Role of calcium and vitamin D in the treatment of osteoporosis

Summary
Our objective has been to develop a position document on the role of calcium and vitamin D in the treatment of osteoporosis, identifying and assessing the grade of evidence which supports the recommendations.
To achieve this aim, the published studies on aspects of pharmacokinetics of calcium, and the usefulness of calcium and vitamin D in the reduction of risk of fragility-related fracture, given on its own, as well as, more commonly used in combination with other drugs, have been reviewed, developing through their analysis, the current recommendations. These have been produced through a pre-specified and reproducible process, which included an accepted model for the evaluation and citing of evidence which supports them. The document, once drafted by the co-ordinators, was reviewed and discussed by all the panel members, to produce the definitive recommendations.
Calcium and vitamin D in themselves have shown their usefulness in the reduction of risk of both vertebral fracture, and hip and non-vertebral fracture. Administered in combination with different drugs they also reduce the risk of new osteoporotic fractures. All treatments indicated for osteoporosis should be administered with a supplement of calcium and vitamin D. To ensure optimum absorption, the calcium and vitamin D should be administered in small doses throughout the day. The calcium salt most used is calcium carbonate, of which there has been the greatest experience, it being, also, the cheapest. Calcium carbonate slightly increases the risk of urolithiasis. Calcium citrate is indicated in those patients with achlorhydria and reduces the risk of urolithiasis, being indicated as the drug of first choice for these patients.
1. Introduction
Osteoporosis. Its importance and the objectives in its treatment
Osteoporosis is the most frequent metabolic bone disease in humans. It was initially defined by Fuller Allbright as “too little bone”. Nowadays, the definition accepted by consensus is “systematic skeletal disease characterised by low bone mass and deterioration in the micro-architecture of the bone tissue, with the consequent increase in bone fragility and susceptibility to fractures”. The essential elements of this definition are the low bone mass and the alteration of the micro-architecture, which distinguishes osteoporosis from other bone diseases. The alterations in micro-architecture are characterised by the loss, thinning and lack of connection between the bone trabeculae, the geometry of the bone itself, etc., which have been grouped under the concept of bone quality. All these factors produce a deterioration in the structural integrity of bone and contribute to bone fragility, which brings with it an increased risk of fractures. In fact, fractures and their complications are the clinical manifestations of osteoporosis. Considered typically osteoporotic are fractures of the proximal extremities of the femur, vertebrae and wrist, although, in general, any bone is susceptible to fracture.

Treatment of osteoporosis. Objectives
The principal objective in the treatment of osteoporosis is to avoid or reduce the appearance of osteoporotic fractures (whether the first time or with the existence of previous fractures), given that these constitute its principle complication and clinical problem. Other objectives, such as the increase in bone mineral density, the modification of the biochemical markers for remodelled bone, or complications and adverse affects, are secondary.

One should also avoid the idea that the treatment of osteoporosis consists solely of the long term administration of a drug which reduces the risk of fractures. The correct treatment indicated requires, in addition, a series of non-pharmacological, but equally important actions, such as abandoning toxic behaviours like tobacco and alcohol abuse, taking daily physical exercise, in accordance with the clinical state of the patient, and having a balanced diet.

Evidence-Based Medicine (EBM) and drugs used for osteoporosis
At present a wide variety of drugs for the treatment of osteoporosis are available. The greatest number of these have shown their effectiveness through clinical trials carried out in accordance with EBM, and are thus indicated for the treatment of osteoporosis in both the United States and the European Union.

Nowadays, the studies of drugs for the treatment of osteoporosis are carried out with the principal objectives of the reduction of risk of fracture, since this constitutes the fundamental clinical complication of osteoporosis, and the reason for its importance. From a practical point of view, there is a tendency to separate the reduction in risk of vertebral fracture from that of other fractures, which have been grouped empirically as non-vertebral fractures, which is the term generally used, given that, as non-vertebral fractures are grouped very different fractures, as much from the point of view of their symptomology as their mortality, such as, for example fractures of the rib and hip. In the past, studies were carried out with the principal objective being to evaluate changes in bone mineral density (BMD). Now, although these are still carried out, their practical usefulness is much less, since it has been observed repeatedly that there is no correlation between increases in BMD and decreased risk of fracture. Thus, with such small increases in BMD, such as 5.4%, a decrease in the risk of fracture of 41% has been observed in the case of risedronate. Also, in the PROOF study, carried out on calcitonin, a reduction in risk of fracture was observed in spite of no changes in BMD being observed. These findings bring to light the important role played by what is now called bone quality, as much in the physiopathology of osteoporosis as in bone resistance.

It is also a rule that patients should be randomly assigned to a treatment or control group, in such a rigorous way that it is subsequently confirmed that there are no statistically significant differences between the groups in their baseline characteristics, with the single exception being the treatment received by one or the other. Thus, the differences subsequently observed can be attributed to the drug. However, although methodologically impeccable, in this type of study the patients in the control group (who, equally to the cases, presented a high risk of suffering fractures) received, up ‘til now, only calcium and vitamin D, as well as the placebo. This has provoked an interesting debate from an ethical point of view.

Another important matter, essential for studies of osteoporosis, is that the sample size should be large. Gone are the days when conclusions were taken on the basis of studies carried out with a few dozen patients. Nowadays, such work is carried out with sample sizes of some thousands of patients. This, on the one hand has the advantage of offering much more solid statistical rigor, but on the other hand, brings the inconvenience of a significantly more costly project proposal, in which, in practice, all studies have to be multi-centred. When databases with this number of patients are handled, it is possible to carry out robust statistical studies, which reach unequivocal conclusions, and, in addition, allow the study of specific subpopulations which begin to reach a respectable size, and to carry out post-hoc analyses.

The studies are usually carried out with a duration of approximately 3 years. When the follow-up is extended for a longer period there is usually a significant number of cases lost, and the final sample size can become so reduced that it becomes difficult to evaluate the results.
Table 1 shows the criteria proposed by the Centre for Evidence-Based Medicine (CEBM) in Oxford, with hierarchical scales of evidence, from which are established recommendations with respect to the adoption of a specific medical procedure or health intervention, as well as an economic evaluation. These are available at http://www.cebm.net/levels_of_evidence.asp, and are kept continually updated.

2. Material and methods
This position document has been produced following the criteria of the Working Group of Evidence-Based Medicine for the development of Guides to Clinical Practice, as well as the criteria proposed by the Centre for Evidence-Based Medicine (CEBM) of Oxford, with scales for hierarchical classification of evidence, from which have been established recommendations with respect to the adoption of a specific medical procedure or health intervention, as well as an economic evaluation.

The content of this position document has been developed in the following stages:

a) Meeting of a group of experts on osteoporosis to raise the relevant clinical questions (Table 2).

b) Creation of a systematic review team, formed of two experts in bone mineral metabolism to carry out the search, standard review, critical analysis and tabulation of relevant articles which were published in Castilian and in English from January 1980 to May 2008. The search was carried out using the MeSH terms (Medical Subject Headings) of the National Library of Medicine of National Institutes of Health – (US), related to the theme. With 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 clinical practice guides previously published on the theme, and articles suggested by the group of experts.

c) The articles with the highest level of evidence available for each question asked were included. The works were classified and scored by two independent evaluators on the basis of the criteria previously described. In the case of disagreement, the decision was submitted to the committee of experts.

d) Subsequently, according to the results obtained in the search and classification of the available evidence, a draft of the position document was produced by the group of clinical experts to respond to the questions previously formulated and to agree the recommendations, taking into account social, economic and health repercussions. In the case of disagreements a majority opinion was formed, making clear the lack of unanimity.

3. Results
3.1. Calcium and vitamin D
We had available various studies which compared the reduction in risk of fracture when only calcium and vitamin D were used, with the control group receiving absolutely nothing, taking a true placebo. Although there are various published guides to clinical practice based on physiopathological principals.

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic review of randomised clinical trials, with homogeneity</td>
</tr>
<tr>
<td>1b</td>
<td>Randomised clinical trial 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” (1), ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic reviews of case-control studies, with homogeneity</td>
</tr>
<tr>
<td>3b</td>
<td>Case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Series of cases or studies of cohorts or case-control studies of low quality (2)</td>
</tr>
<tr>
<td>5</td>
<td>Opinion of experts without explicit critical validation, or based on physiology, “bench research” or “first principles” (3)</td>
</tr>
</tbody>
</table>

A minus sign (-) should be added to indicate that the level of evidence is not conclusive if:
- it is a randomised clinical trial with a broad confidence interval and not statistically significant.
- it is a systematic review with statistically significant heterogeneity.
- it is a case-control study.

(*) Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
(**) For example, with a follow up lower than 80%.
(1) The term “outcomes research” makes reference to cohort studies of patients with the same diagnosis which relate the events which happen to them to the therapeutic measures they receive.
(2) Cohort study: without clear definition of the comparative groups, and/or without objective measurement of the exposures and events (preferably blind), and/or without identifying or controlling adequately known as being variables that may lead to confusion, 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 the exposures and events (preferably blind), and/or without identifying or controlling adequately the known confusing variables.
(3) The term “first principles” makes reference to the adoption of specific evidence-based guidelines.
Table 2. Questions produced by the panel of experts

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do calcium and vitamin D supplements, in themselves, reduce the risk of fragility-related fractures?</td>
</tr>
<tr>
<td>2. Are calcium and vitamin D supplements indicated with other pharmacological treatments for postmenopausal osteoporosis?</td>
</tr>
<tr>
<td>3. How many calcium salts are used in the treatment of osteoporosis and how much calcium element does each contain?</td>
</tr>
<tr>
<td>4. Is there a difference in the absorption of calcium between the different salts?</td>
</tr>
<tr>
<td>5. What would be the ideal model for the administration of calcium?</td>
</tr>
</tbody>
</table>

works which confirm these findings, we preferred to refer ourselves to the meta-analyses (Table 3) because this type of study has the maximum level in the hierarchy of evidence established by the Centre for Evidence-Based Medicine in Oxford (CEBM). Thus, Bischoff-Ferrari et al.\(^4\) published a meta-analysis in JAM in 2005 in which they analyse the effect of calcium and vitamin D in the prevention of hip and non-vertebral fractures. The period of review covered from 1960 to 2005, and in the end they were able to include 5 studies of hip fracture which were carried out with a total of 9294 patients, and 7 studies of non-vertebral fractures which included 9820 patients. The authors observed that at a dose of 700-800 UI/day of vitamin D, the reduction in risk of fracture of the hip was 26% (relative risk, RR: 0.74; IC 95%: 0.61-0.88) and for non-vertebral fractures, 23% (RR: 0.77; IC 95%: 0.68-0.87), whilst with lower doses of vitamin D, below 400 UI/day, no protection against fracture was observed [Level of evidence 1a].

Subsequently, Boonen et al.\(^5\) deepened the earlier meta-analysis of Bischoff-Ferrari and found that in 4 randomised clinical studies which included 9083 patients, the relative risk of fracture of the hip was not statistically significant (RR: 1.10; IC 95%: 0.89-1.36). Whereas, in the 6 randomised studies in which calcium and vitamin D was administered, which included 45509 patients, the risk of fracture of the hip was reduced by 18% (RR: 0.82; IC 95%: 0.71-0.94). There was no heterogeneity observed among the studies, and an adjusted indirect comparison of the combination of relative risks of both meta-analyses obtained a reduction in the risk of fracture of 25% in patients having received calcium and vitamin D as opposed to those only having received vitamin D (RR: 0.75; IC 95%: 0.58-0.96) [Level of evidence 1a].

More recently, Tang et al.\(^6\) carried out another meta-analysis, using 29 randomised studies which included a total of 63897 patients, analysing both the reduction in relative risk of all fractures, and the increase in bone mineral density. Studying publications in which the principal objectives were the reduction in risk of fracture, they obtained 17 studies which included a total of 52025 patients. In these were found a reduction of 12% in the risk of suffering new fractures due to fragility (RR: 0.88; IC 95%: 0.83-0.95; \(p = 0.0004\)). 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 or more years of age, and for a maximum therapeutic effect, a dose of 1,200 mg/day of calcium and 800UI/day of vitamin D was necessary [Level of evidence 1a].

On the other hand, vitamin D supplements reduce the risk of falls, which indirectly influences the risk of fracture. Thus, in a meta-analysis published by Bischoff-Ferrari et al.\(^7\) based on 5 randomised clinical studies in which 1237 patients were included, it was observed that vitamin D corrected the risk of falls by 22% (adjusted OR: 0.78; IC 95%: 0.64-0.92) compared with patients who had received only calcium or placebo [Level of evidence 1a].

### 3.2. Calcium and Vitamin D with anabolic drugs

We referred for each drug to the most representative or pivotal study, the study usually used by the pharmaceutical industry to obtain approval for the treatment of osteoporosis, both in the United States and in the European Union.

Among the anabolic drugs, PTH 1-34, or teriparatide, showed its capacity to reduce the appearance of new vertebral fractures in a study carried out in 1637 postmenopausal women with at least one vertebral fracture, and who were randomly assigned to one of three of the following groups for treatment: PTH 1-34 (20 μg or 40 μg), placebo, daily, subcutaneously, for 3 years. In all these cases 1000 mg daily of calcium and 400-1200 UI/day of vitamin D were also administered. A reduction of 65% in the relative risk of suffering new vertebral fractures was observed in those women who received 20 μg of teriparatide, compared with the placebo group (RR: 0.35; IC 95%: 0.22-0.55), and of 69% in the group which received 40 μg, as against the placebo group (RR: 0.31; IC 95%: 0.19-0.50)\(^8\) [Level of evidence 1b].

Another study called TOP (Treatment of Osteoporosis with PTH), was carried out with the intact molecule of PTH (1-84), in which a reduction in the risk of vertebral fracture was shown. Carried out in 2532 women with postmenopausal osteoporosis, it consisted, the same as the earlier studies, of a double blind randomised trial controlled by placebo. The patients were assigned to one of two following treatment groups: PTH (1-84) 100 μg/day, or placebo, subcutaneously. The study lasted 18 months. Once more, all patients in the study were given 700 mg daily of calcium citrate and 400 UI of vitamin D. A reduction of 61% in the risk of new vertebral fractures was obtained in the women in the group who received intact PTH compared with the control group. The relative risk was 0.42 (IC 95%: 0.24-0.72; \(p < 0.001\))\(^9\) [Level of evidence 1b].
Table 3. Meta-analysis which analyses the effect of vitamin D and calcium, alone or together, on the risk of fracture

<table>
<thead>
<tr>
<th>Meta-analysis first author (Citation)</th>
<th>Year</th>
<th>Nº of studies analysed</th>
<th>Group treated</th>
<th>Drug analysed</th>
<th>% reduction in risk of Fx</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff-Ferrari (44)</td>
<td>2005</td>
<td>5 (Hip Fx)</td>
<td>&gt; 60 years</td>
<td>Vitamin D vs calcium or placebo</td>
<td>&gt; 700-800 UI/day; Hip Fx: 26%; NV Fx: 23%</td>
<td>---</td>
</tr>
<tr>
<td>Boonen (45)</td>
<td>2007</td>
<td>10 (Hip Fx)</td>
<td>Postmenopausal women and/or men &gt; 50 years</td>
<td>Vitamin D, with or without calcium</td>
<td>Vitamin D + calcium; Hip Fx: 18%</td>
<td>p= 0.0005</td>
</tr>
<tr>
<td>Tang (46)</td>
<td>2007</td>
<td>29 randomised</td>
<td>Men and women &gt; 50 years</td>
<td>Calcium, with or without vitamin D</td>
<td>---</td>
<td>p= 0.0004</td>
</tr>
</tbody>
</table>

Fx: fracture; NV: non-vertebral

### 3.3. Calcium and vitamin D with anti-resorptive drugs

**Etidronate** was used by Storm et al. in a study published in 1990 and carried out in 66 postmenopausal women, in which the group which received the etidronate took it at a rate of 400 mg daily for 14 days, with a 13 week break, followed by a repeat of the cycle. The group which received etidronate and the placebo group both received a supplement of calcium and vitamin D. The study lasted 150 weeks (3.1 years) and obtained a statistically significant reduction in the appearance of new vertebral fractures (p< 0.02)^[36] [Level of evidence 1b].

**Alendronate.** The FIT (Fracture Intervention Trial) study, randomised double blind placebo-controlled, was designed to observe the effect of alendronate on the incidence of vertebral and non-vertebral fractures in postmenopausal women with low bone mass. The research involved 6459 postmenopausal women with bone mineral density (BMD) in the femoral neck 0.68 g/cm² (a T-score equivalent to -1.6 approximately), who were distributed in two branches of the study: in one, those women with vertebral fracture at the baseline; and in the other group, the women with no such fracture. The study of the first branch was carried out in 2027 postmenopausal women with a least one vertebral fracture and a low bone mass (T-score < -2), who were included. Each patient was assigned to receive one of the following treatments: a) alendronate at 2.5 mg/day; b) risedronate at 5 mg/day; and c) a placebo. All the women received a supplement of calcium carbonate (1000 mg/day) in a single dose at lunch or dinner, and those who presented low levels of 25 (OH) vit D (< 16 ng/ml or 40 nmol/l) received vitamin D (500 UI). The group which received 2.5 mg of risedronate left the study after a year due to a protocol correction. At 3 years there was a significant reduction in the relative risk of morphometric vertebral fracture of 41% (IC 95%: 18-58%; p= 0.003) in patients treated with 5 mg of risedronate with respect to the placebo group, and already in the first year a reduction of 65% (IC 95%: 38-81%) was seen, also significant (p< 0.001). The accumulated incidence of non-vertebral fractures at 3 years was 39% less in the group treated with risedronate (IC 95% 6-61), a significant figure (p= 0.02).

**Risedronate.** The pivotal study for risedronate is named VERT (Vertebral Efficacy with Risedronate Treatment). This randomised, double blind, placebo-controlled study, also consisted of two branches, one north American (NA) and the other European-Australian (EA). In the first study 2458 postmenopausal women, younger than 85 and with either at least two vertebral fractures or one vertebral fracture and a low bone mass (T-score < -2), were included. Each patient was assigned to receive one of the following treatments: a) risedronate at 2.5 mg/day; b) vitamin D (500 UI). The group which received 2.5 mg of risedronate left the study after a year due to a protocol correction. At 3 years there was a significant reduction in the incidence of vertebral fracture of 32% (IC 95%: 27-37) and 29% (IC 95%: 24-35) in the NA and EA branches, respectively. The incidence of non-vertebral fractures was reduced by 31% (IC 95%: 26-36) in the NA branch and by 26% (IC 95%: 21-32) in the EA branch. That is to say, the risk of suffering a new vertebral fracture is reduced to almost half in the patients treated with alendronate at the end of 3 years. The second branch of the study was carried out in 4432 women with low bone mass but without vertebral fracture, with random assignment to the two same treatment groups as with the previous branch (with an equal increase in the dose of alendronate at 24 months and equal conditions of calcium and vitamin D supplements). The results show that the risk of suffering a first vertebral fracture were significantly less in those treated with alendronate, with a reduction of 44% (p< 0.002)^[37] [Level of evidence 1b].

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50 [Level of evidence 1b].

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3.1 years was 39% less in the group treated with rise-
In the European-Australian branch 1226 postmenopausal women were recruited with at least two vertebral fractures. The treatment groups were equal, including the calcium and vitamin D supplements, as well as the duration of the study. The group on 2.5 mg of risedronate abandoned the trial after 2 years. The reduction in the risk of incidence of vertebral fracture was 49% with risedronate at 5 mg as opposed to the placebo after 3 years of treatment (p< 0.001). A reduction of risk with risedronate was also seen during the first year, being 61% (p= 0.001). The risk of non-vertebral fractures was reduced by 33% compared with the control group at 3 years (p= 0.06)\(^{52,53}\) [Level of evidence 1b].

Subsequently, another study was published whose objective was to analyse the reduction in the incidence of hip fractures. Named the HIP (Hip Intervention Program) study, it included 9331 women who fulfilled one of the following two criteria: aged 70-79 years, with osteoporosis (n= 5445); or aged > 80 years with at least one clinical risk factor (non-densitometric) for hip fracture. They were assigned to one of the three treatment groups indicated in the VERT study, also over 3 years. The results, analysed for all the women, showed that risedronate diminishes the incidence of hip fractures in 30% (IC 95%: 10-40%; p= 0.02). In the group of women with osteoporosis (70-79 years of age) the reduction in risk in those treated with risedronate was 40% (IC95%: 20-60%; p= 0.009). The reduction in risk of hip fracture in the group of women with non-densitometric risk factors (RR: 0.8; IC 95%: 0.6-1.2; p= 0.55), was not, however, significant. The design being identical to the early studies, the supplements of calcium and vitamin D were also of calcium carbonate (1000 mg/day) in a single dose at lunch or dinner, and those who presented low levels of 25(OH) vit D (< 16 ng/ml or 40 nmol/l) received vitamin D (500 UI/day)\(^{54}\) [Level of evidence 1b].

### Ibandronate

Ibandronate has, as its reference study, a study called BONE (Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe). It consists of a randomised double blind study controlled by placebo, and was carried out in 2946 postmenopausal women with a BMD T-score of <-2 in at least one lumbar vertebra (L1-L4), and between 1 and 4 vertebral fractures (T4-L4). Each patient was assigned to one of the following treatment groups: a) 2.5 mg of oral ibandronate daily; b) 20 mg of oral ibandronate on alternate days until 12 doses had been taken, repeated every 3 months; and c) placebo. All the patients received calcium daily, (500 mg of calcium element) and vitamin D supplements (400 UI). By tracking over three years a significant reduction in risk of incidence of new morphometric fractures was noted in the women who took oral ibandronate, both daily (reduction of 62%; p= 0.0001; IC 95%: 43-75) and intermittently (50%; p= 0.0005; IC 95%: 26-65), compared with the placebo group. With respect to clinical vertebral fractures, a reduction in relative risk of 45% was produced in the 2.5 mg ibandronate group and of 48% in the 20 mg group\(^{55}\) [Level of evidence 1b].

### Zoledronate

Zoledronate is the last bisphosphonate which has been accepted for use in the treatment of osteoporosis in Europe. It has as its reference study ZOL (Zoledronic Acid Osteoporosis Reduction in Incidence and Outcome of Fractures). It shows a reduction in vertebral and hip fractures in postmenopausal women treated with 5 mg of zoledronate annually, given intravenously, along with daily supplements of calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU). It was a randomised double blind study in which 3889 women, with an average age of 73 years received 5 mg of intravenous zoledronate, while 3786 women formed the control group. The study lasted 3 years and the principal objectives were the reduction in risk of vertebral and hip fracture. The results showed a decreased risk of vertebral fracture at 3 years of 70% (3.3% in the group treated as opposed to 10.9% in the placebo group), which shows a relative risk of 0.30, with an IC 95% of 0.24 to 0.38, and a reduction in risk of hip fracture of 41% (1.4% in the group treated with zoledronate as opposed to 2.5% in the placebo group; hazard ratio of 0.59, with an IC at 95% of 0.42 to 0.83). The non-vertebral fractures, clinical fractures and clinical vertebral fractures were reduced by 25%, 33% and 77% respectively, with p< 0.001 in all cases\(^{56}\) [Level of evidence 1b].

### Raloxifene

Raloxifene is the principal study which demonstrates the efficacy of raloxifene is MORE (Multiple Outcome Research): multi-centric, randomised, double blind, placebo-controlled, carried out in 7705 women with at least 2 years of menopause and who fulfilled the densitometric criteria for osteoporosis. The women were assigned randomly to one of the following treatment groups: a) 60 mg/day of raloxifene; b) 120 mg/day of raloxifene; and c) placebo, and they were followed for 3 years. The results showed a decreased risk of vertebral fracture at 3 years of 70% (3.3% in the group treated as opposed to 10.9% in the placebo group), which shows a relative risk of 0.30, with an IC 95% of 0.24 to 0.38, and a reduction in risk of hip fracture of 41% (1.4% in the group treated with zoledronate as opposed to 2.5% in the placebo group; hazard ratio of 0.59, with an IC at 95% of 0.42 to 0.83). The non-vertebral fractures, clinical fractures and clinical vertebral fractures were reduced by 25%, 33% and 77% respectively, with p< 0.001 in all cases\(^{56}\) [Level of evidence 1b].

### Calcitonin

Calcitonin has its reference study in PREDICT (Prospective Reduction of Osteoporotic Fractures) a randomised, double blind, placebo-controlled trial carried out in 1255 postmenopausal women with established osteoporosis. The treatment groups to which they were assigned were: intranasal salmon calcitonin at doses of 100, 200 and 400 UI daily, and a placebo group. All the women received 1000 mg daily of calcium element divided into two doses and 400 UI/day of vitamin D.

This is one of the few studies designed with a follow up of 5 years, at the end of which it was observed that the daily dose of 200 UI salmon calcitonin produced a decrease of 33% in the risk of new vertebral fractures compared with the placebo (RR: 0.67; IC 95%: 0.47-0.97; p< 0.03)\(^{57}\) [Level of evidence 1b].
Table 4. Pivotal studies with drugs used in the treatment of osteoporosis in postmenopausal women. Principal objective: incidence of fractures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Name of study</th>
<th>Year</th>
<th>First author (citation)</th>
<th>Group treated</th>
<th>Calcium and Vitamin D</th>
<th>Follow up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>---</td>
<td>1990</td>
<td>Storm (50)</td>
<td>Women with postmenopausal OP</td>
<td>Calcium and vitamin D (quantities NA)</td>
<td>3 years</td>
</tr>
<tr>
<td>Alendronate</td>
<td>FIT</td>
<td>1996</td>
<td>Black (51)</td>
<td>Postmenopausal women with BMD with VFx/without VFx</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 (52/53)</td>
<td>Postmenopausal women &lt; 85 years with at least 2 VFx or one VFx and low DMO (T-score &lt; -2)</td>
<td>Calcium carbonate (1,000 mg/day), and vitamin D (500 UI/day) if 25 (OH) vit D &lt; 16 ng/ml or 40 nmol/l</td>
<td>3 years</td>
</tr>
<tr>
<td></td>
<td>HIP</td>
<td>2001</td>
<td>McClung (54)</td>
<td>Women of 70-79 years and osteoporosis; or aged ≥ 80 years with at least one clinical risk factor for hip Fx</td>
<td>Calcium carbonate (1,000 mg/day), and vitamin D (500 UI/day) if diet low in calcium (&lt;1,000 mg/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>BONE</td>
<td>2004</td>
<td>Chesnut (55)</td>
<td>Postmenopausal women with T-score ≤ -2 in at least one lumbar vertebra and between 1-4 VFx</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 (56)</td>
<td>Women with densitometric OP with T-score &lt; -2.5 without fractures; or T-score &lt; -2.5 and 1 VFx</td>
<td>Calcium (100-1,500 mg/day) and vitamin D (400-1,200 UI/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Raloxifen</td>
<td>MORE</td>
<td>1999</td>
<td>Ettinger (57)</td>
<td>Women with ≥ 2 years of menopause with densitometric OP</td>
<td>Calcium (500 mg/day) and colecalciferol (400-600 UI/day)</td>
<td>3 years</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>---</td>
<td>2001</td>
<td>Neer (48)</td>
<td>Postmenopausal women with at least one VFx</td>
<td>Calcium (1,000 mg/day) and vitamin D (400-1,200 UI/day)</td>
<td>3 years initially (19 months)</td>
</tr>
<tr>
<td>PTH intacta</td>
<td>TOP</td>
<td>2007</td>
<td>Greenspan (49)</td>
<td>Postmenopausal women of 45 to 54 years with T-score &lt; -3; or T-score &lt; -2.5 and 1 VFx</td>
<td>Calcium citrate (700 mg/day) and vitamin D (400 UI/day)</td>
<td>18 months</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>TROPOS</td>
<td>2005</td>
<td>Reginster (58)</td>
<td>Postmenopausal women with T-score &lt; -2.5; or, if ≥ 70 years, also with 1 risk of Fx</td>
<td>Calcium (&gt;1,000mg/day) and vitamin D (400-800 UI/day)</td>
<td>5 years (first 3 years)</td>
</tr>
<tr>
<td></td>
<td>SOTI</td>
<td>2004</td>
<td>Meunier (59)</td>
<td>Postmenopausal women (&gt; 5 years), aged &gt;50 years, with at least 1 VFX and DMO ≤ 0.84 g/cm²</td>
<td>Calcium (&gt;1,000mg/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 (21)</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>
</tr>
</tbody>
</table>

OP: osteoporosis; BMD: bone mineral density; Fx: fracture; VFx: vertebral fracture; NA: not available
3.4. Calcium and Vitamin D with dual action drugs. Strontium Ranelate

Strontium ranelate is a dual action drug, anabolic and anti-resorptive, with which the TROPOS study was carried out to evaluate its efficacy in the prevention of non-vertebral fractures, and the SOTI study, for the prevention of vertebral fractures.

The TROPOS (Treatment of Peripheral Osteoporosis Study) study was carried out in 5091 postmenopausal women affected by osteoporosis to whom were administered, randomly, either 2 g/day of strontium ranelate or a placebo. All the women received daily supplements of calcium (> 1000 mg) and vitamin D (400-800 UI) before and throughout the study. The study lasted over 5 years, with the first statistical analysis carried out after 3 years. It was observed that the women who received strontium ranelate plus calcium and vitamin D presented a decrease in relative risk for all non-vertebral fractures of 16% (p=0.04) and a decrease of 19% for the most important fragility-related fractures (hip, pelvis, sacrum, humerus, etc.), with p = 0.0314.

In the SOTI (Spinal Osteoporosis Therapeutic Intervention) study, 1649 postmenopausal women who had densitometric osteoporosis and at least one vertebral fracture, were included. They were randomised and the group which received treatment was given 2 g of strontium ranelate daily over 3 years. Both the group which had been given the strontium and the placebo group received a supplement of calcium and vitamin D in a similar way as the previous study: depending on the intake of calcium in the diet at least 1000 mg daily of calcium, and, depending on the baseline levels of PTH and bone resorption, calcium and vitamin D were administered. In the women treated a reduction of 41% in the risk of presenting new vertebral fractures was obtained (RR: 0.59; IC 95%: 0.48-0.73)59 [Level of evidence 1b].

Table 4 shows a summary of these studies. It is observed that in all of them the drug being studied was always administered with a supplement of calcium and vitamin D.

3.5. Absorption and dosage of calcium and vitamin D

The higher the dose of calcium administered in one go the lower its fractional absorption. Thus, Heaney et al.60, in healthy volunteers, using radioactive calcium to assess the absorption of calcium, observed that with the administration of 300 mg of calcium 36% of the mineral was absorbed, while if 1000 mg of calcium was administered its absorption was reduced to 23.5%. In the same study, the authors verified that when administered with meals the absorption of salts of calcium (carbonate and citric) was similar.

The same authors carried out a similar study in 24 postmenopausal women to whom they administered an excess of calcium, taken orally, both citrate and carbonate of calcium, in repeated doses, and analysed the increases in total blood calcium, and blood ionic calcium, the decrease in PTH and the increase in the urinary excretion of calcium, arriving at the conclusion that the absorption and bio-availability of the carbonate and citrate of calcium is similar, but that the lower price of the carbonate makes it more recommendable, from a cost-benefit point of view of61.

On the other hand, different doses of calcium also affect in different ways changes in the levels of PTH. Karkkainen et al. carried out a study in 30 young healthy women to study these dose-dependent effects on the calciotropic hormone and found no evidence of there being more or less benefit in taking them in the morning or the evening62. From the physiopathological point of view it would probably be more useful in people with low intake of calcium to divide the daily dose to reduce the levels of PTH and bone resorption63.

The absorption of calcium is similar, independent of the source. A study carried out by Recker et al. compared the absorption of radioactive calcium (45Ca) in a group of healthy volunteers, administering it through means of whole milk, milk with chocolate, yoghurt, milk substitutes (those prepared using milk derivatives or not), cheese and calcium carbonate. The absorption of calcium varied between 21% and 26% and not one type of administration was significantly superior to the rest64.

For these reasons the Osteoporosis Society of Canada recommended that calcium supplements be administered in divided doses65. More recently, the North American Menopause Society in their 2006 recommendations indicated that to maximise its absorption calcium supplements should be taken in doses of 500 mg of calcium element, or less, throughout the day and with meals66. The consumption of calcium supplements with meals can also minimise the possible, although infrequent, secondary effects.

Calcium salts available on the Spanish market

There are various calcium salts which are now available and approved for sale in our country: calcium carbonate, pidolate, phostate, acetate and lactate. There are many pharmaceutical preparations which contain these salts, and their calcium element content varies from one to the other, the most common quantities being between 0.5 and 1g. According to data provided by IMS Health, the company charged with carrying out market studies of pharmaceutical products covering 90% of the country and extrapolated to the rest, calcium carbonate is the type of calcium salt most used in our country, with an annual growth rate higher than the others.

3.6. The importance of complementary therapy in osteoporosis

Adherence to treatment has recently been recognised as a key factor for the successful treatment of osteoporosis67. As might be expected, patients who take their medicine for osteoporosis regularly have the best results, both with regard to changes in bone mineral density, and, more importantly, in the reduction in the rate of fractures and decrease in mortality.
Thus, a study published by SIRIS et al.10 based on a broad population of postmenopausal women over 45 years of age, for whom had been indicated a biphosphonate as treatment for osteoporosis, observed that after 2 years of follow up, those women who took the treatment correctly (43%) had a reduction in risk of fractures, both vertebral and non-vertebral, of 21% compared to the 57% of patients which did not follow the treatment correctly. Similar results had previously been published by Caro et al., who found a reduction in the appearance of new fractures of 16% between those patients who complied as against those who did not. In this study, the follow up period was 2 years, and the drugs being evaluated were calcitonin, THS and the biphosphonates. The same authors repeated this study using a broader database, with a cohort of more than 38000 women affected by osteoporosis, and obtained the same figures: the lack of adherence to treatment was associated with an increase in risk of fracture of 17% after a follow up after 1.7 years.

Various studies have also endorsed these results. Hence, McCombs et al.11 carried out similar work, studying the adherence of a population of 58109 postmenopausal women of more than 55 years of age, diagnosed with osteoporosis, which showed that adherence to treatment over a period of 1 year translates into a greater reduction in risk of fracture, in both hip and vertebral.

4. Recommendations of the panel of experts

1. There is evidence at the highest level (1st, grade of recommendation A) that calcium and vitamin D supplements themselves reduce the risk of vertebral, non-vertebral and hip fractures, but at a minimum dose of 800 UI/day of vitamin D. In relation to calcium, the maximum benefit is obtained with doses equal to or greater than 1200 mg/day.

2. All the studies carried out with drugs which have been shown to reduce the risk of fracture in menopausal osteoporosis have used calcium and vitamin D supplements, for which reason it is advisable that all drug treatments indicated, be they anabolic, anti-resorptive, or dual action, be administered with calcium and vitamin D supplements. It is recommended that the measures intended to guarantee the compliance with treatment be reinforced and improved.

3. The calcium salts on the market in our country (Spain) for the treatment of osteoporosis are: calcium carbonate, pidolate, phosphate, acetate, and lactate, with calcium carbonate being the most used. There are many pharmaceutical preparations which contain these salts, and their calcium element content varies from one to another, with the most common quantities being between 0.5 and 1 g.

4. The absorption of the different calcium salts is similar, as long as they are administered with meals.

5. The ideal model for the administration of calcium is in divided doses and with meals.

Bibliography


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