Role of calcium and vitamin D in treating hip fracture patients

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INTRODUCTION
The proximal femur fracture, or hip fracture, is the most serious complication of osteoporosis, due to its high mortality and morbidity, as well as the significant social, economic and welfare cost it entails. In fact, the hip fracture is capable, on its own, of decreasing life expectancy in almost two years and one in five patients who suffer from it will require permanent health care1. Risk factors that favor this type of fracture include a greater tendency to fall and a decrease in bone resistance.

Since the discovery of vitamin D in 1922, it has been associated not only with bone health but also with muscle health2. Therefore, and although there is no evidence that determines its effectiveness, calcium and vitamin D administration is recommended for every patient with osteoporosis, to avoid their deficiency, which may be harmful. Thus, in most clinical practice guidelines, treatment with antiresorptive or anabolic drugs must be accompanied by an adequate intake of vitamin D, in addition to an appropriate amount of calcium, which usually ranges between 1,000 and 1,200 mg daily3–5.

SERUM VITAMIN D LEVELS IN PATIENTS WITH OSTEOPOROSIS
Calcium should be administered with the diet, whenever possible, while vitamin D is recommended to be taken as supplements. One controversial aspect is that of the serum levels of 25(OH) vitamin D [25(OH)D] that osteoporosis patients should reach, although most authors and scientific societies, including Spanish ones, consider that they would recommend serum concentrations to be above 30 ng/ml6–9. To achieve these aims, a daily dose of 800 to 1,000 IU of vitamin D (in Europe the vitamin D used is vitamin D3, known as colecalciferol) is advised, although its weekly, biweekly or monthly equivalent can also be administered10. This recommendation is especially relevant in patients who have already suffered a hip fracture. It is well known that the history of fragility fracture is, together with age, sex and bone mineral density (BMD), one of the main risk factors for osteoporotic fractures3–5. In fact, in the fracture risk prediction scales, such as the FRAX® scale or the Q-Fracture® scale, the presence of a fracture implies an increased risk of fracture in subsequent years. On the other hand, the risk of fracture is especially important if the fracture is recent. Thus, in a study carried out in Iceland11, people with a history of major osteoporotic fracture (hip, radius, humerus or clinical vertebral) reportedly presented an especially high risk of suffering another fracture in the first 24 months and that subsequently it stabilized, although always remaining above the risk of the population without a history of fracture. In the specific case of hip fracture, refracture incidence can reach up to 10% during the first years12.

On the other hand, the prevalence of hypovitaminosis D (serum levels of 25OHD <20 ng/ml) is very high in patients suffering from a hip fracture, reaching, for example, 36% in Finland13, 40-68% in United Kingdom14, between 50-78% in the US15, between 62-90% in Japan16 and between 67-91% in Spain17. These rates are much higher than those found in people without hip fracture, although lower than those found in institutionalized subjects18.

However, only a small percentage of patients who suffer a hip fracture receive antiosteoporotic treatment, including calcium and vitamin D supplements. Thus, in a study that included more than 85,000 hip fracture patients from different geographical areas (the USA, Spain and Korea), it was observed that only 11% of American patients, 25% of Spaniards, and 39% of Koreans, followed some type of antiosteoporotic treatment three months after discharge after the fracture19.

In a similar study20 carried out in the USA involving almost 100,000 patients with hip fractures, less than 30% received treatment during the first 12 months after discharge and this percentage decreased in recent years (2002-2011 period). Finally, a recent work carried out in Spain21 indicates that only 21% of hip fracture patients receive antiosteoporotic treatment
after hospital discharge, increasing this percentage to 32% and 38%, one month and 4 months afterwards, respectively. Nor is the percentage of patients receiving only calcium and/or vitamin D much higher. Thus, in a study conducted in Finland with more than 30,000 patients who had suffered a hip fracture, 13% of men and 22% of women received treatment with calcium and/or vitamin D, while this percentage reached 8% and 27%, respectively, in the case of bisphosphonates or other antiosteoporotic drugs. In another study in North America, Europe and Australia, more than half of the patients who underwent surgery after suffering a hip fracture, reportedly did not take calcium and/or vitamin D supplements, or did so irregularly, two months after being discharged. This percentage was close to 50% in another study carried out in Italy.

**Hypovitaminosis D in Patients with Hip Fracture**

In the absence of preventive treatment, hypovitaminosis D in patients who have suffered a hip fracture can cause proximal muscle weakness and reduce dynamic balance and gait speed, which would make it difficult to mobilize patients during the postoperative and rehabilitation period. In this regard, Di Monaco et al. observed that patients with hip fractures who had levels of 25(OH)D below 12 ng/ml had a worse recovery than those who had levels between 12 and 20 ng/ml, and these, in turn, were associated with a worse recovery than those with value between 21 and 29 ng/ml. On the contrary, no significant differences were found between this last group and those patients with levels ≥30 ng/ml. In addition, in some randomized controlled trials, although with a small number of patients, benefits have been reported in subjects who received vitamin D supplements after suffering a hip fracture. Thus, Harwood et al. observed that oral or parenteral vitamin D reduced the risk of falls after one year of presenting a hip fracture, in a study with 150 women who remained functionally independent before the fracture. Mak et al. found that a single dose of cholecalciferol load (250,000 IU) followed by 800 IU daily, reduced the risk of falls compared to the isolated daily dose in 218 patients (77% women) followed for 26 weeks. Finally, Bishoff-Ferrari et al. observed that the administration of high doses of vitamin D (2,000 IU/day) to patients discharged after suffering a hip fracture, reduced the rate of readmissions during the first 40% year. These authors have also observed that performing physical exercise at home together with the administration of 800 IU of vitamin D3 improved functional recovery after a hip fracture.

As stated above, calcium and vitamin D play an essential role in the treatment of osteoporosis. First, this is because, although there is no conclusive evidence of its effectiveness in reducing fractures when used in isolation, in virtually all clinical trials conducted to demonstrate the anti-fractural effects of antiosteoporotic medication, Patients received oral calcium and vitamin D supplements. Secondly, the existence of hypovitaminosis D increases the risk of fragility fractures and reduces the protection against fractures provided by some drugs widely used in clinical practice in the treatment of patients with osteoporosis. In the specific case of the hip fracture, Degli Esposti et al. carried out a cohort study that included 3,475 patients 50 years of age or older hospitalized for a vertebral or hip fracture during the years 2011 to 2015, and they were followed for 3 years. These authors found that the risk of refracture was 44% lower in patients treated with anti-osteoporotic drugs (anti-resorptive or anabolic) along with calcium and/or vitamin D, compared to those who did not receive supplements.
In addition, the incidence of new fractures was almost 65% lower in patients who received calcium/vitamin D supplements compared to those who only received antiresorptive or anabolic therapy.

On the other hand, mild and, especially, severe hypovitaminosis may increase the symptomatic hypocalcaemia that is sometimes observed after the administration of potent parenteral antiresorptive drugs, such as zoledronic acid or denosumab, widely used in the treatment of patients with hip fracture. In fact, in the classic study by Lyles et al. in which a 28% reduction in mortality was demonstrated in hip fracture patients treated with zoledronic acid, all patients also received calcium and vitamin supplements. D. In this regard, it is worth commenting that the beneficial effect on mortality has also been observed with other antiosteoporotic drugs, including calcium and vitamin D supplements themselves. For example, in the aforementioned cohort of Degli Esposti et al., patients treated with antiresorptive or anabolic drugs, in addition to calcium and vitamin D, presented a 64% reduction in the risk of overall mortality in relation to those who did not receive treatment. In addition, mortality rates were even lower among treated patients receiving calcium and/or vitamin D supplements. Finally, Cancio et al. in a recent retrospective study conducted in our country, with more than 30,000 patients out of 65 or more years with hip fracture followed for two years, observed that treatment with calcium and/or vitamin D reduced total mortality by 16% (HR: 0.84; 95% CI 0.79-0.88; p<0.001).

**CONCLUSION**

Although there is no evidence of its effectiveness when administered in isolation, it is considered that calcium and vitamin D should be prescribed to every patient with osteoporosis, especially if they have suffered a fragility fracture. In our usual clinical practice, it is advisable that patients with hip fractures receive an adequate intake of vitamin D (daily dose between 800-1,000 IU), in addition to an appropriate amount of calcium (between 1,000-1,200 mg/day), preferably with diet.

**Conflict of interests:** The authors declare no conflict of interest.
SELF ASSESSMENT TEST

1. The most serious osteoporotic fracture is:
   a. Vertebral
   b. Distal radius
   c. Humerus
   d. None of the above

2. The prevalence of vitamin D deficiency, defined as (serum 25OHD levels <20 ng/ml) is very high in patients suffering from a hip fracture, reaching in Spain figures between:
   a. 36-40%
   b. 40-68%
   c. 50-78%
   d. 67-91%

3. The presence of a fracture implies an increased risk of fracture in subsequent years. In the specific case of the hip fracture, the incidence of refracture can reach:
   a. 5%
   b. 10%
   c. 15%
   d. 20%

4. In randomized studies it has been proven that the administration of vitamin D produces:
   a. Fall risk reduction
   b. Reduction of the risk of new hip fractures
   c. Reduction of the risk of readmissions after a hip fracture
   d. All of the above is true

5. Point out the answer that seems false:
   a. Calcium and vitamin D should be prescribed to every patient with osteoporosis
   b. The amount of vitamin D should range between 800 and 1,000 IU/day
   c. The amount of calcium should range between 1,000 and 1,200 mg/day
   d. Pharmacological supplementation is preferable

Correct answers can be found on pages 23 and 24