Calcifediol in patients with hip fractures

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ABSTRACT

Vitamin D deficiency has a high prevalence in the elderly population. This condition can cause sarcopenia and osteoporomalacia, which are associated with an increased risk of falls and fractures, especially of the proximal femur. These fractures have devastating consequences in terms of mortality, disability, and healthcare and social costs. Considering that 60% of hip fracture patients have hypovitaminosis D, and a serum 25(OH)D₃ increase of 10 ng/ml reduces the risk of hip fracture by 20%, correction of vitamin D status is clearly essential. Among the available preparations of vitamin D, calcifediol is preferred in cases with liver disease, malabsorption, obesity, and concomitant use of corticosteroids. Calcifediol administration corrects vitamin D deficiency and suppresses parathyroid hormone within 1 week, reaching the serum 25(OH)D₃ threshold of 30 ng/ml in 2 weeks. Correction of hypovitaminosis D with calcifediol also improves muscle strength and physical performance, reducing the risk of falls. Evidence about the role of calcifediol in the management of hip fracture patients is still scarce. Compared with placebo, administration of calcifediol in combination with strengthening exercise led to increased overall survival in patients with hip fracture. The efficacy of calcifediol in rapidly normalizing vitamin D status might be particularly useful in patients at imminent risk of fracture, such as those with hip fracture who need to receive immediate treatment with anti-osteoporotic drugs.

KEYWORDS

Hip fractures, vitamin D deficiency, calcifediol, osteoporosis.

Background

Vitamin D deficiency has a high prevalence in the general population, and is estimated to affect more than one billion people across all races, ethnicities, and age groups [1]. Older people, in particular, are at high risk of vitamin D deficiency for several reasons: lifestyle (fewer or no outdoor activities), considerably reduced vitamin D synthesis in the skin, and reduced kidney function [2]. Hypovitaminosis D increases the risk of falls and fragility fractures, because of skeletal muscle impairment and osteoporomalacia, respectively [3]. Fragility fractures are “fractures that result from mechanical forces that would not ordinarily result in fracture, known as low energy trauma” [4]. Hip fracture is the main osteoporotic fracture in terms of morbidity, disability, poor quality of life, and mortality [5]. Fall and fracture prevention are public health goals [6], and include adequate intake of vitamin D and calcium. Despite evidence of vitamin D deficiency in about 80% of people with fragility fractures [7], vitamin D supplementation is commonly perceived by patients and physicians as an excessive drug treatment, which should be excluded to avoid polypharmacy [8]. In patients with fragility fractures, vitamin D deficiency is commonly treated with cholecalciferol or calcifediol [8]. The use of calcifediol should be preferred in the presence of impaired 25-hydroxylation, obesity, and malabsorption, and when rapid correction of vitamin D deficiency is needed to allow early administration of anti-osteoporotic drugs.

This article examines the rationale for calcifediol administration in patients with fragility hip fracture.

The role of vitamin D deficiency and secondary hyperparathyroidism in falls and fractures

Hypovitaminosis D is very common, especially in elderly patients with orthopedic diseases. According to a study including 1083 patients aged ≥70 years admitted to an orthopedic surgery department, 86% had insufficient serum 25(OH)D₃ levels. Similarly, a prospective study of 317 Japanese postmenopausal women (PMW) with osteoporotic fractures found that 78% had 25(OH)D₃ levels <20 ng/mL [9]. Considering the well-known musculoskeletal issues associated with vitamin D deficiency, and taking into account a dual effect of vitamin D on the risk of falls and fractures, the recommended intake of vitamin D for older people is 1000 IU/day. Moreover, evidence suggests that serum levels of 25(OH)D₃ ≥24 ng/ml significantly reduce the risk of falls5 and fractures in elderly patients [10].

Secondary hyperparathyroidism due to vitamin D deficiency further contributes to the pathophysiology of falls and osteoporotic fractures, as suggested by an observational study reporting a higher risk of concomitant hip and upper limb fra-
Fragility fractures in PMW affected by secondary hyperparathyroidism. It has been reported that institutionalized individuals show a high prevalence of vitamin D deficiency and secondary hyperparathyroidism, leading to significantly increased hip fracture risk (more than 7 times) in this population. In this context, serum 25(OH)D₃ and parathyroid hormone (PTH) measurement is a useful and cost-effective means of identifying patients at high risk of falls and fractures.

Vitamin D status also seems to affect the severity and type of hip fractures. Patients with hypovitaminosis D were found to have a 47% higher risk of severe hip fracture (Garden III-IV, Kyle III-IV) compared with those in whom serum 25(OH)D₃ >25 ng/ml was reported. Additionally, secondary hyperparathyroidism increased the risk of extracapsular fractures (+10% for every 1 pmol/L increase in PTH), which can be caused by a fall on the greater trochanter.

From a pathophysiological point of view, the susceptibility to fragility fractures observed in the context of vitamin D deficiency seems to be attributable to defective mineralization of the osteoid, an increase in the surfaces covered by the osteoid, which hinders mineralized bone tissue remodeling, and an increased presence of micro-cracks.

It has been demonstrated that with increasing age, serum 25(OH)D₃ and PTH progressively decrease and increase, respectively. A retrospective analysis of 268 patients investigated the relationship between vitamin D status, bone mineral density (BMD), and PTH in elderly populations with hip fractures. This study showed that with ageing there is a gradual reduction in 25(OH)D₃ and increase in serum PTH (p=0.044), and that almost 50% of patients had vitamin D deficiency (<10 ng/ml). Moreover, 74.6% of cases had a BMD T-score of ≤ −2.5 in any part of the femoral neck, hip, and lumbar vertebrae, while 27.6% of patients had BMD T-scores ≤ −2.5 in all three skeletal sites. The results showed that BMD was significantly higher in men than in women (p<0.001), particularly PMW, who showed a higher proportion of vitamin D deficiency.

In older people, hypovitaminosis D, low dietary calcium intake, and impaired bone microarchitecture are associated with a higher risk of hip fractures. A cross-sectional analysis of 1064 men aged under 65 years found vitamin D status to be irrelevant to changes in bone microarchitecture, while in elderly people, secondary hyperparathyroidism was associated with reduced trabecular volumetric BMD, cortical thinning due to endocortical resorption, and cortical trabecularization.

Optimal levels of serum 25(OH)D₃ are also needed to maximize the effects of anti-osteoporotic drugs. Indeed, a retrospective study including 111 elderly patients with osteoporosis investigated the relationship between vitamin D status, serum PTH, and BMD changes after treatment with zoledronate and denosumab, and found that patients with lower serum PTH had significant improvements in total hip BMD. In particular, serum 25(OH)D₃ levels of at least 20 ng/mL are required to reduce PTH as well as improve skeletal response to antiresorptives.

Vitamin D and skeletal muscle

Vitamin D has pleiotropic effects, influencing different organ and system functions. This hormone’s actions on skeletal muscle are expressed as short-term and long-term mechanisms involving non-genomic and genomic pathways, respectively (Figure 1). In the non-genomic pathway, vitamin D binds to a receptor located on the cell membrane or within the cytoplasm; this binding activates the cellular second messengers...
which regulate intracellular calcium flows, thus leading to an improvement in muscle contractility and an increase in the growth of skeletal muscle fibers [19].

In the genomic pathway, however, vitamin D enters the muscle cell and binds to its receptor (vitamin D receptor, VDR). This binding causes conformational changes in the receptor and subsequent translocation within the nucleus. In the core, VDR links to its heterodimeric partner (RXR) and forms the 1,25D-VDR-RXR complex; finally, this complex binds the vitamin D response element to DNA [19,20]. Furthermore, in the genomic pathway, vitamin D stimulates the proliferation and differentiation of muscle cells through gene transcription, at the DNA level, of myoblasts, inducing increased synthesis of muscle-specific proteins, such as myosin and calcium-binding protein, especially in type II fibers [21].

In elderly people, serum levels of 25(OH)D₃ and VDR expression in skeletal muscle cells are both reduced, leading to significant loss muscle mass and strength [22]. The identification of the VDR in human skeletal muscle supports the role of vitamin D in muscle cell proliferation and differentiation. A multicenter study including 401 PMW showed that women with hypovitaminosis D had reduced muscle strength and physical performance compared with those with normal serum 25(OH)D₃ [23].

A prospective study in 100 older patients with hip fracture investigated the association of serum levels of 25(OH)D₃ with handgrip strength, mid-upper arm muscle circumference (MUAMC), and length of hospital stay after fracture. Patients with hypovitaminosis D showed lower handgrip strength, but not lower MUAMC, suggesting that vitamin D deficiency might be associated with dynapenia (i.e., poor muscle strength only) but not with sarcopenia [24].

Taken together, the available evidence supports the idea that an adequate vitamin D status is essential for functional recovery after hip fracture, as confirmed by a prospective study including 1350 elderly patients hospitalized for hip fracture. In this study, serum 25(OH)D₃ levels were measured two weeks after surgery, and four classes were identified according to vitamin D status (class I: 25(OH)D₃<12 ng/mL; class II: 12-20 ng/mL; class III: 21-29 ng/mL; class IV: ≥30 ng/mL). A positive correlation between serum 25(OH)D₃ and functional recovery was found, although no differences between class III and class IV was reported [22].

Pharmacokinetics and pharmacodynamics of calcifediol

Calcifediol is the most abundant circulating vitamin D metabolite. It has the highest bioavailability (absorption, 62-77%), a high affinity for vitamin D binding protein (VDBP) (99%), and the epimer 25(OH)-3-epi-D binds and activates the VDR [26]. Calcifediol increases serum 25(OH)D₃ within 2 hours of administration and the level peaks after 4-8 hours; a 33% reduction of peak level is evident after 1 week [27]. Compared with cholecalciferol, calcifediol, due to its high polarity, has greater solubility in organic solvents such as water. Furthermore, given its high affinity for VDBP, calcifediol has higher bioavailability than cholecalciferol. The half-life of a drug is a pharmacokinetic parameter that indicates the time required to reduce the plasma concentration of the drug by 50% [28]. Orally administered calcifediol has a shorter half-life than cholecalciferol, but a longer one than calcitriol. Calcifediol has a half-life of about 15 days, cholecalciferol of 2-3 months, and calcitriol of 2-4 hours. Furthermore, calcifediol is useful in the presence of pathologies associated with poor intestinal absorption (Crohn’s disease, celiac disease, etc.) because it shows a higher intestinal absorption rate than cholecalciferol. Finally, due to the lower degree of entrapment in adipose tissue, calcifediol represents the best formulation in obese patients needing vitamin D supplementation [29].

The pharmacokinetics of calcifediol versus native vitamin D was investigated in a randomized double-blind study in 35 healthy PMW. The authors showed that calcifediol administered daily, weekly, or as a single bolus was 2-3 times more effective in increasing plasma concentrations of 25(OH)D₃ than vitamin D3. The threshold of 30 ng/ml of 25(OH)D₃ was achieved after approximately 2 weeks with calcifediol administration, whereas only 70% of women treated with cholecalciferol reached this level, and not before than two months [30]. Calcifediol therapy has good predictability of serum 25(OH)D₃ levels in the short term, along with effective PTH suppression [31]. Indeed, in PMW with vitamin D deficiency randomized to receive different dosages of calcifediol (20 µg/day, 40 µg/day, and 125 µg/week for 3 months), secondary hyperparathyroidism was effectively controlled by the intervention. Furthermore, calcifediol also seems to be safe, as suggested by a study in women aged 24 to 72 years treated with a dosage of 500 µg/month for 4 months, where no episodes of hypercalcemia or hypercalciuria were reported [32].

Efficacy of calcifediol in patients with fragility hip fracture

Evidence about the role of calcifediol in the management of hip fracture patients is still scarce [33]. A beneficial role of calcifediol in this population might be hypothesized if we consider indirect evidence of its effectiveness in treating secondary hyperparathyroidism due to vitamin D deficiency, in improving muscle strength and physical performance, and in reducing the risk of falls. In PMW treated with calcifediol, significant changes in 25(OH)D₃ and PTH were reported on the second day of follow up, along with improved knee extension strength (+17%) and limb function (OR 2.79, 95% CI 1.18-6.58), compared with patients treated with cholecalciferol [34]. In a double-blind randomized controlled trial, four months of treatment with calcifediol resulted in a significant improvement in gait speed (+18%) compared with vitamin D3 administration in PMW, even though no significant benefit on trunk sway was reported [35]. Another study investigating the effectiveness of two different daily doses of calcifediol (20 µg vs 30 µg) in osteopenic or osteoporotic women with vitamin D deficiency reported that both dosages rapidly corrected hypovitaminosis D, whereas the higher dosage significantly increased upper limb strength at 6-month follow up [36].
The effectiveness of calcifediol on muscle function and in fall reduction was demonstrated in a prospective observational study of 113 PMW with vitamin D deficiency which showed significant improvements in serum 25(OH)D$_3$ levels, muscle strength, and physical performance, along with a significant reduction in falls after 6 months of treatment with calcifediol (20µg, 4 drops/day) [37].

As regards direct evidence about the role of this pro-hormone of vitamin D, an old study including 58 elderly women with hip fracture treated with 1 g/day of calcium combined with 600 µg/week of calcifediol versus calcium only for 1 year showed an increased femoral neck BMD and correction of secondary hyperparathyroidism [33]. More recently, another study including 88 patients (aged 62 to 99 years) who had undergone surgery for hip fracture demonstrated that 3 mg oral calcifediol every 3 months plus daily strengthening of hip muscles for 1 year significantly improved survival at 1- and 4-year follow up compared with placebo [38].

**Conclusions**

Since vitamin D plays an important role in the musculoskeletal system, the achievement of sufficient serum levels of 25(OH)D$_3$ is essential for functional recovery after fragility fracture [39]. Hip fracture patients generally have comorbidities that impair vitamin D metabolism, such as liver disease, obesity, and malabsorption. Due to its pharmacokinetic profile and rapidity of action, calcifediol is effective and safe for the treatment of vitamin D deficiency, particularly in patients at imminent risk of fracture who need rapid correction of serum 25(OH)D$_3$ levels. Also, this approach should be combined with an adequate dietary calcium intake, considering that reduced calcium intake contributes to secondary hyperparathyroidism [40].

Therefore, an appropriate diet that includes foods rich in calcium or supplementation of this element where required, in association with calcifediol, should be guaranteed to adequately manage patients with fragility hip fractures.

**Table I**

Summarizes the results of the studies.

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>STUDY</th>
<th>NUMBER OF PATIENTS INVOLVED IN THE STUDY</th>
<th>TREATMENT</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff-Ferrari H.A. et al. (2012)</td>
<td>Randomized controlled trial</td>
<td>20 PMW, 4 groups</td>
<td>20 µg 25(OH)D$_3$ (calcifediol) daily; 20 µg (800 IU) vitamin D$_3$ daily; 140 µg calcifediol weekly; 140 µg (5600 IU) vitamin D$_3$ weekly, for 4 months</td>
<td>2nd day of follow-up: - significant changes in 25(OH)D$_3$ and PTH levels - improved knee extension strength (+17%) and limb function (OR 2.79, 95% CI 1.18-6.58) in PMW treated with calcifediol</td>
</tr>
<tr>
<td>Meyer O. et al. (2015)</td>
<td>Randomized controlled trial</td>
<td>20 PMW, 2 groups</td>
<td>Calcifediol (20 µg/day) vs cholecalciferol (20 µg/day)</td>
<td>- significant improvement of gait speed (+18%) in the group treated with calcifediol</td>
</tr>
<tr>
<td>Gonnelli S. et al. (2021)</td>
<td>Clinical trial</td>
<td>50 osteopenic/osteoporotic women with vitamin D insufficiency, two groups</td>
<td>Calcifediol (20 µg vs 30 µg/day) for 6 months</td>
<td>- rapid correction of hypovitaminosis D in both groups - modest but significant increase in upper limb strength after 6 months with 30 µg/day</td>
</tr>
<tr>
<td>Iolascon G. et al. (2017)</td>
<td>Prospective cohort study</td>
<td>113 PMW with osteoporosis and/or vitamin D deficiency</td>
<td>Calcifediol (20 µg, 4 oral drops/day) for 6 months</td>
<td>- improvement of serum levels of 25(OH)D$_3$ - improvement of muscle function - reduction of falls</td>
</tr>
<tr>
<td>Sosa M. et al. (2000)</td>
<td>Clinical trial</td>
<td>58 females over 65 years of age with osteoporosis and proximal femoral fractures, two groups</td>
<td>1 g calcium/day + 600 µg/week of calcifediol vs 1 g calcium/day for 1 year</td>
<td>- increase in femoral neck BMD - correction of secondary hyperparathyroidism in the group treated with calcium and calcifediol</td>
</tr>
<tr>
<td>Laiz A. et al. (2017)</td>
<td>Randomized controlled trial</td>
<td>88 patients (aged 62 to 99 years) who had undergone surgery for hip fracture</td>
<td>3mg oral calcifediol every 3 months + daily strengthening of hip muscles vs placebo</td>
<td>- increased survival at 1 and 4 years of follow up in the calcifediol and exercise group compared with placebo</td>
</tr>
</tbody>
</table>

BMD = bone mineral density; PMW = post-menopausal women; PTH = parathyroid hormone; IU = international units; OR = Odds Ratio; CI = confidence interval.
References