

# Calcium and vitamin D supplementation in the management of osteoporosis. What is the advisable dose of vitamin D?

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## Summary

The pathophysiological foundations justifying calcium and vitamin D supplements in osteoporosis are supported by extensive scientific evidence that has been obtained through several randomized clinical trials and subsequent meta-analyses that have shown a statistically significant and clinically relevant reduction in the risk of osteoporotic fractures. This evidence has led to its recommendation by several scientific societies interested in the management of osteoporosis.

In order to optimize the efficacy and the benefit/risk balance of these, calcium and vitamin D should be administered together with the drugs that are prescribed for the treatment of osteoporosis, since calcium and vitamin D have been used in all these reference studies, both in the arm that receives the drug and also in the placebo arm. The most commonly used calcium salt is carbonate and the metabolite of vitamin D, cholecalciferol or vitamin D<sub>3</sub>.

There is no consensus or conclusive scientific evidence on the dose to be used in vitamin D deficiency associated with osteoporosis. However, the trend has always been to increase these amounts, from the 400 IU recommended 30 years ago to the 2,000 IU daily today. We will review in this article which recommendations are made by means of the clinical guidelines, as they collect the available scientific evidence.

## Rationale for using calcium and vitamin D in osteoporosis

Osteoporosis is the most common bone metabolism disease<sup>1</sup> and is characterized by a significant decrease in bone mineral density that is accompanied by alterations in the microarchitecture of the bone, which results in increased skeletal fragility and, consequently, an increase risk of fractures<sup>2</sup>. Clearly related to aging, its prevalence, which in women between 50 and 59 years of age has been estimated at 4%, increases to 52% in women older than 80 years<sup>2</sup>. Hip fracture in osteoporotic women produces an increase in mortality over the first two years post-fracture of between 12 and 20%, and more than 50% of survivors are not able to return to an independent life, many of them requiring long-term home help<sup>3</sup>.

Calcium is a mineral-type nutrient that plays key roles in human physiology. In relation to bone, it is a basic constituent of calcium hydroxyapatite crystals, a form that contains 99% of the body's calcium and a fundamental component of bones and teeth. Insufficient calcium accumulation leads to low bone mineralization and a decrease in peak bone mass, this being one of the key factors for the appearance of osteoporosis and associated osteoporotic fractures. In this sense, bone tissue acts as a calcium reservoir to guarantee the efficiency of all these physiological processes, regulating its exit from the bone through the bone remodeling process<sup>4</sup>.

Furthermore, vitamin D, hormone D, or 1,25 (OH)<sub>2</sub> D (1,25 dihydroxycholecalciferol, or calcitriol) facilitates

the intestinal absorption of calcium by regulating calcium transport proteins and the consequent promotion of transport of transcellular calcium at the level of the intestine<sup>5</sup>. The main function of the endocrine system of vitamin D at the bone level is to preserve serum calcium homeostasis. Therefore, vitamin D deficiency causes secondary hyperthyroidism that normalizes serum calcium through increased renal synthesis of hormone D from its immediate precursor, calcidiol or 25 (OH) D (25-hydroxy cholecalciferol), increasing both the intestinal absorption of dietary calcium as compensatory bone resorption at the expense of increased bone turnover and consequent loss of bone mass<sup>5</sup>. Even moderate vitamin D deficiency can promote age-mediated physiological bone loss and thus accelerate the pathophysiological process of osteoporosis, significantly increasing the risk of osteoporotic fragility fractures<sup>6</sup>. Furthermore, the important impact of vitamin D on muscle biology cannot be ignored, since it has been observed that the increased risk of falls associated with hypovitaminosis D may lead to an increased risk of osteoporotic fractures<sup>5</sup>.

## Calcium and vitamin D in randomized clinical trials and meta-analyses

### Meta-analysis with positive results

We have several meta-analyses carried out with the many randomized, double-blind, placebo-controlled clinical trials (RCTs) in the treatment of osteoporosis. The



vast majority of these studies have been carried out with calcium carbonate and with cholecalciferol as the metabolite of vitamin D, and, therefore, the most physiological form<sup>7</sup>, in patients with different levels of risk of osteoporosis and, even some of them, with objectively diagnosed osteoporosis.

Most of the meta-analyses of these RCTs have shown a reduction in the risk of fractures, both vertebral and non-vertebral, including hip fractures, the latter undoubtedly the most relevant from the point of view of morbidity and mortality and social health impact. As many of the RCTs mentioned were carried out in the 1980s and nineties, with perhaps different clinical research methodologies in bone mineral metabolism, we have focused our review mainly on the most recent meta-analyses, that is, those published in the last decade.

Thus, in 2014 the data of a systematic review carried out according to the Cochrane methodology on the role of vitamin D in the prevention of fractures in postmenopausal women and elderly men were published. This work included data from 91,791 patients (including non-institutionalized, institutionalized, and even hospitalized) with different risks of osteoporotic fracture, from 53 RCTs. Selected 10 RCTs (n=49,976) in which joint supplementation of calcium and vitamin D was used (the majority carried out with cholecalciferol as the form of vitamin D used), the researchers concluded that calcium and vitamin D reduced the risk of fracture statistically significant (RR: 0.95; 95% CI -95% confidence interval-: 0.90-0.99). Furthermore, by type of fracture -good quality evidence again- they found statistically significant risk reductions for both hip fracture (9 RCTs; n=49,853; RR: 0.84; 95% CI: 0.73-0.96), as for other non-vertebral fractures (8 RCTs; n=10,380; RR: 0.86; 95% CI: 0.78-0.96). The analysis did not detect a statistically significant risk reduction associated with treatment with calcium and vitamin D in relation to vertebral fractures<sup>8</sup>, although it is known that this type of osteoporotic fracture usually has a better prognosis and fewer complications than the previous ones, sometimes even asymptotically.

That same year, Bolland and Reid's research group in New Zealand, well known in the field of bone mineral metabolism for their unfavorable opinion of the need for calcium and vitamin D supplementation, published a sequential meta-analysis. In this paper, along with other extra-osseous health parameters, they analyzed the reduction in fracture risk appearance. According to their cut-off point of minimum risk reduction of 15% as a clinically significant limit, they did not find treatment with calcium and vitamin D relevant in reducing the risk of total fractures or hip fracture. However, according to the results of their own analysis, statistical significance was reached in total fractures, with a risk reduction of 8% (RR: 0.92; 95% CI: 0.85-0.99), and even more so in hip fracture, with a risk reduction that reached 16% (RR: 0.84; 95% CI: 0.74-0.96; p=0.009)<sup>9</sup>.

Another study was carried out with the support of the US NOF (National Osteoporosis Foundation), encompassing data from 30,970 individuals grouped in a total of 8 RCTs to analyze effects on the incidence of total fractures and 6 RCTs regarding only hip fracture. The results pointed to a positive effect of calcium and vitamin D treatment, again cholecalciferol in almost all RCTs, achieving a risk reduction of 14% (RR: 0.86; 95% CI: 0.75-0.98) for

total fractures, and with a robust risk reduction of up to 39% (95% CI: 0.46-0.82) for hip fractures<sup>10,11</sup>.

Finally, 3 studies with positive results have recently been published: a meta-analysis of 6 RCTs grouping data from 49,282 patients that yielded a discrete, albeit statistically significant, risk reduction in favor of the combined calcium/vitamin D treatment of 6% of total fractures (RR: 0.94; 95% CI: 0.89-0.99), and more relevant in terms of hip fracture, reaching a 16% risk reduction (RR: 0.84; 95% CI: 0.72-0.97)<sup>12</sup>. Another that analyzed data from up to 47 RCTs (n=58,424) found a statistically significant reduction in risk of falls of 0.88 (95% CI: 0.821-0.945; p<0.01) for cholecalciferol and calcium and, additionally, reduction risk of total fractures of 0.85 (95% CI: 0.741-0.996; p=0.045)<sup>13</sup>. A third meta-analysis also concluded significant reductions in the risk of osteoporotic fractures, both total and hip<sup>14</sup>. Table 1 shows a summary of the results of the aforementioned meta-analyses.

#### *Meta-analysis with negative results*

Probably the work with the greatest impact in this regard was that published by the group by Zhao et al., who carried out a meta-analysis with data from 33 RCTs that included 51,145 non-institutionalized adults over 50 years of age at risk of fracture. These investigators did not find statistically significant risk reductions from the combination of calcium and vitamin D in hip fractures (RR: 1.09; 95% CI: 0.85-1.39) or in other non-vertebral fractures (RR: 0.88; 95% CI: 0.75-1.03); neither in vertebral fractures (RR: 0.63; 95% CI: 0.29-1.40), nor in total fractures (RR: 0.90; 95% CI: 0.78-1.04)<sup>15</sup>. This meta-analysis has subsequently received some criticism, as it could have had some methodological biases such as: 1) the exclusion of RCTs of institutionalized patients, usually at higher risk of fracture than non-institutionalized patients and with lower 25(OH)D levels and, therefore, more sensitive to the effect of supplementation; 2) the inclusion of numerous RCTs with treatment follow-ups too short (less than 12 months) to detect positive effects; 3) the fact that in one of the most important RCTs included for data analysis (known as the WHI study -Women's Health Initiative-) adherence to supplementation was notably low<sup>16</sup>; and 4) the inclusion of several RCTs in which the form of vitamin D supplementation was by oral or intramuscular bolus mega-doses, which have been clearly relegated from routine clinical practice due to their demonstrated negative effect of increasing the risk of falls and fractures<sup>17</sup>.

Along the same lines, in 2019, another meta-analysis from another research group was published with also negative results<sup>18</sup>. In this meta-analysis, some of the methods criticized in the previous work were repeated, such as the non-inclusion of RCTs with institutionalized patients, as well as the inclusion of RCTs in which mega-doses of vitamin D were used.

#### **Calcium and vitamin D in combination with drugs used in the treatment of osteoporosis and clinical guidelines**

##### *The evidence on the need to combine these drugs*

Apart from the intrinsic activity of calcium and vitamin D supplementation in the prevention of osteoporotic fractures, it should be noted that the large RCTs carried out for the regulatory approval of the drugs we use for the treatment of osteoporosis have been carried out by admi-

**Table 1. Summary of calcium and vitamin D meta-analyses with positive results**

First author and reference	Patients included	RR non-vertebral fracture	RR hip fracture	RR total fractures
Avenell <sup>8</sup>	91,791	14% [0.86 (0.78-0.96)]	16% [0.84 (0.73-0.96)]	5% [0.95 (0.90-0.99)]
Bolland <sup>9</sup>	76,497	N/A	16% [0.84 (0.74-0.96)]	8% [0.92 (0.85-0.99)]
Weaver <sup>10,11</sup>	30,970	N/A	39% [0.61 (0.46-0.82)]	14% [0.86 (0.75-0.98)]
Yao <sup>12</sup>	49,282	N/A	16% [0.84 (0.72-0.97)]	6% [0.94 (0.89-0.99)]
Thanapluetiwong <sup>13</sup>	58,424	N/A	15% [0.85 (0.74-0.99)]	NS
Eleni <sup>14</sup>	74,325	N/A	39% [0.61 (0.40-0.92)]	26% [0.74 (0.58-0.94)]

N/A: data not available; NS: not statistically significant; RR: risk reduction.

nistering to all patients calcium and vitamin D supplements. Regardless of the pharmacological class, whether they are bisphosphonates, PTH analogues, RANK ligand inhibitors or any other mechanisms of action, it is of great importance that these drugs are accompanied by calcium and vitamin D so that they can produce an optimal benefit/risk balance in patients with osteoporosis.

The form of vitamin D used to accompany these anti-osteoporotic drugs in their respective reference RCTs was always cholecalciferol, and none of them used intermediate vitamin D metabolites such as calcifediol, nor hormone D (calcitriol)<sup>19</sup>. A summary of the different reference studies can be seen in table 2.

*Recommendations of the clinical guidelines of the societies interested in osteoporosis*

As far as Spain is concerned, the Spanish Society of Rheumatology (SER)<sup>29</sup>, the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM)<sup>30</sup>, the Spanish Society of Endocrinology and Nutrition (SEEN)<sup>31</sup>, the SEMFYC (Spanish Society of Family and Community Medicine – rheumatological diseases working group)<sup>32</sup> or the Spanish Association for the Study of Menopause (AEEM)<sup>33</sup>, just to mention some of those that we have found most relevant, recommend the use of calcium and vitamin D supplements in the therapeutic management of osteoporosis of different origin.

Similarly, at the international level, it is recommended by the following societies: European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) in conjunction with the advisory committees and national societies of the International Osteoporosis Foundation (IOF)<sup>34</sup>; British National Osteoporosis Guideline Group (NOGG)<sup>35</sup>; National Osteoporosis Foundation (NOF)<sup>36</sup>, and the joint American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)<sup>3</sup> in the USA; and Endocrine Society (ES), together with the European Society of Endocrinology (ESE)<sup>37</sup>.

In table 3 we summarize the recommendations made by the scientific societies mentioned above on the supplementation of calcium and, especially, vitamin D.

Despite the fact that these scientific societies recommend the joint administration of calcium and vitamin D with the indicated treatment for osteoporosis, it is surprising and at the same time worrying that in our country there is still a significant proportion of patients, close to 40%, who start treatments for osteoporosis without the accompaniment of supplementation with calcium and vitamin D<sup>38</sup>.

**Drugs of choice and future dosage trends**

Although it seems quite evident that patients with osteoporosis and vitamin D deficiency should be treated with calcium and vitamin D, it is also true that there is no solid scientific evidence and, therefore, no consensus among scientific societies, regarding the dose to use. However, there is a clear trend in this regard:

*Calcium*

The most widely used form of calcium in our country is undoubtedly calcium carbonate<sup>39</sup>, a calcium salt with greater bio-availability of element calcium than others also available, but less common, such as calcium citrate<sup>40</sup>.

As for the appropriate amounts of calcium in the context of osteoporosis, since 2010 the most replicated and internationally accepted reference is the Food and Nutrition Board of the Institute of Medicine (IOM) guideline of the United States which recommends a daily intake (contained in the diet or through exogenous supplementation when the above is not possible) of 1,200 mg of calcium for men over 70 years old or women over 51 years old<sup>4</sup>. Unfortunately, the majority of the population at risk of osteoporosis do not ingest the 1,200 mg/day recommended by the IOM. This has recently been verified in the epidemiological study ANIBES (Anthropometry, Intake and Energy Balance in Spain), published in 2017. Carried out through surveys on nutritional habits of more than 2,000 individuals of a very wide age range in our country, it estimated that the average daily amounts of calcium ingested through the diet of women and men older than 65 years were 662 and 629 mg, respectively<sup>41</sup>. Therefore, if we were to reach the IOM guideline, we would have to supplement with about 600 mg of calcium daily in the form of exogenous calcium carbonate supplement to reach 1,200 mg/day.

*Vitamin D*

Cholecalciferol is the form of vitamin D most used in RCTs and therefore the metabolite specifically recommended in most of the aforementioned published clinical guidelines on the management of osteoporosis. We do not have conclusive scientific evidence that establishes the recommended daily doses in the treatment of osteoporosis in a consensual way. It is possible that the trend is to increase the daily 800-1,000 IU of vitamin D that is used mostly in routine clinical practice at higher doses, since this has been the norm up to now in the design of clinical trials.

**Table 2. Reference studies of drugs used for the treatment of osteoporosis. Dose of vitamin D (cholecalciferol) used**

Drug	Year of publication	Study acronym	First author	Cholecalciferol (dose in IU)	Bibliographic reference
Alendronate	2000	FIT	Black	250	20
Risedronate	1999	VERT	Harris	500	21
Ibandronate	2004	BONE	Delmas	400	22
Zoledronate	2007	HORIZON	Black	400-1,200	23
Raloxifen	1999	MORE	Ettinger	400-600	24
Calcitonin	2000	PROOF	Chesnut	400	25
Teriparatide	2001		Neer	400-1,200	26
Denosumab	2009	FREEDOM	Cummings	400-800	27
Romozosumab	2016	FRAME	Cosman	50,000-60,000 initially; subsequently 600-800 IU	28

**Table 3. List of recently published guidelines from national and international scientific societies specialized in the clinical management of osteoporosis that recommend supplementation with calcium and vitamin D**

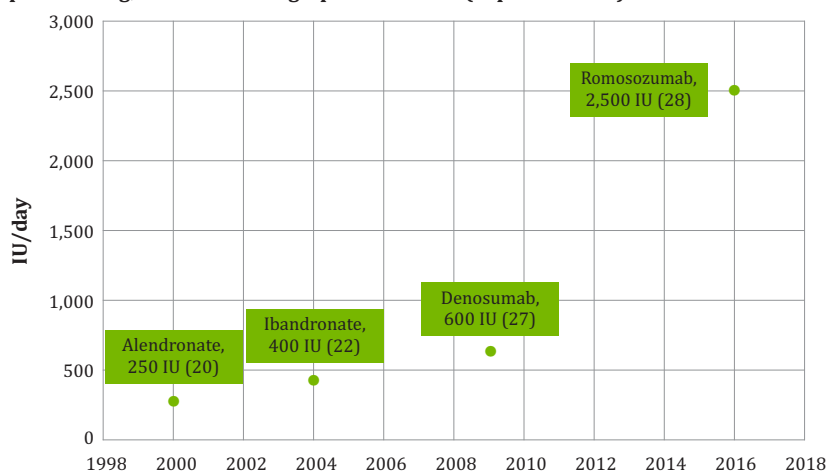
Scientific society	Geographical scope	Year of publication	Vitamin D. Drug and dose in IU	Bibliographic reference
Spanish Society of Rheumatology (SER)	Spain	2019	NE 800	29
Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) <sup>30</sup>	Spain	2015	NE 800-1,000	30
Spanish Society of Endocrinology and Nutrition (SEEN)	Spain	2015	NE Variable according to type of osteoporosis	31
Spanish Society of Family and Community Medicine (SEMFYC)	Spain	2014	NE 800	32
Spanish Association for the Management of Menopause (AEMM)	Spain	2012	NE 800	33
European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO)/International Osteoporosis Foundation (IOF)	Global	2019	Cholecalciferol 800	34
National Osteoporosis Guideline Group (NOGG)	Great Britain	2017	Cholecalciferol 800	35
National Osteoporosis Foundation (NOF)	EE.UU.	2014	Cholecalciferol 800-1,000	36
American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/ACE)	EE.UU.	2016	Cholecalciferol 1,000-2,000	3
Endocrine Society/European Society of Endocrinology (ES/ESE)		2019	NE Unspecified dose	37

NE: vitamin D with unspecified drug.

Thus, more than 30 years ago, the reference trials with alendronate were designed with a supplement of vitamin D of 250 IU/day<sup>20</sup>, an amount that increased 4 years later to 400 IU/day with ibandronate<sup>22</sup>, and by 2009 reached 800 cholecalciferol IU/day in patients with baseline 25(OH) D levels of 12-20 ng/ml or 400 IU/day for levels greater than 20 ng/ml in the FREEDOM study with denosumab<sup>27</sup> (average in the first month of 600 IU/day treatment). Thus, we observe that this up-

ward trend is consolidated in the most recent reference study with romozosumab, published in 2016, and in whose design a loading dose of 50,000-60,000 IU/day of cholecalciferol was established (the use of vitamin D<sub>2</sub> or ergocalciferol was also allowed) and then daily doses of 600-800 IU for patients with baseline levels of 25 (OH) D between 20 and 40 ng/ml<sup>28</sup>, which would mean an average in the first month of treatment of about 2,500 IU/day (see figure 1).

**Figure 1. Evolution of the daily doses of the first month of treatment (IU/day) of cholecalciferol associated with anti-osteoporotic drugs. Year of publication, anti-osteoporotic drug, dose and bibliographic reference (in parentheses) are indicated**



In our opinion, it would be advisable to transfer this trend of increasing the dose of cholecalciferol in drugs under development to our usual clinical practice of supplementation in patients with vitamin D deficiency and osteoporosis. Similarly, some renowned scientific societies, in their clinical guidelines and consensus documents, recommend a supplementation of up to 2,000 IU/day of cholecalciferol in patients with osteoporosis. Among these groups, the International Osteoporosis Foundation (IOF)<sup>42</sup>, the Endocrine Society (ES)<sup>43</sup> or the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)<sup>3</sup> stand out.

We will be better able to reach the optimal levels of 25(OH)D higher than 30 ng/ml widely recommended by the main scientific societies which manage osteoporosis if

we treat patients with 2,000 IU/day than if we treat them only with 800-1,000 IU/day, and that this can produce an additional clinical benefit in osteoporosis. In fact, there are already studies that provide some evidence that this could be the case. The Zurich Hip Fracture Trial carried out by the Dawson-Hugues and Bischoff-Ferrari groups, a clinical trial in which it was compared in a bi-factorial way the administration of 2,000 IU/day or 800 IU/day of cholecalciferol to 173 patients who had suffered a hip fracture, in combination or not with a physical exercise program for 12 months, concluding that the administration of 2,000 IU/day was associated to a more limited deterioration in the quality of life between months 6 and 12, evaluated by means of the EuroQol EQ-5D-3L scale scores<sup>44</sup>; also, a systematic review of the literature that analyzed 12 publications on different guidelines for supplementation with cholecalciferol in menopausal women at risk of osteoporosis with vitamin D deficiency, in which the authors observed that only daily doses of 2,000 IU/day increased 25 (OH) D levels consistently above 30 ng/ml<sup>45</sup>.

## CONCLUSION

To date, scientific evidence confirms the need to treat all patients with osteoporosis and vitamin D deficiency with calcium and vitamin D (preferably cholecalciferol), regardless of their other osteoporosis treatment. The daily doses of cholecalciferol to be used should reach at least 2,000 IU.

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