Contents lists available at ScienceDirect

Bone Reports



journal homepage: www.elsevier.com/locate/bonr

Real-world effectiveness and safety of combined calcium 600 mg and cholecalciferol 2000 IU for treating vitamin D deficiency: Results from a nationwide study with focus in osteoporosis

Rosa Pinto-Bonilla^a, José Baeza-Noci^a, Clara Casado Blanco^b, Guillermo Javier Valls Gumbau^c, Rubén Juarez Fernández^b, María Pascual-Pastor^d, Blanca García Magallón^e, Blanca Panero Lamothe^f, Carmen Moragues Pastor^g, Rafael Izquierdo Aviñó^h, Eva García Aguilarⁱ, Paula Saz-Leal^{i,*}, On behalf of the DOSTEO Research Group¹

^c Servicio de Medicina Interna, Hospital IMED, Valencia, Spain

^d Servicio de Reumatología, Hospital Universitario Vall d'Hebron, Barcelona, Spain

^e Servicio de Reumatología, Hospital Universitario Puerta de Hierro, Madrid, Spain

^f Servicio de Reumatología, Hospital Universitario Virgen de la Victoria, Málaga, Spain

^g Servicio de Reumatología, Hospital Universitari de Bellvitge, Barcelona, Spain

^h Servicio de Cirugía Ortopédica y Traumatología, Hospital Provincial Ntra. Sra. de Gracia, Zaragoza, Spain

ⁱ Medical Department, ITF Research Pharma S.L.U., Alcobendas, Madrid, Spain

ARTICLE INFO

Keywords: Calcium Vitamin D Cholecalciferol 2000 IU Osteoporosis Bone metabolism

ABSTRACT

Introduction: Treatment of calcium (Ca) and vitamin D (VD) deficiency (VDD) is crucial for health, especially in bone conditions, such as low bone mineral density (BMD) and osteoporosis. Despite updates in clinical guideline recommendations, no studies have evaluated the efficacy and safety of administering 2000 IU of cholecalciferol combined with calcium. Thus, the main objective of this study was to evaluate VD levels following treatment with Ca 600 mg/ cholecalciferol 2000 IU in real-life clinical practice.

Methods: This multicenter, retrospective, observational study included 302 adult patients receiving Ca 600 mg/D3 2000 IU orodispersible tablets, daily for \geq 24 weeks. The primary outcome was 25-hydroxivitamin D [25(OH) D] serum levels following treatment. Key secondary outcomes included changes in serum 25(OH)D levels and other bone metabolism (BM) parameters, safety and tolerability. The protocol was approved by a Research Ethics Committee.

Results: 285 patients were evaluated (mean age [SD]: 67.4 [12.6] years old; 88.4 % women; basal serum 25(OH) D: 20.0 [8.6] ng/mL); 80.7 % reported previous history of osteoporosis/low BMD (osteopenia) and 37.2 % had received other Ca/VD prior to start study treatment. Median treatment duration was 38.5 weeks [range 24.0–82.4]. Overall, 94.4 % of patients increased serum 25(OH)D following treatment to a mean of 36.3 [11.8] ng/mL (p < 0.001 vs. baseline). Patients with basal VDD, significantly increased serum 25(OH)D to a mean over 30 ng/mL; no significant change found in repleted patients (basal 25(OH)D level \geq 30 ng/mL). PTH was significantly reduced after treatment, with no clinically relevant effect on serum Ca or phosphate. Three non-serious treatment-emergent adverse events were reported. A post-hoc analysis on osteoporotic patients revealed virtually identical results in this population.

Conclusion: Treatment with Ca 600 mg/cholecalciferol 2000 IU for at least 24 weeks is effective and safe, especially in osteoporosis. Patients with VDD significantly increase plasma 25(OH)D to optimal range for bone health, with no clinically relevant changes on other bone metabolism parameters other than reducing secondary

* Corresponding author at: Medical Department, ITF Research Pharma S.L.U., Alcobendas, Spain.

https://doi.org/10.1016/j.bonr.2024.101796

Received 31 May 2024; Received in revised form 22 July 2024; Accepted 23 July 2024 Available online 26 July 2024

2352-1872/© 2024 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).





^a Servicio de Traumatología, Hospital Vithas Valencia Consuelo, Spain

^b Servicio de Rehabilitación, Hospital General Universitario Gregorio Marañón, Madrid, Spain

E-mail address: p.saz@italfarmacogroup.com (P. Saz-Leal).

¹ List of researchers and institutions at the end of the text.

1. Introduction

Vitamin D deficiency (VDD) is significantly prevalent worldwide (Holick, 2017), even in Mediterranean countries such as Spain (Navarro-Valverde and Quesada-Gómez, 2014). Different risk factors including limited sun exposure, skin pigmentation, age, or obesity, as well as clinical conditions such as malabsorptive disorders or bone disorders such as osteoporosis may contribute to this deficiency (Bleizgys, 2021). Despite lack of universal consensus, it is widely accepted that 25-hydroxy-vitamin D [25(OH)D] concentration in the range of 30-50 nanograms per milliliter (ng/mL) constitutes optimal vitamin D status to ensure bone health, particularly for high-risk groups (Casado et al., 2021; Pludowski et al., 2022; Camacho et al., 2020; Bouillon and Carmeliet, 2018). Daily doses of up to 2000 IU of cholecalciferol are recommended by clinical guidelines, particularly in patients with low bone mineral density (BMD, also referred as osteopenia), osteoporosis or at high risk of VDD, to achieve and maintain these optimal levels in the long-term. Higher doses may be needed according to the magnitude of the deficiency (Casado et al., 2021; Camacho et al., 2020; Naranjo Hernandez et al., 2019; Presa Lorite et al., 2022; Holick et al., 2011; Dawson-Hughes et al., 2010; Francis et al., 2013; Cosman et al., 2014; Cancio Trujillo et al., 2023).

The recommended daily intake of calcium (Ca) is set between 1000 and 1200 mg for adults, the latter required for men over 70 years old or women of 51 years and older (Camacho et al., 2020; Ross et al., 2011). Despite our conception of a tending increase in consumption of calciumrich food, recommended daily allowances are often not satisfied (Shlisky et al., 2022). This is evident in Spain, where daily intakes for the adult population average only 600–700 mg (Olza et al., 2017). Moreover, the upper limit for total calcium intake is set at 2500 mg/day (Ross et al., 2011).

Special consideration should be given to the role of calcium and vitamin D in low BMD (osteopenia) and osteoporosis, conditions resulting from an imbalance in bone resorption and formation, leading to weak and fragile bones and increased risk of fractures (Camacho et al., 2020; Riancho et al., 2022; Shoback et al., 2020). Being more common in postmenopausal women, it affects both genders. As mentioned above, osteoporosis is a well-known risk factor for vitamin D and calcium deficiency (Bleizgys, 2021; Riancho et al., 2022; Quesada-Gomez et al., 2013). Nevertheless, VDD and deficient calcium intake are being reported for osteoporotic women, regardless of the treatment received (Riancho et al., 2022; Shoback et al., 2020; Quesada-Gomez et al., 2013).

Altogether, calcium and vitamin D are often placed as a combined treatment for promoting bone health, and the recommended coadjuvant therapy for antiosteoporosis treatments (Casado et al., 2021; Shoback et al., 2020). Demilos 600 mg/2000 UI® is a unique combination containing 600 mg of calcium and 2000 IU of cholecalciferol, formulated as orodispersible tablets (Italfarmaco, 2020). This combination has been approved in Europe following Decentralized Procedure and it was first introduced in Spain in April 2021, and other countries later on.

To gather clinical evidence with this formulation under clinical practice settings, the overall objective of this study was to determine changes in vitamin D status and bone metabolism parameters following at least 24 weeks of treatment. We also aimed to evaluate the patient medical profile associated to the prescription of this drug based on medical criteria, and factors affecting vitamin D restoration during supplementation.

2. Material and methods

2.1. Study design

DOSTEO is an observational, multicenter (N = 44 study sites in Spain, outpatient care), multispecialty (Rheumatology, Internal Medicine, Geriatrics, Traumatology and Rehab), retrospective study to evaluate vitamin D levels and characterize patients who had received treatment with calcium 600 mg and cholecalciferol 2000 IU orodispersible tablets (Demilos® 600 mg/2000 IU) for at least 24 weeks. The study protocol was approved by the Research Ethics Committee at Puerta de Hierro hospital (Spain).

2.2. Participants

Data were retrospectively collected from patients who received 600 mg calcium/2000 IU cholecalciferol treatment and met the following established selection criteria: \geq 18 years of age, a minimum of 24 weeks under study treatment, with serum 25(OH)D determination performed in the 30 days prior to treatment initiation and at least following 24 weeks. Patients were not excluded due to any type of concomitant medication that the physician considered according to standard clinical practice. Data were obtained from the medical records of the patients in each participating study site.

2.3. Treatment

Demilos® 600 mg/2000 IU are round orodispersible tablets, containing 1500 mg calcium carbonate (600 mg calcium) and 2000 IU (50 μ g) cholecalciferol (vitamin D₃). Tablets are dissolved in the mouth without being swallowed and are administered preferably after meals.

The dosage was determined by the physician according to usual clinical practice and patient needs. The justification for the use of the drug was recorded in the patient's medical records as part of the study documentation.

2.4. Outcome measures

The primary endpoint of the study was to determine serum 25(OH)D levels after at least 24 weeks of treatment. These values were classified according to response categories defined by the following cut-off points: 20 ng/mL, 30 ng/mL, 50 ng/mL, 60 ng/mL and 90 ng/mL.

As secondary variables, the final mean value of 25(OH)D and change from baseline value were obtained for the whole sample and according to different basal 25(OH)D status: <10 ng/mL, [10–20) ng/mL, <20 ng/mL, [20–30) ng/mL and \geq 30 ng/mL. The mean values and change from baseline of parameters related to bone metabolism, including parathyroid hormone (PTH), serum calcium, phosphate, glomerular filtration rate and alkaline phosphatase were also collected. Other variables such as incidence of adverse events throughout the study, assessment of tolerability and physician satisfaction (three-item questionnaire) were assessed. Sociodemographic and clinical characteristics, concomitant medication and Ca/VD treatments received prior to the initiation of the study treatment were also recorded.

Outcomes were determined in the overall study sample and in three subgroups of patients: Group 1. Patients who did not receive previous VD at least for 12 weeks prior to initiate the study treatment. Group 2. Patients who did receive any VD treatment in the 12 weeks prior to initiate the study treatment. Group 3. Patients diagnosed with osteoporosis, with/without osteoporotic fractures.

2.5. Statistical analysis

Summary statistics are presented as number (frequency, %) for categorical data and median (interquartile range, IQR, or 95 % CI) and mean [SD] for quantitative variables. We calculated absolute differences between given timepoints as the mean of individual subject change. Paired continuous data were analyzed with the paired Student's *t*-test or the Wilcoxon sign-ranked, according to normal distribution analyzed by means of the Shapiro-Wilk test.

Univariate analyses based on odds ratios (OR) were performed to evaluate factors associated with VD restoration (age, sex, body mass index, diagnosis of bone disorder, medication). We tested the associations between categorical variables with the Fisher's exact test or the chi-square test when two or more variables were analyzed, respectively. For continuous variables, hypothesis testing was done for independent samples, using Student *t* or Mann-Whitney *U* tests, according to normal distribution. Multivariate analysis was performed using likelihood ration and Wald tests. The multivariate regression models were validated by the Hosmer-Levmeshow test. Statistical analyses were performed using SAS software (version 9.4). A *p* < 0.05 was considered statistically significant.

3. Results

Three hundred and two patients were included in this study, 285 were evaluable (N = 5 was <24 weeks under treatment and N = 18 lacked any serum 25(OH)D determination). Baseline characteristics of the participants are shown in Table 1 (and Supplementary Table 1). Of note, the mean age was 67.4 years (SD 12.6) and 88.4 % of the study subjects were women. Most patients suffered from bone disorders: low BMD/osteopenia (28.8 %), osteoporosis (56.1 %), and a history of osteoporotic fracture (35.1 %), predominantly recent (<2 years) and vertebral fractures. The mean 25(OH)D level was 20.0 ng/mL (SD 8.6), with 91.6 % patients below 30 ng/mL. Except for an elevated PTH (mean [SD] 73.3 [43,3] pg/mL), other parameters of bone metabolism were found in the normality range (Table 1).

Once included in our study, the mean duration of the 600 mg Ca/2000 IU cholecalciferol treatment was 38.5 weeks (range 24.0–82.4), and 16.5 % and 8.4 % of patients were treated for over 48 and 72 weeks, respectively. All patients initially took one tablet per day. Six subjects (2.1 %) temporarily interrupted the treatment or changed the dose during the study, without discontinuation. Investigator-reported adherence was 93.3 %.

Following at least 24 weeks of treatment, 94.4 % of patients increased their levels of 25(OH)D, with 272 patients (95.4 %) reaching serum 25(OH)D values \geq 20 ng/mL and 208 patients (73.0 %) \geq 30 ng/mL. Besides, 10.5 % and 2.1 % of patients exceeded 50 and 60 ng/mL, respectively. None of the patients reached values of 90 ng/mL.

The mean serum 25(OH)D was 36.3 [11.8] ng/mL following treatment (Table 2 and Fig. 1A), with a mean change of 16.4 ng/mL (95%CI 14.9–17.9; p < 0.001) from baseline. Of note, the increase of serum 25 (OH)D was only statistically significant in VD-deficient patients. The magnitude of this increase correlated with the severity of the basal VDD: patients with basal 25(OH)D < 10 ng/mL raised levels in a 379.4 % (~4 times), while for individuals initially between 20 and 30 ng/mL, this figure represented a 58.6 % (Table 2). No significant changes were found in VD-replete patients, *i.e.* individuals with basal 25(OH)D \geq 30 ng/mL (p > 0.05) (Table 2).

We additionally performed a univariate statistical analysis to assess the association between baseline characteristics and the correction of VDD (25(OH)D \geq 20 ng/mL). Age and BMI were identified as risk factors negatively influencing this restoration of VD. A subsequent multivariate analysis showed that age was the only factor independently associated (Table 3).

Likewise, we evaluated the association between different factors and the change of serum 25(OH)D following the treatment with 600 mg Ca/

Table 1

Baseline characteristics of study participants. Unless otherwise indicated, data are shown as mean [SD] or n (%). ALP, alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; Ca, calcium; GFR, glomerular filtration rate; IU, international units; OP, osteoporosis; PTH, parathyroid hormone; VD, vitamin D.

	Total study population (N = 285)		
Demographic and antropometric features			
Age, years old	67.4 (range 21–97)		
Sex (female/male)	252 (88.4 %)/33 (11.6 %)		
Ethnicity (Caucasian)	284 (99.6 %)		
BMI, kg/m ²	25.9 [4.3]		
Delever to the isol for the set of the direction			
Leve PMD [#]			
LOW BIND Octoopprosis (OP)	82 (28.8 %) 160 (56.1.%)		
OB notionto with frontunes	100 (35.1 %)		
Ere etures (n)	100 (35.1 %)		
Practices (II)	113		
$\frac{1}{2} = \frac{1}{2} $	33 (31.0 %) 49 6 04 /2E 7 04 /9 6 04		
Boggent (<2 years)	48.0 %/23.7 %/8.0 %		
Leastion (vortabral / viriat / bin)	78 (09.0 %) 41 0 % (10 2 % (20 E %		
Brior Ca and/or VD treatment	41.0 %/19.2 %/20.5 %		
	100(37.2%)		
	52 (50.2 %) 6 (E 7 %)		
Combined Co (UD)	6 (5.7 %)		
Combined Ca/VD	08 (04.2 %)		
Laboratory findings (serum)			
25(OH)D, ng/mL	20.0 [8.6]		
<10 ng/mL	29 (10.2 %)		
<20 ng/mL	153 (53.7 %)		
<30 ng/mL	261 (91.6 %)		
Calcium, mg/dL	9.4 [0.6]		
Phosphate, mg/dL	3.6 [0.7]		
PTH, pg/mL	73.3 [43.3]		
GFR, mL/min/1.73m ²	79.2 [14.4]		
ALP (IU/L)	85.4 [37.0]		

[#] Also referred as osteopenia.

2000 IU cholecalciferol. Patients with osteoporosis or receiving any medication prior to the study (1 month) virtually doubled the risk of not getting deltas of 10 ng/mL. A subsequent multivariate analysis showed that both factors were independently associated (Table 3).

Regarding other bone metabolism parameters, elevated PTH was significantly reduced following treatment with Ca 600 mg/cholecalciferol 2000 IU to 65.6 [60.3] pg/mL (p < 0.001) (Table 4). No relevant changes were obtained for calcium or phosphate, maintaining their normality range.

Eleven adverse events (AEs) were reported in 11 patients (3.9 %), mostly gastrointestinal disturbances (N = 4). Of the 11 AEs, three were treatment related (TEAE, N = 2, likely; N = 1, possible). These three TEAEs were non-serious gastrointestinal events, and only one required temporary interruption of the treatment. Two unrelated AEs were categorized as serious (endometrial cancer and hip fracture).

Regarding physicians' opinion on the study treatment, a remarkable 98.9 % expressed to find the product highly tolerable, rating it as either good or excellent. A substantial 98.2 % of the physicians reported being satisfied or very satisfied with the treatment. In this line, 99.3 % expressed their willingness to subsequently recommend this treatment.

3.1. Prior vitamin D treatment

In our study population, 106 patients (37.2 %) were receiving a different Ca and/or VD treatment, prior to initiating the study treatment. Doses of vitamin D ranged from 400 to 1666 IU daily cholecalciferol or weekly-to-monthly 0.266 mg calcifediol. Calcium daily doses ranged from 500 to 1500 mg. Over 40 % of individuals presented levels of 25 (OH)D below 20 ng/mL despite of previous treatment, regardless of the dose and the metabolite used (Supplementary Table 2). These figures <20 ng/mL surpassed 50 % (*i.e.* 51.5 %) in case of calcifediol-treated

Table 2

Change in 25(OH)D levels according to basal VDD deficiency. SD, standard deviation; CI, confidence interval.

Patients/basal 25(OH)D	25(OH)D levels mean [SD] (ng/mL)		25(OH)D change mean [95 % CI]		
	Basal	Final	Absolute change (ng/mL)	р	Relative change (%)
Total study population ($N = 285$)	20.0 [8.6]	36.3 [11.8]	16.4 [14.9–17.9]	0.001	119.8 [103.0-136.6]
<10 ng/mL (N = 29)	7.0 [2.3]	30.4 [10.8]	23.3 [19.4-27.2]	0.001	379.4 [278.1-480.7]
<20 ng/mL (N = 153)	14.0 [4.3]	34.2 [11.2]	20.2 [18.4-22.1]	0.001	179.9 [85.9-221.3]
\geq 20 & <30 ng/mL (N = 108)	24.4 [2.7]	38.3 [11.9]	13.9 [11.5–16.2]	0.001	58.6 [48.4-68.8]
\geq 30 ng/mL (N = 24)	38.1 [9.0]	41.1 [12.6]	3.0 [-3.2-9.2]	0.322	11.9 [-3.9-27.8]
Osteoporotic patients ($N = 160$)	20.2 [9.5]	35.7 [10.9]	15.5 [7.3–23.0]	0.001	121.7 [95.7–147.8]
<10 ng/mL (N = 15)	6.2 [2.2]	30.7 [11.8]	24.5 [18.1–31.0]	0.001	465.4 [277.5-653.3]
<20 ng/mL (N = 153)	13.9 [4.4]	33.6 [10.2]	19.7 [17.5–21.9]	0.001	186.6 [143.8-229.4]
\geq 20 & <30 ng/mL (N = 108)	24.5 [2.6]	37.4 [10.8]	12.9 [10.0–15.8]	0.001	54.0 [41.8-66.2]
\geq 30 ng/mL (N = 24)	39.7 [10.2]	41.7 [12.7]	1.9 [-6.7-10.6]	0.637	10.4 [-10.5-31.3]



Fig. 1. Change in 25(OH)D levels according to basal VDD deficiency. (A) Total study population (N = 285) and (B) subgroup of patients previously diagnosed with osteoporosis (N = 160). (A, B) Data are shown as mean (SEM), for the whole population analyzed (left pair of bars — Total) and categorized according to basal VDD (second to fifth pair of bars — <10, <20, <30 and \geq 30 ng/mL). Refer to Table 2 for N. ***, p < 0.001.

Table 3

Influence of baseline characteristics on 25(OH)D change. OR: odds ratio. 95 % CI: 95 % confidence interval. BMD: bone mineral density.

	Univariate analysis		Multivariate analysis			
	OR	95 % CI	<i>p</i> -Value	OR	95 % CI	<i>p</i> -Value
25(OH)D < 20 ng/mL						
Age*	1.071	1.017 - 1.128	0.010	1.072	1.013-1.134	0.015
BMI (kg/m ²) ^{\$}	1.145	1.009-1.299	0.036	1.109	0.978-1.257	0.108
Sex	0.707	0.150-3.341	0.662			
Low BMD [#]	5.089	0.651-39.788	0.121			
Osteoporosis	0.500	0.134-1.859	0.301			
Osteoporotic fracture	0.616	0.201-1.886	0.396			
Other comorbidities	1.151	0.366-3.618	0.809			
Previous Ca and/or VD treatment ^{&}	0.294	0.064-1.351	0.116			
Other medication ^{&}	1.070	0.341-3.357	0.908			
Δ 25(OH)D < 10 ng/mL						
Age*	0.998	0.978-1.017	0.804			
BMI (kg/m ²) ^{\$}	0.992	0.935-1.053	0.793			
Sex	1.687	0.730-3.897	0.221			
Low BMD [#]	1.236	0.712-2.146	0.452			
Osteoporosis	2.358	1.418-3.921	0.001	2.238	1.340-3.738	0.002
Osteoporotic fracture	1.276	0.756-2.153	0.362			
Other comorbidities	1.153	0.686-1.936	0.592			
Previous Ca and/or VD treatment ^{&}	1.444	0.872-2.392	0.153			
Other medication ^{&}	1.907	1.131-3.213	0.015	1.770	1.040-3.011	0.035

* Per completed year.

[#] Also referred as osteopenia.

^{\$} Per unit increase.

& Received in the 12 weeks (Ca/VD) or the month (other medication) prior to start the study treatment.

Table 4

Change in bone metabolism parameters. SD, standard deviation; CI, confidence interval.

	Levels, mean [SD]		Change, mean [95 % CI]			
	Basal	Final	Change	р		
Total study population ($N = 285$)						
Calcium, mg/dL	9.4 [0.5]	9.5 [0.5]	0.1 [0.0-0.2]	0.022		
Phosphate, mg/ dL	3.5 [0.5]	3.5 [0.6]	0.0 [-0.1-0.1]	0.692		
PTH, pg/mL	75.0 [44.0]	65.6 [60.3]	-9.5 [-17.2-(-1.8)]	0.001		
Ostooporotia pation	$t_{0} (N - 160)$					
Calcium mg/dI	113(N = 160) 9.4 [0.6]	95 [05]	0.1 [0.0_0.2]	0.011		
Phosphate, mg/	5.4 [0.0]	5.5 [0.5]	0.1 [0.0-0.2]	0.011		
dL	3.5 [0.5]	3.5 [0.6]	0.0 [-0.1-0.1]	0.545		
PTH, pg/mL	79.4 [49.9]	68.8 [72.5]	$-10.6 \left[-25.0 - 2.0\right]$	0.001		

patients. Interestingly, treatment with cholecalciferol at lower or intermediate doses put a notable percentage of patients at 20–30 ng/mL (41.5 %–53.1 %), but most were below 30 ng/mL (85.4 %–96.9 % depending on the dosage).

Once included in the study and treated with 600 mg Ca/2000 IU cholecalciferol, no clinically relevant differences were identified in subjects according to their prior vitamin D treatment, when compared with the global study population analysis.

3.2. Osteoporosis

One hundred and sixty subjects included in the study had been previously diagnosed with osteoporosis. Their baseline characteristics are shown in Supplementary Tables 1 and 2. Similar sociodemographic and clinical features, and laboratory findings were obtained with respect to the total study population. Of note, patients with osteoporotic fractures displayed lower basal 25(OH)D levels compared to those without (18.6 [9.3] vs. 23.0 [9.2] ng/mL, p < 0.001). In this osteoporosis group, before initiating the study treatment, 46.3 % of patients were receiving a different Ca and/or VD treatment. Forty-four percent of patients (N = 71) were treated with any antiosteoporosis drug. From them, only 62.0 % and 5.6 % received VD or calcium as coadjutant therapy. None of these patients were prescribed with a combined treatment of Ca/VD.

Following at least 24 weeks of treatment, the mean serum 25(OH)D was 35.7 [10.9] ng/mL (Table 2 and Fig. 1A), with a change of 15.5 ng/mL (95%CI 7.3–23.0; p < 0.001) from baseline. Again, the increase of serum 25(OH)D was only statistically significant in VD-deficient patients and no significant changes were found in VD-replete patients, *i.e.* individuals with basal 25(OH)D \geq 30 ng/mL (p > 0.05). No differences were observed in the restoration of 25(OH)D levels when sub-analyzing according to the presence of osteoporotic fractures, as both groups reached virtually identical values, over 30 ng/mL (25(OH)D: 35.5 [11.0] vs. 36.2 [10.9] ng/mL, p = 0.912).

Likewise, an elevated PTH was significantly reduced following treatment with Ca 600 mg/cholecalciferol 2000 IU and no relevant changes were obtained for calcium or phosphate, maintaining their normality range.

In this subgroup, 6 adverse events occurred (all mild intensity), and of these, only one was classified as probably related to the treatment.

4. Discussion

Despite becoming a very common dosage recommended by clinical guidelines (Casado et al., 2021; Camacho et al., 2020; Naranjo Hernandez et al., 2019; Presa Lorite et al., 2022; Holick et al., 2011; Dawson-Hughes et al., 2010; Cosman et al., 2014; Aspray et al., 2014; Baixauli García et al., 2022), few studies have evaluated the efficacy and safety of administering 2000 IU cholecalciferol (Tayem et al., 2022; Dedeckova et al., 2023; Bischoff-Ferrari et al., 2020; LeBoff et al., 2022).

None of them evaluated the use of 2000 IU of cholecalciferol in combination with calcium (at dosages of 600 mg) and, to our knowledge, no such a study has been performed in Spain.

In our present DOSTEO study, based on real-life data, we found that treatment with calcium 600 mg/cholecalciferol 2000 IU for at least 24 weeks was safe and effective in increasing 25(OH)D levels to mean values over 30 ng/mL, both in the global study population and particularly in osteoporotic patients. A significant reduction in PTH was noted, thus reverting secondary hyperparathyroidism, with no clinically relevant alteration of calcium and phosphate homeostasis. These findings underscore the effectiveness and safety of calcium 600 mg/cholecalciferol 2000 IU in individuals for whom vitamin D and calcium supplementation is deemed necessary based on medical criteria. As said before, as far as we are concerned, this is the first study evaluating the effectiveness and safety of this combination and dosages in clinical practice.

Following a median 24-week treatment period, 95.4 % and 73.0 % of participants reached and maintained 25(OH)D levels over 20 and 30 ng/ mL, respectively. This denotes an outstanding effectiveness, considering the real-world nature of this study, where patient compliance cannot be monitored, and comorbidities or concomitant medication have not been excluded (Hess, 2004; Sherman et al., 2016). Regarding the notable clinical effectiveness found with our calcium/cholecalciferol combination, previous prospective clinical studies using doses of cholecalciferol 2000 IU reported serum 25(OH)D levels >30 ng/mL in 60–62.5 % of the treated subjects (Dedeckova et al., 2023; Talwar et al., 2007).

Restorage of 25(OH)D to adequate levels occurred regardless of the severity vitamin D deficiency (<10, 20 or 30 ng/mL) and particularly in vitamin D-deficient but not in replete patients (\geq 30 ng/mL). Notably, subjects initially below 10 ng/mL displayed a remarkable mean change of 23.3 ng/mL in their 25(OH)D serum levels, while those with baseline levels between 20 and 30 ng/mL exhibited a mean change of 13.9 ng/mL. Moreover, no significant further increase was revealed in replete patients receiving the treatment, *i.e.* individuals with basal 25(OH)D \geq 30 ng/mL.

As described in the literature, conversion rate of cholecalciferol into 25(OH)D follows a non-linear increase, giving rise to a plasmatic 25 (OH)D curve that reaches a true plateau at levels about 30-50 ng/mL (Fassio et al., 2020; Navarro-Valverde et al., 2016; Charoenngam et al., 2021; Jetter et al., 2014; Bischoff-Ferrari et al., 2012; Quesada-Gomez and Bouillon, 2018; Gallagher et al., 2012; Jones, 2008), widely accepted as optimal range by clinical guidelines (Casado et al., 2021; Pludowski et al., 2022; Camacho et al., 2020; Bouillon and Carmeliet, 2018). A greater increase (steeper curve) in serum 25(OH)D results from cholecalciferol administration in case of more severe vitamin D deficiency, compared with lower delta 25(OH)D observed in insufficient or even vitamin D-replete patients (Quesada-Gomez and Bouillon, 2018). Feedback inhibition of enzyme activity at adequate 25(OH)D amounts or intrinsic kinetic features of 25-hydroxylase have been proposed as potential mechanisms for regulation of the cholecalciferol-to-25(OH)D hepatic conversion (Quesada-Gomez and Bouillon, 2018; Hall, 2020). This pharmacokinetic profile also avoids 25(OH)D fluctuations in serum following individual administrations, otherwise getting sustained 25 (OH)D levels (Charoenngam et al., 2021), which was ideally suggested elsewhere (Vieth, 2020). Altogether, the hepatic hydroxylation step, together with the lack of a linear relationship in the 25(OH)D production, may prevent an indefinite increase of serum values once under treatment, presented by other metabolites such as calcifediol (Jetter et al., 2014; Bischoff-Ferrari et al., 2012; Minisola et al., 2017; Sosa Henriquez et al., 2020; Bouillon and Quesada Gomez, 2023). Cholecalciferol allows to obtain more predictable and stable levels over time at a given target level. In other words, the efficiency of cholecalciferol supplementation in replete patients is being physiologically reduced by the organism, arguably to avoid intoxication. Our clinical study results further support and confirm this mechanism described for cholecalciferol, as 25(OH)D levels maintained within the optimal range (30-50 ng/ mL), regardless of the patient profile or the basal VD status.

Our study demonstrated that 2000 IU of cholecalciferol for at least 24 weeks adequately increased 25(OH)D levels. Generally, supplementation with 2000 IU of vitamin D3 is adequate to increase the 25(OH)D levels to normal within a few weeks (Dawson-Hughes et al., 2010; Weaver et al., n.d.). Different studies have demonstrated a superiority of this dose in restoring 25(OH)D levels when compared with lower doses (Talwar et al., 2007; Aloia et al., 2014). Of note, comparison of 1000 vs. 2000 IU doses demonstrated that the latter increased and maintained 25 (OH)D levels within 30–50 ng/mL for longer periods of time, even upon discontinuation (Dedeckova et al., 2023).

The multivariate logistic regression analysis revealed age as a significant factor influencing the restoration of 25(OH)D levels (cut-off 20 ng/mL). Age-related changes in VD absorption (impaired gastrointestinal function and dietary habits) and less efficient conversion rate of vitamin D into its active form may underlie this finding (Cancio Trujillo et al., 2023; Giustina et al., 2023). These results emphasize the importance of careful dosing and monitoring in the elderly, with approximately a ten-fold increase in the risk of inadequate levels for each decade of life. Conversely, this multivariate regression did not identify BMI as a risk factor influencing the achievement of 20 ng/mL, when adjusted with other confounding factors. This result would further support that cholecalciferol supplementation is effective in correcting VDD in obese patients.

The main function of the endocrine system of vitamin D at the bone level is to preserve serum calcium, at the expense of causing secondary hyperparathyroidism (HPT, increased PTH) and increasing bone turnover (Holick, 2017). PTH was significantly reduced following treatment, thus reversing secondary HPT associated with the VD deficiency. Moreover, no clinically significant change was noted in levels of serum calcium and phosphate, which were maintained within the normality range. Despite improvements in bone mass were not evaluated in the study, these results point to an optimization of bone metabolism. In this line, no association with hypercalcemia or hyperphosphatemia were noted, reinforcing the safety profile of the combined product.

Our study revealed exceptional tolerability, with almost 100 % of physicians rating it highly. Moreover, a very low rate of adverse events was also observed. Only 3 non-serious treatment-emergent adverse events were reported, being all gastrointestinal disturbances, and expected as already recorded in the product data sheet (Italfarmaco, 2020). Altogether, these data reinforce the safety and tolerability of this 600 mg of calcium carbonate, in a therapeutic class (calcium-containing products) where tolerability is often discussed (Van der Velde et al., 2014).

According to selection criteria, patient should have been treated for at least 24 weeks. Nevertheless, individuals with long-term treatment (up to 82 weeks) were also included, with comparable results. The use of chronic doses of up to 2000 IU/day of cholecalciferol undoubtedly remains in the safety margin, as previously described (Glade, 2012; Galior et al., 2018).

The most common patient profile depicted in our study for the prescription of Demilos® 600 mg/2000 IU is a postmenopausal woman (aged 65 and over), mostly with a bone disorder (osteopenia/Osteoporosis), vitamin D insufficiency (91.6 % <30 ng/mL) and secondary HPT, despite of being already treated with Ca and or VD prior to inclusion in the study (37.2 %). In this regard, most patients getting VD prior to the study were receiving low-to-intermediate doses of cholecalciferol (400-1666 IU daily) or calcifediol (bi-weekly/monthly); nevertheless, they displayed high rates of VDD and insufficiency (Supplementary Table 2). Therefore, theses dosages seemed clearly insufficient to get the patient to an adequate 25(OH)D status and calcium homeostasis, afterwards achieved with 2000 IU/day of cholecalciferol. This patient profile further supports the updates carried out by the most relevant clinical guidelines to increased daily doses of vitamin D in the osteoporosis population (Camacho et al., 2020; Riancho et al., 2022; Shoback et al., 2020).

treatment were sub-analyzed, obtaining virtually identical results in terms of effectiveness and safety compared with the total study population. Restoration of 25(OH)D to adequate levels occurred regardless of the presence of osteoporotic fractures, even though these patients initiated treatment with a worse 25(OH)D status. Of note, even though 62.5 % of these patients had suffered previous osteoporotic fractures, only 44.4 % received antiosteoporosis treatment. For those under antiosteoporosis drugs, 62.0 % received adjuvant treatment with vitamin D, 5.6 % calcium but none were prescribed with a combination of calcium/ vitamin D as adjuvant prior to the study. Our results go in line with other studies showing a large room for improvement in terms of the low percentage of prescriptions combining antiresorptive treatments and calcium/vitamin D, despite clinical guidelines recommendations (Quesada-Gomez et al., 2013; Carbonell, 2019; Hagino et al., 2023). These results are surprising, since antiresorptive and/or anabolic drugs used in treatment of osteoporosis can cause hypocalcemia due to antiosteoclastic effects and are associated with hypovitaminosis D, whose wide prevalence in the osteoporotic population is well known. Therefore, the effectiveness of osteoporosis treatment may be reduced if patients do not get enough calcium and vitamin D. It should be also noted that the large pivotal studies for antiosteoporosis drugs were carried out with concomitant administration of calcium and vitamin D supplements, thus, same efficacy cannot be anticipated under different settings (i.e. without adjutancy) (Sosa Henriquez and Gómez de Tejada, 2021; Sosa-Henriquez and Murias-Henriquez, 2024).

Regression analysis indeed revealed osteoporosis and concomitant medication as risk factors for not achieving at least a 10 ng/mL-increase from baseline, pointing out the challenge for an adequate treatment in osteoporosis, and supporting the prescription of high doses within the interval recommended by guidelines (800–2000 IU) (Casado et al., 2021; Camacho et al., 2020; Naranjo Hernandez et al., 2019; Presa Lorite et al., 2022; Holick et al., 2011; Dawson-Hughes et al., 2010; Cosman et al., 2014; Aspray et al., 2014; Baixauli García et al., 2022).

Our real-world study possesses various strengths, including national and multispecialty representation and minimum selection and recall biases. We consider this as an added value, since the selection of candidate patients to receive 600 mg Ca/2000 IU cholecalciferol was undertaken by clinicians from different medical specialties. Risk factors that healthcare professionals should consider for tailored dosage are also revealed. Limitations include its retrospective nature, the clinical (and not radiographic) diagnosis of bone disorders, but also clinical outcomes such as bone markers or bone mineral density were not evaluated.

5. Conclusions

In summary, the results of our first-in-class real-world study demonstrate that treatment with calcium 600 mg/cholecalciferol 2000 IU for at least 24 weeks is effective and safe in increasing 25(OH)D levels to mean values over 30 ng/mL, especially in osteoporosis. This raise takes place regardless of the severity of vitamin D deficiency, particularly in vitamin D-deficient but not in replete patients (\geq 30 ng/mL) and without association with hypercalcemia or hyperphosphatemia. Age, use of concomitant medications and particularly osteoporosis should be considered as features demanding an adjustment to 2000 IU of cholecalciferol.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2024.101796.

Funding sources

This study was promoted and funded by ITF Research Pharma SLU.

DOSTEO Study Group

Estrada Álvarez F¹; Fernández López JC²; Moreno Muelas JV³; De la Hera Martínez⁴; Juarez Fernández R⁵; Romero Pérez MC⁶; Montalà

Osteoporotic patients (N = 160) under Demilos® 600 mg/2000 IU

Palau N⁷; García Magallón B⁸; Cobeta García JC⁹; Montero Sáez A¹⁰; Marqués Gil D¹¹; Panero Lamothe B¹²; Graña Gil J²; Mifsut Miedes D¹³; Blasco Mollá MC¹⁴; Valls Gumbau GJ¹⁵; Pinto Bonilla R¹⁶; Baeza Noci¹⁷; Cervero Jiménez M⁶; Arnáiz García AM¹⁷; Sanjoaquín Romero AC¹⁸; Valls García R¹⁹; Rotés Mars J²⁰; Álvaro Sanz M⁵; Pascual-Pastor M²¹; Casado Blanco C⁵; Sanz García RM²²; Atxotegi Sáenz de Buruaga J²³; Ventín Rodríguez C²⁴; Moragues Pastor C²⁵; Izquierdo Aviñó R²⁶; del Blanco Barnusell J²⁷; Sanz Sanz J⁸; Pinto-Tasende JA²; Olmo Fernández-Delgado JA²⁸; De las Heras Soto J²⁹; Mirón Hernández VM³⁰; García Aguilar E³¹; and Saz-Leal P³¹.

¹Servicio de Medicina Interna, Hospital Begoña, Gijón, Spain.

²Servicio de Reumatología, Complejo Universitario Hospitalario de La Coruña, Spain.

³Servicio de Reumatología, Hospital Sagrat Cor y HM Sant Jordi, Barcelona, Spain.

⁴Servicio de Reumatología, Escuela Hospital Mompia, Cantabria, Spain.

⁵Servicio de Rehabilitación, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

⁶Servicio de Medicina Interna, Hospital Universitario Severo Ochoa, Madrid, Spain.

⁷Servicio de Reumatología, Hospital Universitari Arnau de Vilanova, Lleida, Spain.

⁸Servicio de Reumatología, Hospital Universitario Puerta de Hierro, Madrid, Spain.

⁹Servicio de Reumatología, Centro Médico Calatayud, Spain.

¹⁰Servicio de Medicina Interna, Hospital Universitario de Bellvitge, Barcelona, Spain.

¹¹Clínica Perpetuo Socorro HLA, Lleida, Spain.

¹²Servicio de Reumatología, Hospital Universitario Virgen de la Victoria, Málaga, Spain.

¹³Servicio de Traumatología, Hospital Universitario Francesc de Borja, Valencia, Spain.

¹⁴Servicio de Traumatología, Hospital Clínico Universitario de Valencia, Spain.

¹⁵Servicio de Medicina Interna, Hospital IMED, Valencia, Spain.

¹⁶Servicio de Traumatología, Hospital Vithas Valencia Consuelo, Spain.

¹⁷Servicio de Medicina Interna, Hospital Sierrallana, Cantabria, Spain.

¹⁸Servicio de Geriatría, Hospital Nuestra Señora de Gracia, Zaragoza, Spain.

¹⁹Servicio de Reumatología, Hospital de Palamós, Girona. Spain.

²⁰Servicio de Reumatología, Clínica Médica de Especialidades Poblenou, Barcelona, Spain.

²¹Servicio de Reumatología, Hospital Universitario Vall d'Hebron, Barcelona, Spain.

²²Servicio de Medicina Interna, Complejo Hospitalario Ruber Juan Bravo, Madrid, Spain.

²³Servicio de Reumatología, Hospital Universitario de Cruces, País Vasco, Spain.

²⁴Servicio de Reumatología, Complejo Hospitalario Universitario de Vigo, Spain.

²⁵Servicio de Reumatología, Hospital Universitari de Bellvitge, Barcelona, Spain.

²⁶FLS-UFRA, Servicio de Cirugía Ortopédica y Traumatología, Hospital Provincial Ntra. Sra. De Gracia, Zaragoza, Spain.

²⁷Servicio de Reumatología, Hospital Comarcal Sant Jaume de Calella, Barcelona, Spain.

²⁸Servicio de rehabilitación, Clinimur, Murcia, Spain.

²⁹Servicio de Cirugía Ortopédica y Traumatología, Hospital Ruber Internacional, Madrid, Spain.

³⁰Servicio de Traumatología. Clínica Corachan, Barcelona, Spain.

 $^{31}\mathrm{Medical}$ Department, ITF Research Pharma S.L.U., Alcobendas, Madrid, Spain.

CRediT authorship contribution statement

Rosa Pinto-Bonilla: Investigation, Methodology, Writing - review & editing. José Baeza-Noci: Investigation, Methodology, Writing - review & editing. Clara Casado Blanco: Investigation, Methodology, Writing - review & editing. Guillermo Javier Valls Gumbau: Investigation, Methodology, Writing - review & editing. Rubén Juarez Fernández: Investigation, Methodology, Writing - review & editing. María Pascual-Pastor: Investigation, Methodology, Writing - review & editing. Blanca García Magallón: Investigation, Methodology, Writing - review & editing. Blanca Panero Lamothe: Investigation, Methodology, Writing - review & editing. Carmen Moragues Pastor: Conceptualization, Investigation, Methodology, Supervision, Writing review & editing. Rafael Izquierdo Aviñó: Conceptualization, Investigation. Methodology. Supervision. Writing - review & editing. Eva García Aguilar: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing - review & editing. Paula Saz-Leal: Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The following authors declare potential conflicts of interest in relation to the proposed research:

Juan A. Olmo Fernandez-Delgado has conducted work or training for Theramex, Grunenthal, Stada laboratories.

Abelardo Montero Sáez has conducted work or training for Amgen, Stada, Ferrer, Theramex.

Jenaro Graña Gil has conducted work or training for Theramex, Italfarmaco, Faes, Rubió, Gebro.

Eva García Aguilar and Paula Saz-Leal are employed by the medical department of ITF Research Pharma SLU.

The remaining authors signing this manuscript have no conflicts of interest to declare.

The laboratory funding this research (ITF Research Pharma SLU, Alcobendas. Spain) has participated in the study design and manuscript preparation but not in the data analysis or the results obtained.

Data availability

Data will be made available on request.

Acknowledgments

We are grateful to CRO ADKNOMA for their support in the management and data analysis of the study, as well as to Simplifying Research Institute for data analysis and medical writing support.

References

Aloia, J.F., Dhaliwal, R., Shieh, A., et al., 2014. Vitamin D supplementation increases calcium absorption without a threshold effect. Am. J. Clin. Nutr. 99, 624–631. Aspray, T.J., Bowring, C., Fraser, W., et al., 2014. National Osteoporosis Society vitamin

D guideline summary. Age Ageing 43, 592–595.

Baixauli García, F., Cancio Trujillo, J.M., Cuadra Llopart, L., et al., 2022 (Coord.). Algoritmo de fractura de cadera. Atención al adulto mayor con fractura de cadera. SEGG. Available at: https://www.segg.es/media/descargas/guia-fracturas-de-cadera .pdf.

Bischoff-Ferrari, H.A., Dawson-Hughes, B., Stocklin, E., et al., 2012. Oral

supplementation with $25(OH)D_3$ versus vitamin D3: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. J. Bone Miner. Res. 27, 160–169.

Bischoff-Ferrari, H.A., Vellas, B., Rizzoli, R., et al., 2020. Effect of Vitamin D supplementation, Omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. JAMA 324, 1855–1868.

Bleizgys, A., 2021. Vitamin D dosing: basic principles and a brief algorithm (2021 update). Nutrients 13 (12).

Bouillon, R., Carmeliet, G., 2018. Vitamin D insufficiency: definition, diagnosis and management. Best Pract. Res. Clin. Endocrinol. Metab. 32, 669–684.

R. Pinto-Bonilla et al.

- Bouillon, R., Quesada Gomez, J.M., 2023. Comparison of calcifediol with vitamin D for prevention or cure of vitamin D deficiency. J. Steroid Biochem. Mol. Biol. 228, 106–248.
- Camacho, P.M., Petak, S.M., Binkley, N., et al., 2020. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update executive summary. Endocr. Pract. 26, 564–570.
- Cancio Trujillo, J.M., Cuadra Llopart, L., Formiga Pérez, F., et al., 2023. (Coord.) Guía de buena práctica clínica en Geriatría. Vitamina D en adulto mayor. SEGG. Available at: https://www.segg.es/media/descargas/Guia-Vitamina-D.pdf.
- Carbonell, Abella C., 2019. Vitamina D: indicaciones para el cribado y tratamiento. FMC 26, 441–447.
- Casado, E., Quesada, J.M., Naves, M., et al., 2021. SEIOMM recommendations on the prevention and treatment of vitamin D deficiency. Rev. Osteopor. Metab. Miner. 13, 84–97.
- Charoenngam, N., Kalajian, T.A., Shirvani, A., et al., 2021. A pilot-randomized, doubleblind crossover trial to evaluate the pharmacokinetics of orally administered 25hydroxyvitamin D3 and vitamin D3 in healthy adults with differing BMI and in adults with intestinal malabsorption. Am. J. Clin. Nutr. 114, 1189–1199.
- Cosman, F., de Beur, S.J., LeBoff, M.S., et al., 2014. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos. Int. 25, 2359–2381.
- Dawson-Hughes, B., Mithal, A., Bonjour, J.P., et al., 2010. IOF position statement: vitamin D recommendations for older adults. Osteoporos. Int. 21, 1151–1154.
 Dedeckova, E., Vitak, R., Jirasko, M., et al., 2023. Vitamin D₃ supplementation:
- comparison of 1000 IU and 2000 IU dose in healthy individuals. Life (Basel) 13, 808. Fassio, A., Adami, G., Rossini, M., et al., 2020. Pharmacokinetics of oral cholecalciferol in
- healthy subjects with Vitamin D deficiency: a randomized open-label study. Nutrients 12, 1553.
- Francis, R., Aspray, T., Fraser, W., et al., 2013. Vitamin D and bone health: a practical clinical guideline for patient management. NOS. Available at: https://www.aub.edu. lb/fm/CaMOP/Documents/Vitamin-D-Bone-Health.pdf.
- Galior, K., Grebe, S., Singh, R., 2018. Development of vitamin D toxicity from overcorrection of vitamin D deficiency: a review of case reports. Nutrients 10, 953.
- Gallagher, J.C., Sai, A., Templin, T., et al., 2012. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. Ann. Intern. Med. 156, 425–437.
- Giustina, A., Bouillon, R., Dawson-Hughes, B., et al., 2023. Vitamin D in the older population: a consensus statement. Endocrine 79 (1), 31–44.
- Glade, M.J., 2012. A 21st century evaluation of the safety of oral vitamin D. Nutrition 28, 344–356.
- Hagino, H.Y.Y., Hamaya, E., Lin, T.C., et al., 2023. A real-world study of treatment patterns among patients with osteoporotic fracture: analysis of a Japanese hospital database. Arch. Osteoporos. 18, 23.
- Hall, J., 2020. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone, and teeth. In: Elsevier (Ed.), Guyton and Hall Textbook of Medical Physiology, 14th ed.
- Hess, D.R., 2004. Retrospective studies and chart reviews. Respir. Care 49 (10), 1171–1174. Oct.
- Holick, M.F., 2017. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev. Endocr. Metab. Disord. 18, 153–165.
- Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., et al., 2011. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. 96, 1911–1930.
- Italfarmaco, S.A., 2020. Demilos 600 mg/2.000 UI comprimidos bucodispersables. Summary of Product Characteristics.
- Jetter, A., Egli, A., Dawson-Hughes, B., et al., 2014. Pharmacokinetics of oral vitamin D₃ and calcifediol. Bone 59, 14–19.
- Jones, G., 2008. Pharmacokinetics of vitamin D toxicity. Am. J. Clin. Nutr. 88, 5828–5865.
- LeBoff, M.S., Chou, S.H., Ratliff, K.A., et al., 2022. Supplemental Vitamin D and incident fractures in midlife and older adults. N. Engl. J. Med. 387, 299–309.

- Minisola, S., Cianferotti, L., Biondi, P., et al., 2017. Correction of vitamin D status by calcidiol: pharmacokinetic profile, safety, and biochemical effects on bone and mineral metabolism of daily and weekly dosage regimens. Osteoporos. Int. 28, 3239–3249.
- Naranjo Hernandez, A., Del Campo, Diaz, Fontecha, P., Aguado Acín, M.P., et al., 2019. Recommendations by the Spanish Society of Rheumatology on osteoporosis. Reumatol. Clin. (Engl. Ed). 15, 188–210.
- Navarro-Valverde, C., Quesada-Gómez, J.M., 2014. Deficiencia de vitamina D en España: ¿realidad o mito? Rev. Osteopor. Metab. Miner. 6, 5–10.
- Navarro-Valverde, C., Sosa-Henríquez, M., Alhambra-Expósito, M.R., et al., 2016. Vitamin D3 and calcidiol are not equipotent. J. Steroid Biochem. Mol. Biol. 164, 205–208. Nov.
- Olza, J., Aranceta-Bartrina, J., Gonzalez-Gross, M., et al., 2017. Reported dietary intake and food sources of zinc, selenium, and vitamins A, E and C in the Spanish population: findings from the ANIBES study. Nutrients 9, 697.
- Pludowski, P., Takacs, I., Boyanov, M., et al., 2022. Clinical practice in the prevention, diagnosis and treatment of vitamin D deficiency: a Central and Eastern European Expert Consensus Statement. Nutrients 14 (7).
- Presa Lorite, J.C., Martínez Medina, M., Baró Mariné, F., et al., 2022. MenoGuía AEEM. Segunda edición 2022. Osteoporosis.
- Quesada-Gomez, J.M., Bouillon, R., 2018. Is calcifediol better than cholecalciferol for vitamin D supplementation? Osteoporos. Int. 29, 1697–1711.
- Quesada-Gomez, J.M., Diaz-Curiel, M., Sosa-Henriquez, M., et al., 2013. Low calcium intake and inadequate vitamin D status in postmenopausal osteoporotic women. J. Steroid Biochem. Mol. Biol. 136, 175–177.
- Riancho, J.A., Peris, P., Gonzalez-Macias, J., et al., 2022. Executive summary clinical practice guideline of postmenopausal, glucocortcioid-induced and male osteoporosis (2022 update). Spanish Society for Bone and Mineral Metabolism Investigation (SEIOMM). Rev. Clin. Esp. (Barc.) 222, 432–439.
- Ross, A.C., Taylor, C.L., Yaktine, A.L., et al., 2011. Dietary reference intakes for calcium and vitamin D. In: Press, N.A. (Ed.), The National Academies Collection: Reports Funded by National Institutes of Health. Washington (DC).
- Sherman, R.E., Anderson, S.A., Dal Pan, G.J., et al., 2016. Real-world evidence what is it and what can it tell us? N. Engl. J. Med. 375, 2293–2297.
- Shlisky, J., Mandlik, R., Askari, S., et al., 2022. Calcium deficiency worldwide: prevalence of inadequate intakes and associated health outcomes. Ann. N. Y. Acad. Sci. 1512, 10–28.
- Shoback, D., Rosen, C.J., Black, D.M., et al., 2020. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. J. Clin. Endocrinol. Metab. 105, 587–594.
- Sosa Henriquez, M., Gómez de Tejada, M.J., 2021. Calcium and vitamin D supplementation in the management of osteoporosis. What is the advisable dose of vitamin D? Rev. Osteoporos. Metab. Miner. 13, 77–83.
- Sosa Henriquez, M., de Tejada, Gomez, Romero, M.J., 2020. Cholecalciferol or calcifediol in the management of vitamin D deficiency. Nutrients 12 (6).
- Sosa-Henriquez, M., Murias-Henriquez, C., 2024. Influence of calcium and cholecalciferol in the treatment of osteoporosis. Med. Clin. Pract. 7 (2).
- Talwar, S.A., Aloia, J.F., Pollack, S., et al., 2007. Dose response to vitamin D supplementation among postmenopausal African American women. Am. J. Clin. Nutr. 86, 1657–1662
- Tayem, Y., Alotaibi, R., Hozayen, R., et al., 2019. Therapeutic regimens for vitamin D deficiency in postmenopausal women: a systematic review. Prz. Menopauzalny. 18, 57–62.
- Van der Velde, R.Y., Brouwers, J.R., Geusens, P.P., et al., 2014. Calcium and vitamin D supplementation: state of the art for daily practice. Food Nutr. Res. 58.
- Vieth, R., 2020. Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. Eur. J. Clin. Nutr. 74, 1493–1497.
- Weaver CM, Dawson-Hughes, B, Rizzoli R, et al. Nutritional Support of Osteoporosis Primer of Metabolic Bone Diseases and Disorders of Metabolism. In: ASBMR, ed.