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 $25(OH)D_3$ 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 $25(OH)D_3$ 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 [1]. Fragility fractures are "fractures that result from mechanical forces that would not ordinarily result in fracture, known as low energy trauma" [3]. Hip fracture is the main osteoporotic fracture in terms of morbidity, disability, poor quality of life, and mortality [4]. Fall and fracture prevention are public health goals [5], and include adequate intake of vitamin D and calcium. Despite evidence of vitamin D deficiency in about 80% of people with fragility fractures [6], vitamin D supplementation is commonly perceived by patients and physicians as an excessive drug treatment, which should be excluded to avoid polypharmacy [7]. 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 $25(OH)D_3$ levels. Similarly, a prospective study of 317 Japanese postmenopausal women (PMW) with osteoporotic fractures found that 78% had $25(OH)D_3$ 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.[6] Moreover, evidence suggests that serum levels of $25(OH)D_3$ ≥24 ng/ml significantly reduce the risk of falls[5] 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-

gility fractures in PMW affected by secondary hyperparathyroidism [11]. 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 [12]. In this context, serum $25(OH)D_3$ and parathyroid hormone (PTH) measurement is a useful and cost-effective means of identifying patients at high risk of falls and fractures [13].

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 $25(OH)D_3$ >25 ng/ml was reported. Additionally, secondary hyperparathyroidism increased the risk of extracapsular fractures (+10% for every 1 pmol/L increase in PTH) [14], 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 [15].

It has been demonstrated that with increasing age, serum $25(OH)D_3$ 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 $25(OH)D_3$ 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 [16].

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 [17].

Optimal levels of serum $25(OH)D_3$ 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 $25(OH)D_3$ levels of at least 20 ng/mL are required to reduce PTH as well as improve skeletal response to antiresorptives [18].

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

Figure 1 Genomic and non-genomic pathway of vitamin D.
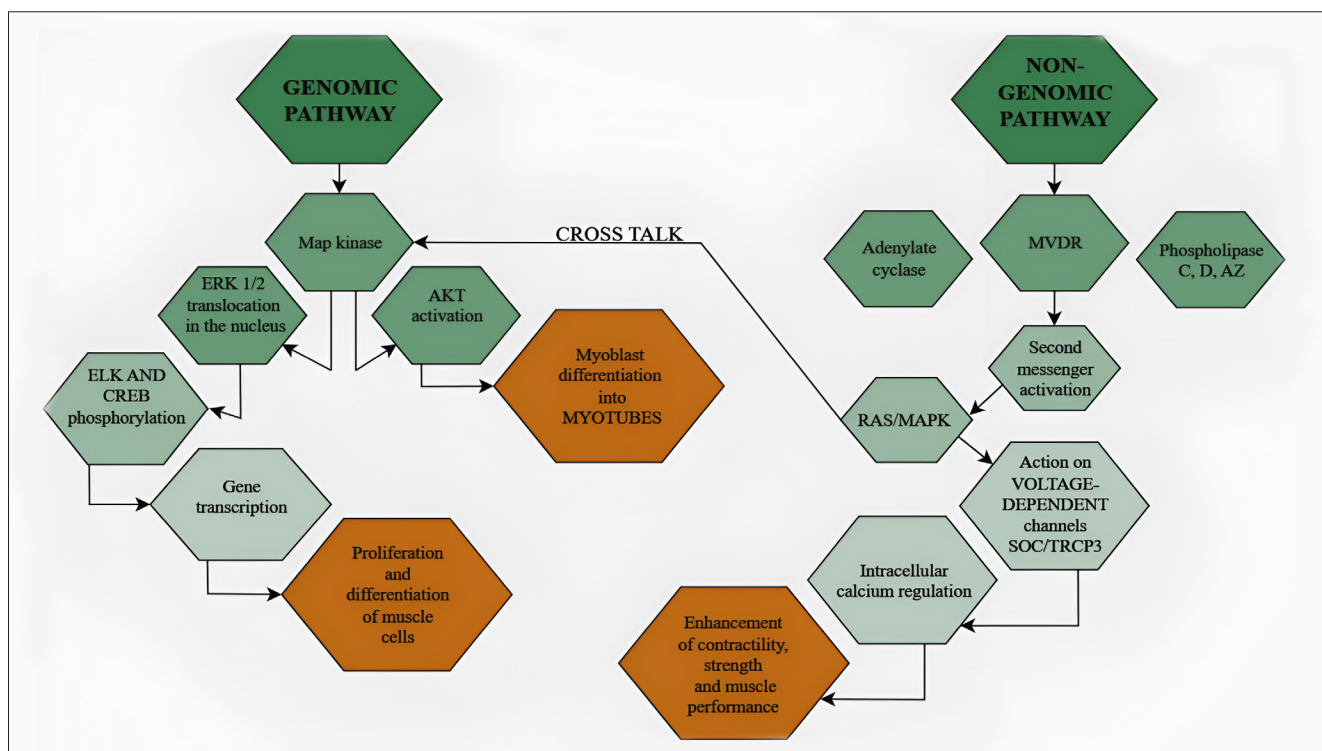
which regulate intracellular calcium flows, thus leading to an improvement in muscle contractility and an increase in the growth of skeletal muscle fibers [19].

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 $25(OH)D_3$ 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 $25(OH)D_3$ [23].

A prospective study in 100 older patients with hip fracture investigated the association of serum levels of $25(OH)D_3$ 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 $25(OH)D_3$ levels were measured two weeks after surgery, and four classes were identified according to vitamin D status (class I: $25(OH)D_3$<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 $25(OH)D_3$ and functional recovery was found, although no differences between class III and class IV was reported [25].

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 $25(OH)D_3$ 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 $25(OH)D_3$ than vitamin D3. The threshold of 30 ng/ml of $25(OH)D_3$ 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 $25(OH)D_3$ 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 $25(OH)D_3$ 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 musculo-skeletal 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.

AUTHORS	STUDY	NUMBER OF PATIENTS INVOLVED IN THE STUDY	TREATMENT	RESULTS
Bischoff-Ferrari H.A. *et al.* (2012)	Randomized controlled trial	20 PMW, 4 groups	20 μg 25(OH)D₃ (calcifediol) daily; 20 μg (800 IU) vitamin D₃ daily; 140 μg calcifediol weekly; 140 μg (5600 IU) vitamin D3 weekly, for 4 months	2nd day of follow-up: - significant changes in 25(OH)D₃ 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
Meyer O. *et al.* (2015)	Randomized controlled trial	20 PMW, 2 groups	Calcifediol (20 μg/day) *vs* cholecalciferol (20 μg/day)	- significant improvement of gait speed (+18%) in the group treated with calcifediol
Gonnelli S. *et al.* (2021)	Clinical trial	50 osteopenic/osteoporotic women with vitamin D insufficiency, two groups	Calcifediol (20 μg *vs* 30 μg/day) for 6 months	- rapid correction of hypovitaminosis D in both groups - modest but significant increase in upper limb strength after 6 months with 30 μg/day
Iolascon G. *et al.* (2017)	Prospective cohort study	113 PMW with osteoporosis and/or vitamin D deficiency	Calcifediol (20 μg, 4 oral drops/day) for 6 months	- improvement of serum levels of 25(OH)D₃ - improvement of muscle function - reduction of falls
Sosa M. *et al.* (2000)	Clinical trial	58 females over 65 years of age with osteoporosis and proximal femoral fractures, two groups	1 g calcium/day + 600 μg/week of calcifediol *vs* 1 g calcium/day for 1 year	- increase in femoral neck BMD - correction of secondary hyperparathyroidism in the group treated with calcium and calcifediol
Laiz A. *et al.* (2017)	Randomized controlled trial	88 patients (aged 62 to 99 years) who had undergone surgery for hip fracture	3mg oral calcifediol every 3 months + daily strengthening of hip muscles *vs* placebo	- increased survival at 1 and 4 years of follow up in the calcifediol and exercise group compared with placebo

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

References

1. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008;87(4):1080S-6S.

2. Timpini A, Pini L, Tantucci C, Cossi S, Grassi V. Vitamin D and health status in elderly. Intern Emerg Med. 2011;6(1):11-21.

3. Osteoporosis: assessing the risk of fragility fracture. London: National Institute for Health and Care Excellence (NICE); 2017 Feb. PMID: 32186835.

4. Pisani P, Renna MD, Conversano F, et al. Major osteoporotic fragility fractures: risk factor updates and societal impact. World J Orthop. 2016;7(3):171-81.

5. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009;339:b3692.

6. Chevalley T, Brandi ML, Cashman KD, et al. Role of vitamin D supplementation in the management of musculoskeletal diseases: update from an European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group. Aging Clin Exp Res. 2022;34(11):2603-23.

7. Maier GS, Horas K, Seeger JB, Roth KE, Kurth AA, Maus U. Vitamin D insufficiency in the elderly orthopaedic patient: an epidemic phenomenon. Int Orthop. 2015;39(4):787-92.

8. Tarantino U, Iolascon G, Cianferotti L, et al. Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology. J Orthop Traumatol. 2017;18(Suppl 1):3-36.

9. Yamanaka Y, Menuki K, Zenke Y, et al. Serum 25-hydroxyvitamin D concentrations in Japanese postmenopausal women with osteoporotic fractures. Osteoporos Sarcopenia. 2019;5(4):116-21.

10. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med. 2012;367(1):40-9.

11. Lv JT, Zhang YY, Tian SQ, Sun K. Serum of 25-hydroxyvitamin D and intact parathyroid hormone levels in postmenopausal women with hip and upper limb fractures. J Am Geriatr Soc. 2016;64(5):1068-72.

12. Shinkov A, Borissova AM, Dakovska L, et al. Differences in the prevalence of vitamin D deficiency and hip fractures in nursing home residents and independently living elderly. Arch Endocrinol Metab. 2016;60(3):217-22.

13. Johnson K, Suriyaarachchi P, Kakkat M, et al. Yield and cost-effectiveness of laboratory testing to identify metabolic contributors to falls and fractures in older persons. Arch Osteoporos. 2015;10:226.

14. Larrosa M, Gomez A, Casado E, et al. Hypovitaminosis D as a risk factor of hip fracture severity. Osteoporos Int. 2012;23(2):607-14.

15. Busse B, Bale HA, Zimmermann EA, et al. Vitamin D deficiency induces early signs of aging in human bone, increasing the risk of fracture. Sci Transl Med. 2013;5(193):193ra88.

16. Yu SJ, Yang Y, Zang JC, Li C, Wang YM, Wang JB. Evaluation of serum 25-hydroxyvitamin D3 and bone mineral density in 268 patients with hip fractures. Orthop Surg. 202;13(3):892-9.

17. Chaitou A, Boutroy S, Vilayphiou N, et al. Association of bone microarchitecture with parathyroid hormone concentration and calcium intake in men: the STRAMBO study. Eur J Endocrinol. 2011;165(1):151-9.

18. Mosali P, Bernard L, Wajed J, et al. Vitamin D status and parathyroid hormone concentrations influence the skeletal response to zoledronate and denosumab. Calcif Tissue Int. 2014;94(5):553-9.

19. Bollen SE, Atherton PJ. Myogenic, genomic and non-genomic influences of the vitamin D axis in skeletal muscle. Cell Biochem Funct. 2021;39(1):48-59.

20. Haussler MR, Jurutka PW, Mizwicki M, Norman AW. Vitamin D receptor (VDR)-mediated actions of $1\alpha,25(OH)_2$vitamin D_3: genomic and non-genomic mechanisms. Best Pract Res Clin Endocrinol Metab. 2011;25(4):543-59.

21. Girgis CM, Brennan-Speranza TC. Vitamin D and skeletal muscle: current concepts from preclinical studies. JBMR Plus. 2021;5(12):e10575.

22. Christakos S, Hewison M, Gardner DG, et al. Vitamin D: beyond bone. Ann N Y Acad Sci. 2013;1287(1):45-58.

23. Iolascon G, Mauro GL, Fiore P, et al. Can vitamin D deficiency influence muscle performance in postmenopausal women? A multicenter retrospective study. Eur J Phys Rehabil Med. 2018;54(5):676-82.

24. Gumieiro DN, Murino Rafacho BP, Buzati Pereira BL, et al. Vitamin D serum levels are associated with handgrip strength but not with muscle mass or length of hospital stay after hip fracture. Nutrition. 2015;31(7-8):931-4.

25. Di Monaco M, Castiglioni C, Di Carlo S, et al. Classes of vitamin D status and functional outcome after hip fracture: a prospective, short-term study of 1350 inpatients. Eur J Phys Rehabil Med. 2019;55(1):56-62.

26. Cianferotti L, Cricelli C, Kanis JA, et al. The clinical use of vitamin D metabolites and their potential developments: a position statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF). Endocrine. 2015;50(1):12-26.

27. Vieth R. Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. Eur J Clin Nutr. 2020;74(11):1493-7.

28. Andrade C. The practical importance of half-life in psychopharmacology. J Clin Psychiatry. 2022;83(4):22f14584.

29. Cesareo R, Falchetti A, Attanasio R, Tabacco G, Naciu AM, Palermo A. Hypovitaminosis D: is it time to consider the use of calcifediol? Nutrients. 2019;11(5):1016.

30. Jetter A, Egli A, Dawson-Hughes B, et al. Pharmacokinetics of oral vitamin D(3) and calcifediol. Bone. 2014;59:14-9.

31. Minisola S, Cianferotti L, Biondi P, et al. Correction of vitamin D status by calcidiol: pharmacokinetic profile, safety, and biochemical effects on bone and mineral metabolism of daily and weekly dosage regimens. Osteoporos Int. 2017;28(11):3239-49.

32. Russo S, Carlucci L, Cipriani C, et al. Metabolic changes following 500 µg monthly administration of calcidiol: a study in normal females. Calcif Tissue Int. 2011;89(3):252-7.

33. Sosa M, Láinez P, Arbelo A, Navarro MC. The effect of 25-dihydroxyvitamin D on the bone mineral metabolism of elderly women with hip fracture. Rheumatology (Oxford). 2000;39(11):1263-8.

34. Bischoff-Ferrari HA, Dawson-Hughes B, Stöcklin E, et al. Oral supplementation with 25(OH)D3 versus vitamin D3: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. J Bone Miner Res. 2012;27(1):160-9.

35. Meyer O, Dawson-Hughes B, Sidelnikov E, et al. Calcifediol versus vitamin D3 effects on gait speed and trunk sway in young postmenopausal women: a double-blind randomized controlled trial. Osteoporos Int. 2015;26(1):373-81.

36. Gonnelli S, Tomai Pitinca MD, Camarri S, et al. Pharmacokinetic profile and effect on bone markers and muscle strength of two daily dosage regimens of calcifediol in osteopenic/osteoporotic postmenopausal women. Aging Clin Exp Res. 2021;33(9):2539-47.

37. Iolascon G, Moretti A, de Sire A, Calafiore D, Gimigliano F. Effectiveness of calcifediol in improving muscle function in post-menopausal women: a prospective cohort study. Adv Ther. 2017;34(3):744-52.

38. Laiz A, Malouf J, Marin A, et al. Impact of 3-monthly vitamin D supplementation plus exercise on survival after surgery for osteoporotic hip fracture in adult patients over 50 years: a pragmatic randomized, partially blinded, controlled trial. J Nutr Health Aging. 2017;21(4):413-20.

39. Chevalley T, Brandi ML, Cavalier E, et al. How can the orthopedic surgeon ensure optimal vitamin D status in patients operated for an osteoporotic fracture? Osteoporos Int. 2021;32(10):1921-35.

40. Moretti A, Liguori S, Paoletta M, et al. Bone fragility during the COVID-19 pandemic: the role of macro- and micronutrients. Ther Adv Musculoskelet Dis. 2023;15:1759720X231158200.