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

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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 2,000 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 2,000 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 ≥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 ≥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 2,000 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 hyperparathyroidism. The magnitude of 25(OH)D increase directly correlates with the severity of VDD, with no effect in basally repleted patients.

INTRODUCTION

Vitamin D deficiency (VDD) is significantly prevalent worldwide (1), even in Mediterranean countries such as Spain (2). 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 (3). 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 (4-7). Daily doses of up to 2,000 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 (4, 6, 8-14).

The recommended daily intake of calcium (Ca) is set between 1,000-1,200 mg for adults, the latter required for men over 70 years old or women of 51 years and older (6, 15). Despite our conception of a tending increase in consumption of calcium-rich food, recommended daily allowances are often not satisfied (16). This is evident in Spain, where daily intakes for the adult population average only 600-700 mg (17). Moreover, the upper limit for total calcium intake is set at 2,500 mg/day (15).

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 (6, 18, 19). 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 (3, 18, 20). Nevertheless, VDD and deficient calcium intake are being reported for osteoporotic women, regardless of the treatment received (18-20).

Altogether, calcium and vitamin D are often placed as a combined treatment for promoting bone health, and the recommended coadjuvant therapy for antiosteoporosis treatments (4, 19). Demilos 600 mg/2000 UI® is a unique combination containing 600 mg of calcium and 2,000 IU of cholecalciferol, formulated as orodispersible tablets (21). 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.

MATERIAL AND METHODS

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 2,000 IU orodispersible tablets (Demilos® 600 mg/2,000 IU) for at least 24 weeks. The study protocol was approved by the Research Ethics Committee at Puerta de Hierro hospital (Spain).

Participants

Data were retrospectively collected from patients who received 600 mg calcium/2,000 IU cholecalciferol treatment and met the following established selection criteria: ≥ 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.

Treatment

Demilos® 600 mg/2,000 IU are round orodispersible tablets, containing 1,500 mg calcium carbonate (600 mg calcium) and 2,000 IU (50 µg) cholecalciferol (vitamin D_3). 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.

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 ≥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.

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 t-student 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.

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/2,000 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 ≥20 ng/mL and 208 patients (73.0%) ≥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 Figure 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 20-30 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 ≥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 ≥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/2,000 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 2,000 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.

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 400-1,666 IU daily cholecalciferol or weekly-to-monthly 0.266 mg calcifediol. Calcium daily doses ranged from 500-1,500 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 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/2,000 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.

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 Figure 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 ≥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 2,000 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.

DISCUSSION

Despite becoming a very common dosage recommended by clinical guidelines (4, 6, 8-11, 13, 22, 23), few studies have evaluated the efficacy and safety of administering 2,000 IU cholecalciferol (24-27). None of them evaluated the use of 2,000 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 600mg / cholecalciferol 2,000 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 600mg / cholecalciferol 2,000 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 (28, 29). Regarding the notable clinical effectiveness found with our calcium/cholecalciferol combination, previous prospective clinical studies using doses of cholecalciferol 2,000 IU reported serum 25(OH)D levels > 30 ng/mL in 60-62.5% of the treated subjects (25, 30).

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 (≥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 ≥ 30ng/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 (31-38), widely accepted as optimal range by clinical guidelines (4-7). 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 (36). 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 (36, 39). This pharmacokinetic profile also avoids 25(OH)D fluctuations in serum following

individual administrations, otherwise getting sustained 25(OH)D levels (33), which was ideally suggested elsewhere (40). 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 (34, 35, 41-43). 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 2,000 IU of cholecalciferol for at least 24 weeks adequately increased 25(OH)D levels. Generally, supplementation with 2,000 IU of vitamin D3 is adequate to increase the 25(OH)D levels to normal within a few weeks (11, 44). Different studies have demonstrated a superiority of this dose in restoring 25(OH)D levels when compared with lower doses (30, 45). Of note, comparison of 1,000 vs. 2,000 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 (25).

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 (14, 46). 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 (1). 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 (21). 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 (47).

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 2,000 IU/day of cholecalciferol undoubtedly remains in the safety margin, as previously described (48, 49).

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 (400-1,666 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 2,000 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 (6, 18, 19).

Osteoporotic patients (N=160) under Demilos® 600 mg / 2000 IU 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 (20, 50, 51). These results are surprising, since antiresorptive and/or anabolic drugs used in treatment of osteoporosis can cause hypocalcemia due to anti-osteoclastic 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) (52, 53).

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 – 2,000 IU) (4, 6, 8-11, 13, 22, 23).

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/2,000 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.

CONCLUSIONS

In summary, the results of our first-in-class real-world study demonstrate that treatment with calcium 600 mg / cholecalciferol 2,000 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 (≥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 2,000 IU of cholecalciferol.

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DOSTEO Study Gorup

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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. #Also referred as osteopenia.

	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]
Relevant clinical features and medication	
Low BMD#	82 (28.8%)
Osteoporosis (OP)	160 (56.1%)
OP patients with fractures Fractures (n) Previous (≥ 2 years) Location (Vertebral/wrist/hip) Recent (< 2 years) Location (Vertebral/wrist/hip)	100 (35.1%) 113 35 (31.0%) 48.6%/25.7%/8.6% 78 (69.0%) 41.0%/19.2%/20.5%
Prior Ca and/or VD treatment Only VD Only Ca Combined Ca/VD	106 (37.2%) 32 (30.2%) 6 (5.7%) 68 (64.2%)
Laboratory findings (serum)	
25(OH)D, ng/mL < 10 ng/mL < 20 ng/mL < 30 ng/mL	20.0 [8.6] 29 (10.2%) 153 (53.7%) 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]

Figure 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 ≥ 30 ng/ml). Refer to Table 2 for N. ***, p<0.001.

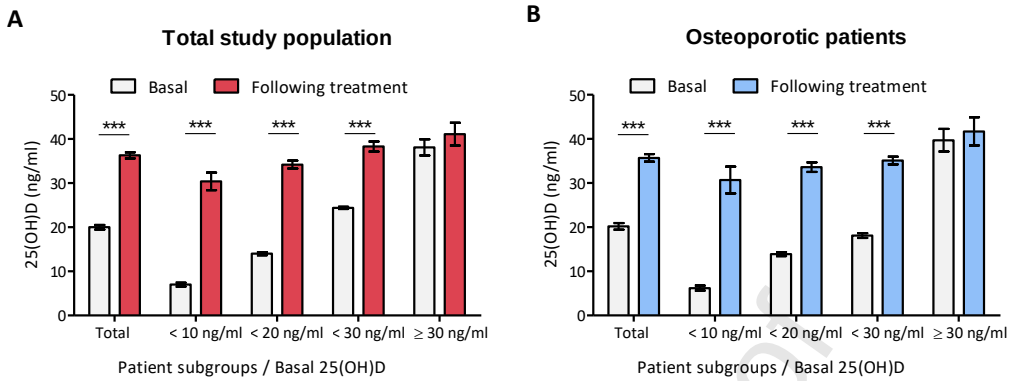

Table 2. Change in 25(OH)D levels according to basal VDD deficiency. SD, standard deviation; CI, confidence interval

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)	**p**	**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]
≥ 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]
≥ 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]
≥ 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]
≥ 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]

Table 3. Influence of baseline characteristics on 25(OH)D change. OR: Odds Ratio. 95% CI: 95% Confidence Interval. BMD: Bone mineral density. * 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.

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-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)[$]	**1.145**	**1.009–1.299**	**0.036**	1.109	0.978-1.257	0.108
Sex	0.707	0.150-3.341	0.662			
Low BMD[#]	5.089	0.651-39.788	0.121			
Osteoporosis	0.500	0.134-1.859	0.301			
Osteoporotic fracture	0.616	0.201-1.886	0.396			
Other comorbidities	1.151	0.366-3.618	0.809			
Previous Ca and/or VD treatment[&]	0.294	0.064-1.351	0.116			
Other medication[&]	1.070	0.341-3.357	0.908			
Δ25(OH)D < 10 ng/mL						
Age*	0.998	0.978-1.017	0.804			
BMI (kg/m^2)[$]	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**

Table 4. Change in bone metabolism parameters. SD, standard deviation; CI, confidence interval

	Levels, mean [SD]		**Change,** mean [95% CI]	
	Basal	**Final**	**Change**	**p**
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
Osteoporotic patients (N=160)				
Calcium, mg/dL	9.4 [0.6]	9.5 [0.5]	0.1 [0.0-0.2]	0.011
Phosphate, mg/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 [-25.0-2.0]	0.001

Conflicts of Interest and Declaration of Laboratory Participation in the Research

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.

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