5$) vs vitamin D_3 800 IU/day (20 µg/day) [$n=5$] or 5600 IU/wk (140 µg/wk) [$n=5$]	At 4 months, significant ($p=0.03$) improvement in knee extension strength with calcifediol vs vitamin D_3 At 4 months, non-significant improvement in knee flexion strength, Timed Up-and-Go test, and repeated Sit-to-Stand test with calcifediol vs vitamin D_3
Vaes et al. 2018 [89] *r, db, pc*	Prefrail or frail men and women ≥ 65 years of age with serum 25(OH)D concentrations of 20–50 nmol/L	Calcifediol 10 µg/day ($n=26$), vitamin D_3 800 IU/day (20 µg/day) [$n=26$], or placebo ($n=26$)	After 6 months, no significant change from baseline in knee-extension strength with calcifediol, vitamin D_3, or placebo After 6 months, mean changes in physical performance tests, muscle mass, and muscle fiber type and size did not differ between groups
Ruggiero et al. 2019 [70] *r, nb, sc*	Elderly men and women > 75 years of age admitted to geriatric acute care ward	Calcifediol 150 µg/wk vs vitamin D_3 6000 IU/wk (150 µg/wk) [$n=67$ total for both groups]	At 7 months after discharge, polypharmacy and low handgrip strength at baseline were predictors of failure of intervention, independent of supplement (calcifediol or vitamin D_3)
Corrado et al. 2021 [71] *r, ol, sc*	Post-menopausal women with serum 25(OH)D concentrations of 20–60 nmol/L	Group 1: vitamin D_3 300,000 IU, single oral dose ($n=32$); group 2: vitamin D_3 100,000 IU every two months ($n=31$); group 3: vitamin D_3 7000 IU weekly ($n=31$); group 4: calcifediol 7000 IU weekly ($n=30$)	At 6 months, all vitamin D regimens induced significant improvement in muscular function (Timed-Up-and-Go test and 30 s repeated Sit-to-Stand test) Significantly greater improvement in lower extremity muscular strength and function with calcifediol 7000 IU weekly vs vitamin D_3 treatment regimens ($p < 0.05$)
Gonnelli et al. 2021 [90] *r, ol, pg*	Post-menopausal osteopenic/osteoporotic women aged 55 to 70 years with serum 25(OH)D concentrations of 25–50 nmol/L	Calcifediol 20 µg/day ($n=25$) or calcifediol 30 µg/day ($n=25$)	At 3 and 6 months, significant improvement from baseline in values for hand grip strength with calcifediol 30 µg ($p < 0.05$), but not calcifediol 20 µg
Iolascon et al. 2017 [91] Prospective cohort	Post-menopausal women aged ≥ 50 years with osteoporosis and/or serum 25(OH)D concentrations < 75 nmol/L	Calcifediol 20 µg/day ($n=113$)	After 6 months' treatment, significant increase from baseline in appendicular muscle strength ($p < 0.001$) using Isometric Hand Grip Strength Test and Knee Isometric Extension Strength Test; and in physical performance ($p=0.002$ at Short Physical Performance Battery and $p=0.010$ at 4 m gain speed) At 6 months, significant reduction in percentage of recurrent fallers ($p < 0.001$) and mean number of falls ($p=0.020$)
Asthma control			

Table 3 (continued)

Study [reference number] design	Patient population	Treatment (no. of pts)	Results
Andújar-Espinosa et al. 2021 [85]; Andújar-Espinosa et al. 2021 [92] r, tb, pc, pg	Patients with asthma and serum 25(OH)D concentrations <75 nmol/L	Calcifediol 266 μg/wk (16,000 IU) [n=56] or placebo (n=56)	At 6 months, significant improvement from baseline in asthma control (Asthma Control Test scores) with calcifediol vs placebo (difference 3.66; 95% CI 0.89–5.43; $p<0.001$) At 6 months, significant improvement in quality of life (Mini Asthma Quality of Life Questionnaire) with calcifediol vs placebo (difference 0.7; 95% CI 0.15–1.25; $p=0.01$)
COVID-19			
Entrenas Castillo et al. 2020 [93] r, ol, pg	Hospitalized patients (mean age 53 years) with COVID-19	Calcifediol 0.532 mg on day of admission, then 0.266 mg on day 3 and 7, then weekly until discharge or ICU admission (n=50) vs no calcifediol treatment (n=26)	One of 50 patients (2%) treated with calcifediol vs 13 of 26 patients (50%) not treated with calcifediol required ICU admission
Maghbooli et al. 2021 [94] r, mc, db, pc	Hospitalized patients (mean age 49 years) with COVID-19 and serum 25(OH)D concentrations <75 nmol/L	Calcifediol 25 μg/day (n=53) vs placebo (n=53)	Trend for lower hospitalization duration (median 5 vs 6 days), intensive care unit duration (7 vs 11 days), need for ventilator assistance (4 vs 9%), and mortality (6 vs 9%) with calcifediol, but differences vs placebo were not statistically significant
Alcala-Diaz et al. 2021 [95] ret, mc, ol, nr	Hospitalized patients (mean age 53 years) with COVID-19	Calcifediol (n=79) vs no calcifediol treatment (n=458)	Patients supplemented with calcifediol had lower risk of death during hospitalization (5 vs 20%; OR 0.22; 95% CI 0.08–0.61; $p<0.01$) vs patients not receiving calcifediol supplementation
Nogues et al. 2021 [96] obs, cohort	Hospitalized patients ≥18 years of age with COVID-19	Calcifediol 0.532 mg on day 1, then 0.266 mg on day 3, 7, 15, and 30 (n=447) vs no calcifediol treatment (n=391)	ICU admission rate was significantly lower in patients treated vs not treated with calcifediol at admission (4.5 vs 21%; $p<0.0001$) Mortality rate was significantly lower in patients treated vs not treated with calcifediol at admission (4.7% vs 15.9%; OR 0.21; 95% CI: 0.10–0.43; $p<0.001$)
Loucera et al. 2021 [97] ret, cohort	Hospitalized patients with COVID-19 (n=15, 968)	Prior prescription of vitamin D_3, calcifediol or calcitriol	Association between prescription of vitamin D_3 or metabolites stronger for calcifediol (HR 0.75; 95% CI 0.61–0.91) than for vitamin D_3 (HR 0.67; 95% CI 0.50–0.91) when prescribed 15 days prior to hospitalization The relation was maintained but weaker when prescribed 30 days prior to hospitalization: calcifediol (HR=0.73; 95% CI 0.57–0.95) and vitamin D_3 (HR 0.88; 95% CI 0.75–1.03)

Table 3 (continued)

Study [reference number] design	Patient population	Treatment (no. of pts)	Results
Oristrell et al. 2022 [98] ret, cohort	Individuals ≥ 18 years old living in Barcelona-Central Catalonia supplemented with vitamin D_3 ($n = 108{,}343$) or calcifediol ($n = 134{,}703$) from April 2019 to February 2020 vs propensity score-matched untreated controls	Vitamin D_3 or calcifediol supplementation	Patients on vitamin D_3 achieving 25(OH)D levels ≥ 75 nmol/L had lower risk of SARS-CoV2 infection, lower risk of severe COVID-19, and lower COVID-19 mortality compared to unsupplemented 25(OH)D-deficient patients (0.6 vs 1.3%; HR 0.66; 95% CI 0.46–0.93; $p = 0.018$) Patients on calcifediol achieving serum 25(OH)D levels ≥ 75 nmol/L had lower risk of SARS-CoV2 infection, lower risk of severe COVID-19, and lower COVID-19 mortality compared to unsupplemented 25(OH)D-deficient patients (0.5 vs 1.3%; HR 0.56; 95% CI 0.42–0.76; $p < 0.001$
Secondary hyperparathyroidism			
Sprague et al. 2014 [99] r, db, pc	Patients with CKD, iPTH > 70 pg/ml and serum total 25(OH)D < 75 nmol/L	Extended-release (ER) calcifediol 30 µg/day ($n = 13$) vs placebo ($n = 14$) and ER calcifediol 60 ($n = 17$) or 90 ($n = 17$) µg/day vs placebo ($n = 17$)	At 6 wks, 90% of calcifediol-treated patients achieved 25(OH)D levels > 75 nmol/L vs 3% of placebo-treated patients ($p < 0.0001$) At 6 wks, mean PTH decreased from baseline by 20.9, 32.8 and 39.3% in the 30, 60 and 90 µg dose groups, respectively, and increased from baseline by 17.2% in the pooled placebo group ($p < 0.005$)
Sprague et al. 2014 [100] r, mc, db, pc	Patients with CKD stage 3 or 4, SHPT and vitamin D insufficiency	Study A: extended-release (ER) calcifediol 30 µg/day ($n = 141$) vs placebo ($n = 72$) Study B: extended-release (ER) calcifediol 30 µg/day ($n = 144$) vs placebo ($n = 72$)	At 12 wks in studies A and B, 80 and 83% of calcifediol-treated patients achieved 25(OH)D levels > 75 nmol/L vs 3 and 7% of placebo-treated patients ($p < 0.001$), respectively At 12 wks in studies A and B, 33% and 34% of calcifediol-treated patients achieved ≥ 30% reduction in plasma iPTH vs 8 and 7% of placebo-treated patients ($p < 0.001$), respectively

Conversion factors for serum 25(OH)D concentrations: for ng/mL to nmol/L, × by 2.5; for nmol/L to ng/mL, ÷ by 2.5

CI confidence interval, *CKD* chronic kidney disease, *db* double-blind, *HR* hazard ratio, *ICU* intensive care unit, *iPTH* intact parathyroid hormone, *mc* multicenter, *nb* nonblind, *nr* nonrandomized, *obs* observational, *ol* open-label, *OR* odds ratio, *pc* placebo-controlled, *pg* parallel group, *r* randomized, *ret* retrospective, *sc* single-center, *SHPT* secondary parahyperthyroidism, *tb* triple-blind, *wk* week

COVID-19

Studies evaluating calcifediol supplementation for COVID-19 have reported favorable clinical outcomes [93–98].

A randomized, non-blinded non-controlled pilot study in 76 patients hospitalized with COVID-19 infection showed a marked reduction in intensive care unit (ICU) admissions among those treated versus not treated with calcifediol (2 vs 50%) [93]. A double-blind placebo-controlled trial identified trends for lower hospitalization and ICU durations, need for ventilator assistance and mortality among 106 hospitalized patients with vitamin D insufficiency (serum 25(OH)D concentrations < 75 nmol/L) treated with calcifediol than placebo, although the differences were not statistically significant. Improved outcomes in calcifediol-treated patients were associated with a higher percent lymphocyte count and lower neutrophil–lymphocyte ratio, which is a surrogate marker for decreased inflammatory activity [94]. A retrospective study of 537 patients hospitalized because of COVID-19 infection reported a statistically significant reduction in in-hospital mortality during the first 30 days (5 vs 20%; $p < 0.01$) among 79 patients who had been treated with calcifediol after admission [95]. Another retrospective study showed statistically significant reductions in the risk of mortality and ICU admission among patients admitted to COVID-19 hospital wards who had versus had not received calcifediol during the first 30 days [96]. A retrospective cohort study involving nearly 16,000 patients hospitalized with COVID in Andalusia found a stronger association between patient survival and prior use of calcifediol (HR 0.67; 95% CI 0.50−0.91) than prior use of vitamin D_3 (HR 0.75, 95% CI 0.61−0.91) [97]. Finally, a large ($n > 240,000$) population-based observational study conducted in Spain showed that adults receiving calcifediol supplementation who achieved serum 25(OH)D concentrations ≥ 75 nmol/L had a lower risk of COVID-19 infection (3.3 vs 5.6%; hazard ratio [HR] 0.69; 95% CI 0.61−0.79; $p < 0.001$), severe COVID-19 infection (0.6 vs 1.3%; HR 0.61; 95% CI 0.46−0.81; $p = 0.001$) and COVID-19-related mortality (0.5 vs 1.3%; HR 0.56; 95% CI 0.42−0.76; $p < 0.001$) compared with those not receiving vitamin D supplementation [98]. Similar findings were observed with vitamin D_3 supplementation in the same study [98]. In contrast, in a recent randomized controlled trial in adults with suboptimal vitamin D status (86.8% with a 25(OH)D concentration < 75 nmol/L), implementation of a test-and-treat approach to vitamin D replacement with vitamin D_3 (3200 IU/day, $n = 1550$; 800 IU/day, $n = 1550$; no testing or supplementation, $n = 3100$) for 6 months did not reduce the risk of acute respiratory tract or COVID-19 infection [45]. As regards calcifediol, the paucity of high-quality prospective trials precludes drawing definitive conclusions about its effect on the incidence and outcome of COVID-19 infections. Nevertheless, based on observational evidence of a reduction in COVID-19 severity, it is proposed that calcifediol may be considered for use in all patients in the early stages of COVID-19 infection to correct vitamin D deficiency [102].

Secondary hyperparathyroidism

As a treatment option for secondary hyperparathyroidism in non-dialysis patients with chronic kidney disease and vitamin D insufficiency [99, 100], extended-release calcifediol was shown to gradually improve serum 25(OH)D concentrations, leading to physiologically regulated increases in serum 1,25(OH)$_2$D concentration and sustained reductions in PTH, without any clinically relevant increases in serum phosphorus, calcium and FGF23 [103].

Conclusions

Vitamin D deficiency is a common problem worldwide. Achieving and maintaining a sufficient serum 25(OH)D concentration is important, since vitamin D has beneficial effects not only on musculoskeletal health, but potentially also on other aspects of health through its immunomodulatory effects specifically in individuals with a vitamin D deficiency. Calcifediol and vitamin D_3 are both effective at achieving and maintaining optimal 25(OH)D concentrations in the general population. From a pharmacokinetic perspective, when administered at similar doses, calcifediol achieves target serum 25(OH)D concentrations more rapidly than vitamin D_3 and has a more predictable and linear dose–response curve. This may be an advantage if rapid correction of vitamin D status is warranted, for example, in symptomatic osteomalacia. Overall, calcifediol is a suitable option for all patients with vitamin D deficiency and is preferable to vitamin D_3 for patients with obesity, severe liver disease, or malabsorption, and those who require a rapid increase in 25(OH)D concentrations.

Declarations

Conflict of interest Esteban Jodar reports grants from Amgen, AstraZeneca, Boehringer Ingelheim, FAES, Janssen, Lilly, MSD, Novo Nordisk, Pfizer, Sanofi, Shire, and UCB; personal fees from Adium, Amgen, Asofarma, AstraZeneca, FAES, Helios-Fresenius, Italfármaco, Lilly, MSD, Mundipharma, Novo Nordisk, UCB, and Viatris. Claudia Campusano Montaño has received honoraria from Amgen, FAES, Novartis, Sanofi, and Tecnofarma. Renata T de Jongh has received a grant from the Dutch Lung Foundation (project number 5113033), an investigator fee from Shire for a pharmacy-initiated study (SHP634-401), and personal fees from Kyowa Kirin, Lilly and UCB. Michael F. Holick has served as consultant for Biogena Inc., Ontometrics Inc. and Solius Inc.; has received grants from Carbogen Amcis BV and Solius Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Consent to participate Not applicable.

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