Position document on the requirements and optimum levels of vitamin D

Introduction
In the last few years there has been a notable interest in vitamin D, not only due to its crucial importance in bone mineral metabolism, but also for its effects outside the bone, which, every day, are becoming better known.

Similarly, the existence of low blood levels of vitamin D, lower than what is desirable, has been found in different populations, both healthy and sick, and there is a discussion as to what would be the optimum levels of vitamin D in the blood.

For all these reasons, the Spanish Society of Bone and Mineral Metabolism Research (Sociedad Española de Investigación Ósea y Metabolismo Mineral – SEIOMM), jointly with all the scientific societies involved in the study of bone metabolism, have produced this position document on the requirements and optimum levels of vitamin D.

Material and method
The content of this document was developed in the following stages:

a) Meeting of a group of experts in osteoporosis to discuss and agree the relevant clinical questions related to vitamin D (Table 1).

b) Creation of a systematic review team, formed by two experts in bone mineral metabolism who carried out the search, a standardised review, critical analysis and tabulation of the articles which had been published in Spanish and English between January 2000 and May 2010. The search was carried out using the MeSH (Medical Subject Headings) terms of the National Library of Medicine of the US National Institutes of Health, related to the topic. Using these terms, the following databases were consulted: PubMed, Medline Plus, Cochrane Library, Up to Date and OVID. Similarly, an ascending search was made of the previously published guidelines to clinical practice relevant to the topic, as well as articles suggested by the group of experts.

c) Those articles which provided the best level of evidence for each of the questions raised were included (Table 2).

d) Subsequently, following on from the results obtain in the search, a draft of the position document was put together by the group of clinical experts to respond to the questions previously formulated and to provide a consensus on recommendations, taking into account social, economic and health repercussions. In cases of disagreement, a majority opinion was formed, leaving the absence of unanimity on record.
PART 1. LITERATURE REVIEW

Introduction

1. Sources of vitamin D

More than 90% of the vitamin D in our bodies comes from the transformation of 7-dehydrocholesterol into previtamin D₃, and subsequently into vitamin D₃ by the action of ultraviolet B radiation from the sun on the skin. There is no danger of vitamin D intoxication due to an excess exposure to the sun, since any excess previtamins and vitamin D synthesised degrade in the skin itself into inactive metabolites.

The rest is obtained through intestinal absorption, either from the diet (although those foods which contain vitamin D do not provide sufficient quantities) or by taking supplements.

2. Physiology of vitamin D. Action inside and outside the bone

Vitamin D is actually formed from a family of chemical substances with similar action. But when we talk generically of vitamin D we are referring both to vitamin D₃ (colecalciferol), and vitamin D₂ (ergocalciferol), the first being part of human physiology, and the second obtained by UV irradiation of ergosterol contained in yeasts. Dietary vitamin D absorbed by the fraction of the kilomicros or synthesised in the skin, and later also its metabolites, circulate bonded to a transporter protein (DBP). In the liver it undergoes a hydroxylation by the action of 25-hydroxylase to form calcifediol or calcidiol (25 hydroxycolecalciferol, 25 hydroxy-vitamin D, 25 (OH)D). The calcifediol has a high concentration and a long average life, of two or three weeks, which means that it is used to evaluate the status of vitamin D in the body (see later), and forms the ideal substrate for the formation of calcitriol or 1.25 dihydroxy-vitamin D (1.25(OH)₂D), the hormonally active metabolite in the endocrine system of vitamin D³.

The complex formed by calcifediol and its transporter protein, [25(OH)D]-DBP, is bonded with megalin (a protein located in the plasmatic membrane of the renal tubular cells), which it introduces into the cells. Here, the 25(OH)D is released and directed to the mitochondria, where, by the action of 25-hydroxyvitamin D-1α-hydroxylase it is transformed into 1.25(OH)₂D, which has as its principal endocrine function, the maintenance of calcium homeostasis. This balance, in turn, is fundamental to the various metabolic functions to be carried out normally, for adequate muscular transmission and for bone mineralisation to happen correctly. Its calciotropic function is carried out by acting on the intestinal, parathyroid, bone and renal cells, as we see below⁴.

In the intestine, the action of vitamin D is fundamental for the absorption of calcium through the saturable transcellular pathway, especially when it derives from foods or compounds with low ionisability. When a deficiency in vitamin D occurs, the absorption of calcium reduces by 15% (and by up to 60% for phosphorus), thus reducing levels of ionized calcium in the blood. This decrease is detected by the calcium sensors in the parathyroid glands, which respond with an increase in the secretion of parathyroid hormone (PTH)¹⁴, whose function is to maintain adequate levels of blood calcium, by acting on the kidneys, as we will see later, and in the bone, where it stimulates bone resorption. This final action it achieves by increasing in the osteoblasts the expression of RANKL, which bonds to the receptor, RANK, in the plasmatic membrane of the monocyte precursors of the osteoclasts, inducing their maturation. The mature osteoclasts then bond with the bone surface to initiate their resorptive action by releasing, above all, hydrochloric acid and collagenase. The calcium and phosphorus released in the process pass into the circulation, and thus increase their blood levels⁸³.

In the kidney, the PTH reabsorbs the filtered calcium (both in the distal and proximal tubules) and reduces the reabsorption of phosphorus, leading to phosphaturia and, therefore, hypophosphotemia. Both (PTH and hypophosphotemia) in turn powerfully stimulate the renal production of 1.25(OH)₂D.

Calcium and phosphorus are essential for mineralisation to happen correctly, when the supply of calcium in the body is inadequate 1.25(OH)₂D helps to maintain calcium homeostasis, acting on the receptors for vitamin D (VDR) of the osteoblasts in which it induces in a similar way to PTH the formation of RANKL.

In addition to these endocrine actions, which we could call “traditional” or “classic”, and which regulate calcium-phosphorus and bone homeostasis, the vitamin D endocrine system has other auto-paracrine functions in the organism as a whole⁵. The majority of tissues and cells, normal or neoplastic, such as muscle, heart, brain, blood vessels, breast, colon, prostate, pancreas, skin and immune system, among others, contain VDR and activator enzymes for 25(OH)D, such as 1-hydroxylase, in those locations not regulated by PTH, to synthesise 1.25(OH)₂D, and, as happens in the kidneys, inactivator enzymes such as 24 hydroxylase, which catabolises both 25(OH)D and 1.25(OH)₂D, and ends up forming calcitroic acid, which is soluble in water and biologically inactive.

The 1.25(OH)₂D bonds with its VDR with a strong affinity and regulates the transcription of approximately 3% of the human genome. It is involved in the regulation of cell growth and maturation, inhibits the production of rennin and increases the secretion of, and sensitivity to, insulin, modulating the function of activated B and T lymphocytes and the macrophages, among other actions, which means that it has important implications for health⁶⁹.

Questions raised by the Committee of Experts: search for evidence

1st. Optimum levels of vitamin D

Adequate levels of vitamin D are vital for the correct working of the endocrine system, not only
in the bone, but also in practically the whole organism. The principal indicator for the system is 25(OH)D, the metabolite with the longest average life and an essential substrate for the synthesis of 1,25(OH)2D, both in the kidneys as well as in other cells and tissues, which makes it commonly accepted as an indicator for the status of vitamin D10.

A fundamental problem in the determination of 25(OH)D consists in the precision and reproducibility of the methods available for its measurement9. For a long time there was no consensus regarding what were the optimum levels of 25(OH)D in the population, although in recent years there has been a growing interest in establishing them. Some studies have shown that with levels of 25(OH)D above 30-40 ng/ml (75-100nmol/l), in adults the maximum intestinal absorption of calcium is achieved8, and at the same time, lower levels of PTH, avoiding the appearance of secondary hyperparathyroidism8. It is assumed that children have the same requirements as adults, although no studies have been carried out which confirm this.

Generalising from these findings the view is that the optimum requirements of vitamin D are those which permit the maintenance of blood levels of 25(OH)D above 30 ng/ml (75 nmol/l)11,12.

Faced with these results, there is ever increasing agreement in accepting these levels as those most beneficial to ensure healthy bone8,9, and at the same time, logically appropriate, and as such, the most recommendable. With respect to higher values, in a review of thirty works there was no evidence of toxicity in patients with levels of 25(OH)D below 100 ng/ml. It has been proposed that the minimum threshold for toxicity is above 150 ng/ml (375 nmol/l)14.

Table 1. Questions raised by the panel of experts

| 1. What are the optimum levels of vitamin D? |
| 2. Are there adequate levels of vitamin D in the Spanish population? |
| - Prevalence of hypovitaminosis D in Spain |
| 3. What are the requirements for vitamin D? |
| a- In the general population |
| b- In specific situations: |
| - In children and adolescents |
| - In the postmenopause |
| - In elderly people |
| c- In pathological situations: |
| - In patients with osteoporosis |
| - In patients with fracture |
| - In patients receiving corticoids |
| 4. Vitamin D and falls, muscle strength and balance |
| - Incapacitated patients |
| 5. Treatment with vitamin D. Alone, or always with calcium? |
| - In the prevention of osteoporosis |
| - In the treatment of osteoporosis itself |
| - Combined with other antosteoporotic drugs |

2nd Levels of vitamin D in the Spanish population

At present, insufficiency, and frankly, deficiency in 25(OH)D constitutes a pandemic which affects more than half the general population17, and both children and adolescents18-21, as well as adults22, postmenopausal women23 and elderly people15-26, in this last group, if they have osteoporotic fractures, the prevalence of hypovitaminosis D reaches 100%. Holick and Chen, in 2008, described vitamin D deficiency as a global health problem with diverse pathological consequences1, and a recent review carried out by Mithal et al. of studies on hypovitaminosis D across the world concluded that this deficit was emerging globally as a major health problem2.

This situation is occurring also in Spain, as can be observed from the various studies carried out in this country20-22. Despite having a propitious climate which could result in an adequate synthesis of vitamin D by solar exposure, the general levels are similar or even lower than those described in central Europe or Scandinavia in earlier studies24-35, although the variation in methodologies between laboratories makes a rigorous comparison difficult.

There has been an attempt to explain the paradoxical state of hypovitaminosis D which is obser-
ved in our country, and which is also seen in other Mediterranean countries, by the scarce supply of dietary vitamin D which cannot be compensated for by cutaneous synthesis. On the other hand, it is important to understand that the greater part of the Iberian peninsula is above the latitude of 35° N, which means that the inclination of the sun’s rays reduces the possibility of synthesising vitamin D during the months of winter and spring.

However, vitamin D deficiency in Spain ought not to be explained solely by geographic factors; some studies have observed low levels of vitamin D in populations with an adequate, or even, abundant, exposure to sun, such as that carried out in habitual surfers in Hawaii, by Binkley et al. In our country, where there is a significant seasonal variation in levels of vitamin D between the months of greater sunshine (summer-autumn) and those with lower (winter-spring), it has been observed, however, that they scarcely normalise after the first months. This insufficiency is observed in children and young people, persists in adults, in healthy postmenopausal women, and with osteoporosis, and, logically, is patent in elderly people, both those living in their own homes as well as, even more so, in those living in residential homes.

3rd Vitamin D requirements

It is logical to think that the requirements for vitamin D should be those which maintain the optimum levels of 25(OH)D. However, the quantities of vitamin D which have come to be recommended until recently for the healthy population (200 UI/day from birth until 50 years of age, 400 UI for adults up to 70 years of age and 600 UI daily for those over 71 years of age) seem insufficient for purpose, as various authors have indicated. Coming to the same conclusion are Ginde et al., who carried out a demographic study to look at the trend of vitamin D insufficiency in the population of the US comparing the levels in the population studies in NHANES during the years 1988 to 1994 (18,883 people), with those recorded in people studied during the years 2001 to 2004 (13,369 people), and observing a marked decrease in levels of 25(OH)D over time.

If we take into account the different population groups, various authors already consider it necessary that children and adolescents should acquire 400 UI daily of vitamin D to reach optimum blood levels of 25(OH)D. In 2008, the American Academy of Pediatrics increased the recommended daily dose of vitamin D for children and adolescents to 400 UI, and when this is not achieved through diet and exposure to sun, it should be acquired through supplements.

For adults, although the daily acquisition of 400 UI of vitamin D has for a long time been recommended in order to reach optimum blood levels of 20-30 ng/ml (50-75 nmol/l) much higher amounts are needed, approximately 1,700 UI/day. When a daily dose of 1,000 UI is given over 3 or 4 months, blood levels of 25(OH) increase 10 ng/ml, so that a subject with levels of 10 ng/ml would need 2,000 UI/daily to reach the 30 ng/ml considered to be optimum. The fear of toxicity has limited the recommendations of authors, since, as we mentioned in the earlier section, the upper safety limit in order to avoid the risk of producing hypercalcemia is 150 ng/ml (375 nmol/l) of blood 25(OH)D. For some years some authors have already been recommending higher quantities, both in women and men, of between 700 to 1,000 UI, and others indicate that even higher daily doses, of 1,000 - 2,000 UI, can be much more effective to achieve more adequate levels of 25(OH)D with no risk of toxicity. In 2007, a panel of experts produced a consensus document for nutritional guides for vitamin D, and in it they stated that the maximum safe intake of vitamin D, established at 2,000 UI daily, should be re-evaluated and raised to allow the carrying out of studies which evaluate the effects of high daily doses of vitamin D in the maintenance of better general health. In the same year, Hathcock et al. in a review on the safety of vitamin D based on the risk of hypercalcemia, concluded that the upper limit for the ingestion of vitamin D in adults should be 10,000 UI daily. This indicates that the safety limit is much higher than any of the recommended quantities. Very recently, the IOF in its position document recommends doses of 800-1,000 UI/day, although with subjects at risk of low blood levels of 25(OH)D (obesity, osteoporosis, malabsorption, low exposure to sunlight, etc.) these daily doses should rise to 2,000 UI.

In postmenopausal women, the same as with elderly people, both populations with a high risk of bone loss, the quantities which the experts recommend become higher, between 2,000 and 3,000 UI/day. Bacon et al. evaluated the safety and effectiveness of high doses, such as 500,000 in a single dose, an initial dose of 500,000 UI and 50,000 UI monthly for maintenance, or 50,000 UI monthly, showing that they were both safe and effective.

Up until now, we have talked of the desirable requirements for healthy subjects; evidently, patients with osteoporosis should be considered in a special way, since in these patients vitamin D plays an important role in the etiopathogeny of the disease. Even though it is not clear whether vitamin D supplements alone, are sufficient to treat osteoporosis, it is recognised worldwide these patients should be supplied with sufficient quantities of vitamin D, which in the majority of cases they do not acquire through diet and exposure to sun. Later we dedicate a specific section to treatment of osteoporosis with vitamin D and its complication, fractures. Related to both osteoporosis and vitamin D, we should not forget that those patients receiving corticoid therapy. In these patients, the action of the drug results in a lower intestinal absorption of calcium, along with a higher rate of urinary elimination, which produces secondary hyperparathyroidism. Although the studies carried out with regard to its effectiveness in preventing bone loss or fractures are highly heterogeneous and involve low
numbers of patients (and are therefore not generally conclusive), it is generally recognised that vitamin D (combined with calcium) should be prescribed in all those patients in long term treatment with corticoids at high doses, with the aim of maintaining bone metabolism; although it is also generally considered that they should not be prescribed alone, but with an antosteoporotic drug (bisphosphonates, teriparatide), especially when dealing with patients with high risk of fracture.

There is neither agreement nor unanimity regarding the dose of vitamin D which patients in treatment with glucocorticoids ought to receive. In the Guide on Corticoid Osteoporosis, published by the Spanish Society of Internal Medicine in 2007 it is recommended that vitamin D be administered at a dose of 800-1,000 UI/day, combined with 500-1,000 mg/day of calcium.

4th. Vitamin D and falls, muscle strength and balance
Apart from the well known effects of vitamin D on bone metabolism, hypovitaminosis D is also associated with muscular weakness, predominantly in the proximal musculature. It has been demonstrated in experimental studies that the metabolites of vitamin D have an influence on the maturation and function of muscle through the receptors for these metabolites which the muscle cells possess. In a sample of 976 people older than 65 years of age it has been confirmed that their levels of vitamin D were inversely correlated with being in poor physical shape. Given the high prevalence of vitamin D deficiency in the older population, studies aimed at clarifying this correlation appear justified, especially since there is an ever-increasing number of elderly people in whom there will have to be identified potentially modifiable risk factors for disability.

Stewart et al. recently carried out a study in 242 healthy postmenopausal women (aged between 48.8 and 60 years) with the aim of understanding the relationship between levels of 25(OH)D to obesity, risk of falls

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of study</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic review of randomised clinical trials, with homogeneity</td>
</tr>
<tr>
<td>1b</td>
<td>Randomised clinical trials with narrow confidence interval</td>
</tr>
<tr>
<td>1c</td>
<td>Clinical practice (“all or nothing”) (*)</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review of cohort studies, with homogeneity</td>
</tr>
<tr>
<td>2b</td>
<td>Cohort study or randomised clinical trial of low quality(***)</td>
</tr>
<tr>
<td>2c</td>
<td>“Outcomes research” (†), ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review of case-control studies, with homogeneity</td>
</tr>
<tr>
<td>3b</td>
<td>Case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series or cohort and case-control studies of low quality (+)</td>
</tr>
<tr>
<td>5</td>
<td>Opinion of experts without explicit critical validation, or based on physiology, “bench research” or “first principles” ($)</td>
</tr>
</tbody>
</table>

A minus sign (-) should be added to indicate that the level of evidence is not conclusive if:
- Randomised clinical trial with wide confidence interval and not statistically significant.
- Systematic review with heterogeneity statistically significant.

(*) When all the patients die before a specific treatment becomes available, with which some patients survive, or when some patients used to die before its availability, and with it, none die.

(***) For example, with follow up lower than 80%.

(†) The term “outcomes research” makes reference to cohort studies of patients with the same diagnosis in whom the events which occur are related to the therapeutic measures which they receive.

(‡) Cohort study: without clear definition of the groups compared and/or without objective measurement of exposures and events (preferably blind) and/or without identifying or adequately controlling known confusion variables and/or without complete or sufficiently prolonged follow up. Case-control study: without clear definition of the groups compared and/or without objective measurement of exposures and events (preferably blind) and/or without identifying or adequately controlling known confusion.

($) The term “first principles” makes reference to the adoption of a specific clinical practice based on physiopathological principles.

<table>
<thead>
<tr>
<th>Adequate vitamin D levels</th>
<th>ng/ml</th>
<th>nmol/l</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 30 ng/ml</td>
<td>&gt; 75 nmol/l</td>
</tr>
<tr>
<td>Vitamin D insufficiency</td>
<td>20 - 30 ng/ml</td>
<td>50 - 75 nmol/l</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>&lt; 20 ng/ml</td>
<td>&lt; 50 nmol/l</td>
</tr>
</tbody>
</table>

1 ng/ml equivalent to 2.5 nmol/l
and muscular weakness. 19.4% had values of 25(OH)D < 50 nmol/l (20 ng/ml). For these subjects, a correlation was sought with some indicators for good physical health, such as the android fat mass, lean body mass, balance and the hand grasp strength, the strength of the torso and of the lower limbs. They found that the levels of vitamin D were correlated with all the indicators, except with the strength of the torso and lower limbs, concluding that the blood levels of 25(OH)D can be a contributor to the indices of physical health in healthy postmenopausal women.

The aforementioned muscular weakness associated with hypovitaminosis D, if it surpasses a certain limit, can affect functional capacity and mobility, which puts, especially elderly people, at greater risk of falls, and therefore, of fractures. The provision of vitamin D supplements to elderly people in situations of deficiency can improve muscle strength and functional capacity, which results in a reduction in falls and therefore, of non-vertebral fractures. Bunout et al. evaluated the effects of resistance training and the provision of vitamin D supplements on the physical condition of 96 healthy elderly people with low levels of vitamin D, concluding that the addition of this treatment improved their walking speed and stability, while the training improved muscle strength.

Some authors have found that in healthy elderly people vitamin D supplements did not prevent a decrease in muscle strength due to age-related involution. In a review carried out by Annweiler et al. the results around the association of vitamin D with physical function were contradictory. Dhesi et al. carried out a study in 139 mobile subjects older than 65 years of age with a history of falls and hypovitaminosis (levels of 25(OH)D ≤ 12 µg/l), and to whom were randomly allocated either a single dose of 600,000 U of intramuscular ergocalciferol, or a placebo. The results showed that at 6 months, the subjects who had received the vitamin D supplement had significant benefits in terms of their physical function, reaction times and balance, although not muscle strength. A more recent study continued the controversy: More-Pfrimer at al. studied muscle strength in 46 institutionalised subjects ≥ 65 years of age, to whom they administered over 6 months either daily calcium plus a placebo, or daily calcium plus oral colecalciferol (initial dose of 150,000 UI monthly for two months followed by 90,000 UI monthly for 4 months), randomly allocated. At 6 months, and without having taken physical exercise, the strength of the hip flexors increased in the group which received vitamin D by 16.4% (p = 0.0001), and the strength of the extensors of the knee by 24.6% (p = 0.0007). Lips et al. carried out a study in which were assigned randomly a dose of 8,400 UI weekly of colecalciferol, or a placebo, to 226 subjects ≥ 70 years of age whose concentrations of 25(OH)D were between 6 and 20 ng/ml. To evaluate muscle function and balance their mediolateral body sway with eyes open was measured at 8 and 16 weeks with an AccuSway platform and a battery of short physical exercises (SPPB, Short Physical Performance Battery) carried out. In the results obtained vitamin D did not reduce the mediolateral body sway or improve the SPPB, although by grouping the subjects according to their baseline mediolateral sway, those who had the greatest instability (≥ 0.46 cm) improved significantly when they had been treated with vitamin D for 16 weeks (p = 0.047). It is important to indicate that even though the levels of 25(OH)D increased in patients treated at 8 weeks, they did not reach adequate levels (30 ng/ml) during the whole period of the study (16 weeks).

In terms of its effect on the reduction in falls, the same studies which showed that the vitamin D supplements favoured muscular function and balance, suggest that there should also be a reduction in falls, and therefore, in fractures. Various meta-analyses published in recent years indicate that vitamin D supplements reduce the risk of falls in the elderly, although some specify that the dose should be 700-1,000 UI daily, since at lower doses (or blood concentrations < 60 nmol/l) this reductor effect is not produced, which could be as much as 22% (adjusted OR: 0.78; 95% CI: 0.64-0.92) compared with those patients who had received calcium alone or a placebo. This is corroborated in a review of Cochrane carried out by Gillespie et al. who observed that vitamin D supplements do not reduce the risk of falls (RR 0.96; 95% CI: 0.92-1.01), but indicate that they may do so in those with low blood levels of vitamin D. Another review carried out more recently, found that these supplements reduce the rate of falls (rate ratio, RR 0.72; 95% CI: 0.55-0.95), but not the risk of falls (risk ratio, RR 0.98; 95% CI: 0.89-1.09) 77. To add more controversy, in a recently published study, carried out in 2,252 women of ≥ 70 years of age who were not institutionalised, to see the effect of a single high dose of 500,000 UI of colecalciferol, it was observed that the group which took the high dose of vitamin D showed an increase in the number of falls and fractures as opposed to the group which had taken the placebo.

On the other hand, it has been suggested that there could be an inverse relationship between levels of vitamin D and intensity of muscular-skeletal pain, which means that optimum levels of vitamin D could be useful in patients with secondary pain due to osteoporotic complications. In this section we should make special mention of the effect vitamin D supplements can have in patients affected by multiple sclerosis (MS). Originally, the hypothesis that a sufficient supply could prevent the disease was established to explain its geographic distribution; and since then, hypovitaminosis D has been considered one of the environmental risk factors for MS. However, recently, studies have been carried out which have shown an association of low blood levels of 25(OH)D with the prevalence of MS, the risk of suffering MS, its incapacity and the frequency between two breaks.
Table 4. Reference studies with drugs used in the treatment of osteoporosis in postmenopausal women. Principal objective: incidence of fractures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study name</th>
<th>Year</th>
<th>First author (ref.)</th>
<th>Group treated</th>
<th>Calcium and vitamin D</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>---</td>
<td>1990</td>
<td>Storm (101)</td>
<td>Women with OP postmenopausal</td>
<td>Calcium and vitamin D (quantities ND)</td>
<td>3 years</td>
</tr>
<tr>
<td>Alendronate</td>
<td>FIT</td>
<td>1996</td>
<td>Black (102)</td>
<td>Postmenopausal women with BMD with FxV/without FxV</td>
<td>Calcium carbonate (500 mg/day of calcium element) and vitamin D (250 UI/day) if diet low in calcium (&lt; 1,000 mg/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Risedronate</td>
<td>VERT</td>
<td>1999/2000</td>
<td>Harris / Reginster (103/104)</td>
<td>Postmenopausal women &lt; 85 years with at least 2 FxV or one FxV and low BMD (T-score &lt; -2)</td>
<td>Calcium carbonate (1,000 mg/day) and vitamin D (500 UI/day) if 25(OH) vit D &lt; than 16 ng/ml or 40 nmol/l</td>
<td>3 years</td>
</tr>
<tr>
<td></td>
<td>HIP</td>
<td>2001</td>
<td>McClung (105)</td>
<td>Women of 70-79 years of age and osteoporosis; or aged ≥ 80 years with at least one clinical risk factor for hip Fx</td>
<td></td>
<td>3 years</td>
</tr>
<tr>
<td>Ibandronato</td>
<td>BONE</td>
<td>2004</td>
<td>Chesnut (106)</td>
<td>Postmenopausal women with T-score ≤ -2 in at least one lumbar vertebra and between 1 and 4 FxV</td>
<td>Calcium (500 mg/day) and vitamin D (400 UI/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>HORIZON</td>
<td>2007</td>
<td>Black (107)</td>
<td>Women with densitometric OP with T-score &lt; -2.5 without fractures; or T-score &lt; -2.5 and ≥ 1 FxV</td>
<td>Calcium (100-1,500 mg/day) and vitamin D (400-1,200 UI/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>MORE</td>
<td>1999</td>
<td>Ettinger (108)</td>
<td>Women with ≥ 2 years of menopause with densitometric OP</td>
<td>Calcium (500 mg/day) y cholecalciferol (400-600 UI/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>---</td>
<td>2001</td>
<td>Neer (109)</td>
<td>Postmenopausal women with at least one FxV</td>
<td>Calcium (1,000 mg/day) and vitamin D (400-1,200 UI/day)</td>
<td>3 initial years (19 months)</td>
</tr>
<tr>
<td>PTH 1-84</td>
<td>TOP</td>
<td>2007</td>
<td>Greenspan (110)</td>
<td>Postmenopausal women of between 45 and 54 years with T-score &lt; -3, or T-score &lt; -2.5 plus 1-4 FxV</td>
<td>Calcium citrate (700 mg/day) y vitamin D (400 UI/day)</td>
<td>18 months</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>TROPOS</td>
<td>2005</td>
<td>Reginsterb (111)</td>
<td>Postmenopausal women with T-score &lt; -2.5; or if &gt; 70 years, also with 1 risk factor for Fx</td>
<td>Calcium (&gt;1,000 mg/day) and vitamin D (400-800 UI/day)</td>
<td>5 years (preliminary 3 years)</td>
</tr>
<tr>
<td></td>
<td>SOTI</td>
<td>2004</td>
<td>Meunier (112)</td>
<td>Postmenopausal women (&gt;5 years), aged &gt; 50, with at least 1 FxV and BMD ≤ 0.840 g/cm²</td>
<td>Calcium (&gt;1,000 mg/day) and vitamin D (400-800 UI/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>PROOF</td>
<td>2000</td>
<td>Chesnut (113)</td>
<td>Postmenopausal women with established OP</td>
<td>Calcium (1,000 mg/day) and vitamin D (400 UI/day)</td>
<td>5 years</td>
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OP: osteoporosis; BMD: bone mineral density; Fx: fracture; FxV: vertebral fracture; ND: unavailable
However, its therapeutic potential in established MS has not yet been sufficiently studied. A recently published work by Burton et al. was carried out in 49 patients with MS of average age of 40.5 years and average blood levels of 25(OH)D of 78 nmol/l, with an average EDSS (Expanded Disability Status Scale) of 1.34. They were randomly assigned to a placebo group (n= 24), or to treatment with a dose which was increased step by step until it reached 40,000 UI/day at 28 weeks, thus rapidly raising their blood levels of 25(OH)D and thereby evaluating its tolerability. The dose was then maintained at 10,000 UI daily over 12 weeks, subsequently being reduced to 0 UI/day (n= 25). During the whole study 1,200 mg/day of calcium was given. In spite of blood levels of 25(OH)D reaching a peak of 413 nmol/l, there were no significant adverse effects. The group treated with vitamin D appeared to have fewer breaks and a persistent reduction in the proliferation of T lymphocytes, compared with the control group. Despite recognising that there were confusion variables in the clinical results, the authors concluded that high doses of vitamin D supplements had an evident immunomodulator effect on the MS, in addition to being safe. All the researchers considered it necessary that more studies be carried out in this area.

5th. Calcium and vitamin D supplements in the prevention and treatment of osteoporosis

There is near unanimity among researchers in concluding that vitamin D on its own is insufficient for the prevention of osteoporotic fractures, and those who find a positive impact on the risk of fracture indicate that this improves with the addition of calcium, with a reduction of 30% in this risk. The same occurs with calcium supplements, which are considered insufficient in themselves in reducing the risk of hip fracture, although some have obtained results which indicate that calcium supplements alone are sufficient to reduce the risk of fractures in general, and even vertebral fractures. But the majority of studies and researchers concede that supplements of calcium plus vitamin D have a positive effect in the reduction of risk of fractures in the region of 20% in the risk. And this is demonstrated in various meta-analyses on this subject. Thus, Bischoff-Ferrari et al. published a meta-analysis in 2005 in which they analysed the effect of calcium and vitamin D on the prevention of hip and non-vertebral fractures. The authors observed that at a dose of 700-800 UI/day of vitamin D, the reduction in the risk of hip fracture was 26% (relative risk, RR: 0.74; 95% CI: 0.61-0.88) and for non-vertebral fractures, 23% (RR: 0.77; 95% CI: 0.68-0.87), while for lower doses of vitamin D, below 400 UI/day, no protection against fractures was observed.

Subsequently, Boonen et al. delved deeper into the earlier meta-analysis of Bischoff-Ferrari and found that in 4 randomised clinical studies, which included 9,083 patients, the relative risk for hip fracture was not statistically significant (RR: 1.10 95% CI: 0.89-1.36). Instead, in the 6 randomised studies in which calcium and vitamin D were administered, which included a total of 45,509 patients, the risk of hip fracture was reduced by 18% (RR: 0.82; 95% CI: 0.71-0.94). No heterogeneity was observed between the studies, and an adjusted indirect comparison of the combined relative risks of both meta analyses found a reduction in risk of fracture of 25% in those patients who had received calcium and vitamin D as against those who had only taken vitamin D (RR: 0.75; 95% CI: 0.58-0.96).

More recently, Tang et al. carried out another meta-analysis using 29 randomised studies which included a total of 63,897 patients, analysing both the reduction in the relative risk of all fractures and the increase in bone mineral density. Studying those publications in which the principal objective was the reduction in risk of fracture, 17 studies were included with a total of 52,625 patients. In these patients a reduction of 12% in the risk of suffering new fragility fractures (RR: 0.88; 95% CI: 0.83-0.95; p = 0.0004) was found, and they concluded that the evidence supported the use of calcium, or calcium combined with a vitamin D supplement in the treatment of osteoporosis in people of 50 years of age or over, and that for a maximum therapeutic effect a dose of 1,200 mg/day of calcium and 800 UI/day of vitamin D was necessary.

According to the last clinical practice guides, for it to be able to be effective in the prevention of risk of fracture, the minimum daily dose of supplements recommended are 1,000-1,200 mg of calcium element, plus 800 UI (or 20 μg) of vitamin D. To guarantee the necessary intake of calcium, should it be needed, it recommended that this be through food, whenever possible.

Administration of calcium and vitamin D jointly with other antosteoporotic drugs

An adequate provision of calcium and vitamin D is essential when a treatment with any antosteoporotic drug is prescribed, be it antiresorptive, anabolic or of mixed action. Given the difficulty in achieving this through diet and exposure to the sun alone, it is necessary to administer jointly supplements of calcium and vitamin D. In all the clinical trials which have been carried out with the different antiresorptive drugs to demonstrate their antifractural efficacy, supplements of calcium and vitamin D were administered to all participants, which indicates that this efficacy has not been demonstrated in the absence of correct levels of calcium and vitamin D. In Table 4 we show these trials and the quantities of calcium and vitamin D which were administered.

2nd PART. RESPONSES TO THE QUESTIONS RAISED. RECOMMENDATIONS

1.- What are the optimum levels of vitamin D?
- We consider that the optimum levels of vitamin D should be between 30 and 75 ng/ml, and that levels below 20 ng/ml are clearly pathological.
2.- Are levels of vitamin D in the Spanish population adequate?
- No. The majority of the Spanish population does not achieve optimum levels of vitamin D. Depending on the type of population studied and the cut off point, the prevalence of vitamin D deficiency (< 20 ng/ml) varies between 30% in young people and 87% in institutionalised elderly people, with the ages in between and the non-institutionalised elderly at between 50% and 70%.

3.- What are the requirements for vitamin D?
- In general, they are those which ensure optimum levels of vitamin D in the blood. The means of acquiring these optimum levels may be through adequate exposure to sun, foods and vitamin D supplements.
- In specific situations, the panel makes the following recommendations, although they take the view that when there is vitamin D deficiency, higher doses are necessary to achieve optimum levels:
  - Children, adolescents: 400-600 UI/day.
  - Postmenopause: 600-800 UI/day.
  - Elderly people: 800-1,000 UI/day.
  - Patients with osteoporosis: 800-1,000 UI/day.
  - Patients with fracture: 800-1,000 UI/day. On the basis of a high prevalence of serious vitamin D deficiency in patients with osteoporotic fractures of the hip, the panel considers it advisable to perform an assessment of levels of vitamin D, and when this not possible it recommends the use of a higher dose.
  - Patients receiving corticoids: 800-1,000 UI/day.

4.- Vitamin D and falls, muscle strength and balance
- The panel estimates that in the special case of institutionalised elderly people, due to the great difficulty in their achieving necessary levels of vitamin D through hygiene-dietetic measures, the requirements should be met through vitamin D supplements. On the other hand, we cannot conclude that the provision of vitamin D improves muscle strength.

5.- Treatment with vitamin D. Alone, or always with calcium?
  a. – In the prevention of osteoporosis:
    - The panel considers that the prevention of osteoporosis should be carried out through good hygiene-dietetic habits (adequate exposure to sun, consuming foods rich in calcium). The use of calcium and vitamin D drugs are not indicated for this task, save in those cases where there is a difficulty in obtaining optimum levels of these substances, when they should be supplemented pharmacologically.
  b. – In the treatment of osteoporosis in itself:
    - The panel considers that there is no evidence that exclusive treatment with calcium and vitamin D has antifractural efficacy, except in specific populations, such as institutionalised elderly people.

  c. – Jointly with other antosteoporotic drugs:
    - When using an antosteoporotic drug supplements of calcium and vitamin D should always be added. However, the panel considers that in those patients in whom there is a guarantee of an adequate provision of calcium in the diet, the use of a calcium supplement is not necessary.

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Rules for publication

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