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Vitamin D and fragility fractures

DOI: http://dx.doi.org/10.4321/S1889-836X2017000200008

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Introduction

The so-called fragility fracture is a low-energy fracture that results from a fall from a height equal to or less than its own, or which occurs in the absence of evident prior trauma. It appears when the bone structure, under specific loading conditions, undergoes biomechanical failure as it is unable to withstand the force received by having its resistance capacity degraded[1].

Among the factors that are related to the genesis of this bone deterioration vitamin D stands out in a relevant way. Indeed, the low levels of vitamin D induce a persistent increase of the level of PTH and with this a stimulus of the bone resorption, which determines A progressive decrease of the amount of bone formed and a thinning of all its structural elements, with the consequent decrease of the bone resistance. In addition, low vitamin D levels are associated with decreased tone and neuromuscular control, and therefore with the increased risk of falls that induce vitamin D deficiency.

In another section of this study, we have seen how vitamin D deficiency is a real health problem worldwide[2] given its high prevalence in all regions and in all population groups and not only in groups traditionally considered at risk[3,4]. Despite this, vitamin D deficiency is notoriously underdiagnosed possibly due to different factors[5], among which, undoubtedly, the failure to consider this disease an etiopathogenic agent stands out[6].

Its prevalence increases progressively in the elderly, in the institutionalized and in those who have suffered one or more fractures[7]. The rates of vitamin D deficiency in patients with hip fracture vary according to the series: 36% in Finland[8,9], 40-68% in the United Kingdom[10-12], 50-78% in the United States[13,14], 62-90% in Japan[15,16], 67-91% in Spain[17,18] and 96,7% in India[19], rates much higher than those found in "healthy" populations and lower than those found in institutionalized individuals[20]. These studies found that a large number of patients with hip fracture and inadequate vitamin D levels had previously suffered vertebral and non-vertebral fractures, excluding hip fractures[9,17-19]. Studies focusing on these fractures have demonstrated the existence of high rates of vitamin D deficiency in patients with peripheral fractures[11,21] and vertebral fractures[15,22,23]. This deficit has also been linked to the recurrence of vertebral fractures after kyphoplasty[24].

However, despite the clear link between low-energy fractures and vitamin D insufficiency, there is still controversy in the literature about the preventive effect of these, as not all studies support this hypothesis.

According to Chapuy et al.,[25] the administration of 1,200 mg/day of tricalcium phosphate associated with 800 IU/day of cholecalciferol to elderly women (mean age 84 years) for 18 months decreased the rate of hip fractures by 29% and non-vertebral fractures in 24%, an effect maintained at 3 years of treatment[26].

Subsequent meta-analyses[27,28] show that administering vitamin D alone is unlikely to prevent fragility fractures, although when administered with calcium supplements it does reduce the risk of hip fractures, especially in institutionalized patients.

Avenell[29] analyzed 53 trials (n=91,791) in which the efficacy of vitamin D administration, whether or not accompanied by calcium, was measured in the prevention of fractures in the community, nursing homes or hospitals. The results revealed that vitamin D was unlikely to be effective in preventing hip fracture, but there was a small reduction in hip fracture risk (9 trials, n=49,853, p=0.01) when given with calcium. The reduction was higher in high-risk, institutionalized populations (54 hip fractures per 1,000 per year or, similarly, nine hip fractures per 1,000 older adults per year) than in low-risk populations (8 hip fractures per 1,000 per year, which is equivalent to one hip fracture per 1,000 older adults per year). This association of vitamin D and calcium only showed evidence of moderate quality of absence of a statistically significant preventative effect on clinical vertebral fractures. However, it proved to be highly effecti-

ve in reducing the risk of any type of fracture (10 trials, n=49,976, RR 0.95, 95% CI 0.90 to 0.99), mainly of non-vertebral fractures.

This efficacy was corroborated by Bischoff-Ferrari et al.[28], after analyzing 12 randomized placebo-controlled trials for non-vertebral fractures (n=42,279 individuals) and 8 randomized clinical trials for hip fracture (n=40,886 individuals) in which they compare vitamin D with or without calcium and with calcium or placebo. They found that the prevention of non-vertebral and hip fractures with vitamin D supplements was dose dependent. In their study, higher doses of vitamin D (>400 IU) reduced non-vertebral fractures in individuals living in the community (-29%) and in institutionalized patients (-15%), and their effect was independent of Additional calcium supplements. The antifracture effect of vitamin D was more important in patients older than 70 years, as well as in those who had low levels of vitamin D at the start of the study, as long as adherence to treatment was adequate.

Now that we are aware that vitamin D is a fundamental element in the appearance of fragility fractures, we must ask: what role does it play in the repair of the same?

Fracture healing is recognized as a complex biological process regulated by genetic, cellular and molecular factors in which four superimposed stages are recognized: inflammation, soft callus formation, hard callus formation, and bone remodeling that behave as if two phases were treated, a catabolic and anabolic[30]. In this context, vitamin D has a plural role, with the cellular effects that it causes in each of the four phases of fracture healing, as outlined in Gorter[31] (Figure 1).

Clinical studies are scarce. We will consider them in a logical sequence.

1. Bioavailability of the vitamin D metabolites at the time of fracture and during the healing process of the same

Studies focusing on the determination of 25HCC, 125DHCC and 24,25[OH]2D3 are performed in small and heterogeneous series of fractured patients.

Based on 25HCC, the results analyzed[32-37] show that after a fracture their levels remained within the range of normality without significant differences with the control group throughout the healing process of the fracture, even up to 6 months after the injury[36]. In the study by Wölfl et al.[37], although there was no significant difference, 25HCC values were slightly lower in patients with low mineral density over the 8 weeks of the study. Only Meller et al.[38] found values significantly lower than 25HCC in 41 geriatric patients with hip fracture within 6 weeks of the fracture. These results contrasted with those found by the same author in an earlier study in which there was no significant difference in young patients with fractures. This led them to consider that it would be due to a deficiency of the hormonal system regulating the calcium metabolism in the geriatric patients.

Concentrations of 125DHCC undergo a significant initial reduction[32,33,35,39,40], up to 21% at 6 weeks after fracture[33], a reduction that gradually disappears during the subsequent year[39]. This reduction would reflect the consumption of this metabolite during healing at the fracture site, according to Tauber[35].

In contrast, Meller et al. found a significant increase of 125DHCC after the fracture that remained above the values of the control group in the 6 subsequent weeks, although it decreased gradually in that same period.

More random is the levels of 2425DHCC. At times, no significant difference was found in their values with respect to the control group[32,33], while at other times they were elevated[34] or significantly decreased[35], which contrasts with the animal model in which 2425DHCC levels are elevated[33].

2. The effect of vitamin D deficiency in cases of altered healing processes of the fracture

Low levels of vitamin D may influence the occurrence of refractures[41] and the rate of pseudo-arthrosis and the time of consolidation[42]. However, Boszczyk et al.[43], in a study with many deficiencies, did not consider vitamin D deficit as a risk factor for the lack of union of the fractures, did not find a difference in the prevalence of vitamin D deficiency in the group that consolidated the fracture and the one that did not.

In patients with problems of fracture consolidation, lower vitamin D levels have been observed than in healthy patients[35,42-46]. This vitamin deficiency would cause elevation of parathyroid hormone and alkaline phosphatase numbers and the decrease of existing calcium levels, a secondary hyperparathyroidism.

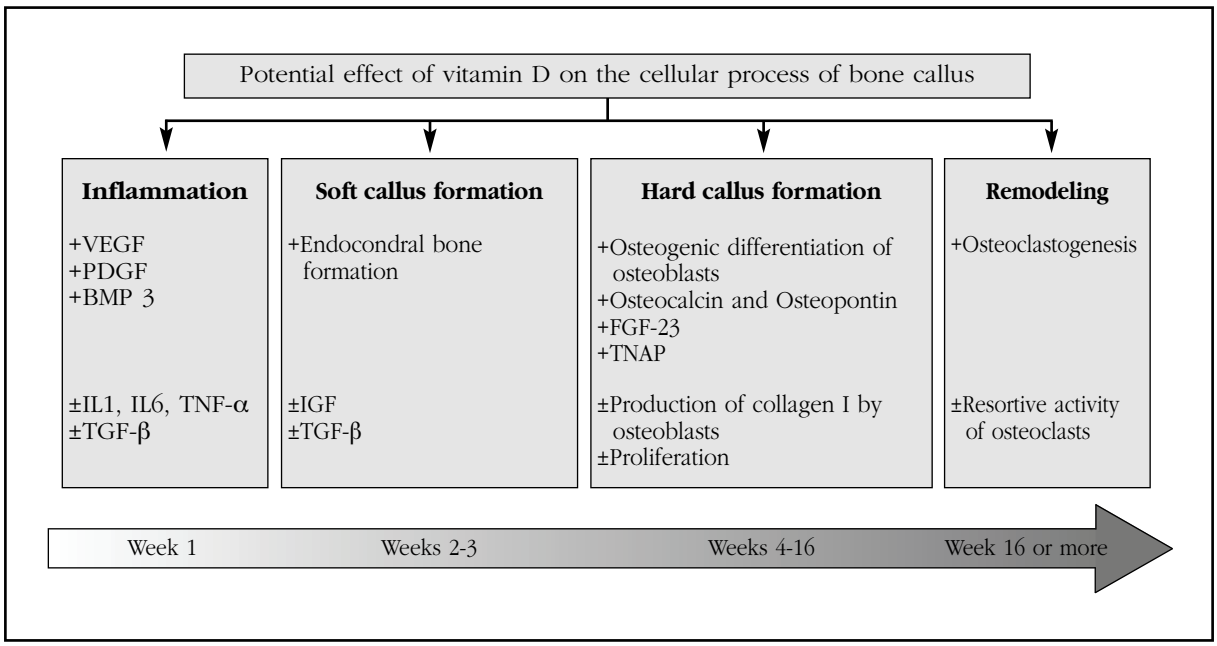
In the case of established pseudo-arthrosis, Haining et al.[47] found no significant difference in serum levels of 25HCC, 125DHCC and 2425DHCC, nor in those of bone markers. His hypothesis is that in patients with established pseudo-arthrosis the metabolic state of the bone normalized after fracture.

3. The effect of vitamin D supplements on fracture healing

Although abundant literature confirms the importance of obtaining and maintaining normal amounts of vitamin D in the serum to prevent falls and fractures, there is precarious evidence of the effectiveness of supplementation with vitamin D to improve the formation of bone callus[31,48,49].

We have only found two studies designed to quantify the healing process of fractures by administering vitamin D3 in terms of callus formation. Doetsch et al.[50] carried out a double-blind randomized study of 30 women with a humeral fracture who received vitamin D and calcium or placebo over 12 weeks. All underwent a radiographic and densitometric study focusing on the fracture focus at the time of fracture, at 2, 6 and 12 weeks. At 6 weeks, the improvement, expressed in g/cm^2, of the treated group was already significant.

Figure 1. Cellular effects of vitamin D during the four stages of fracture healing. + positive effect, - negative effect, ± uncertain effect (both + and -, or no effects described) in *in vitro* or *in vivo* studies. (Adapted from: Gorter EA, Hamdy NA, Appelman-Dijkstra NM, Schipper IB, The role of vitamin D in human fracture healing: a systematic review of the literature. Bone. 2014 Jul;64:288-97)[31]



Kolb et al.[51] conducted a prospective observational study in 94 women with a distal radius fracture who were given vitamin D and calcium. The main objective of the study was to detect the correlation between calcium metabolism and the formation of the fracture callus measured with pQCT. They found that patients who initially had normal levels of calcium and vitamin D had a greater area of callus of fracture. This finding was justified by a stimulating effect of calcium on osteoblasts and increased bone mineralization by normalizing 125DHCC levels above 30 ng/ml[52].

Other studies indirectly support the benefit of vitamin D administration to the formation of the fracture callus. Hoikka et al.[53] postulated that vitamin D could have an effect on fracture healing by finding elevated phosphatase numbers Alkaline solution after treatment for 4 months with 1α-OHD3 and calcium carbonate. It has even been proposed to apply local 2425DHCC in fragility fractures to accelerate its cure and prevent pseudoarthrosis[54].

In this same line, different types of therapeutic interventions with vitamin D and their metabolites have been proposed to improve the formation of the callus of fracture[55,56].

In conclusion:

- It is worth bearing in mind that deficiency in vitamin D levels condition the appearance and repair of low energy fractures.

- There are authors, such as van den Bergh et al.[57], who propose that all patients with osteoporotic frail fractures should be given vitamin D levels and vitamin D treatment should be initiated.

- The cost-benefit associated with the reduction of this type of fracture causes authors such as Sandmann[58] to propose that the public administration prioritize the supplementation of foods with vitamin D and calcium, as it offers significant potential for cost savings for health systems and social.

The reality is that it has improved the sensitivity of doctors on this health problem. Sprague[59] after consulting 397 orthopedic surgeons concluded that 65.8% of them routinely prescribed vitamin D to patients with fragility fractures and 25.7% to patients with other fractures.

Conflict of interest: The author declares that he has no conflict of interest.

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