THE VITAMIN D STORY – A 2023 UPDATE ON FRACTURES AND FALLS

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Abstract. *Vitamin D is more than just a vitamin – it is a real hormone with great importance for the bone-muscle unit and for many other tissues and biological processes in the human organism. This narrative review is focused on the available evidence for skeletal effects of vitamin D – possible reduction of falls and fractures in elderly people. We follow the natural path of the vitamin D story with the growing interest and hopes followed by some disappointment and then by mere realism. A number of meta-analyses are discussed in an attempt to better describe the available knowledge and the up-to-date consensus on vitamin D. In short, the existing evidence shows a modest effect of vitamin D supplements on fractures and falls, which may be comparable to that of some older antiresorptives. Current consensus statements identified the following subgroups that would benefit most from vitamin D supplements: the elderly, the institutionalized, those with vitamin D insufficiency/deficiency or secondary hyperparathyroidism, those at higher risk of fractures and falls (osteoporosis included). As fractures and falls seem to be dependent from the baseline levels of vitamin D, serum levels should be measured and supplementation should be tailored accordingly (800-2000 IU daily). A combination with daily calcium of 600-1200 mg, is highly recommended to enhance the skeletal effects of vitamin D. The clinician should be aware of the low patients' adherence with long-term supplements. In conclusion, vitamin D is a cheap and quite effective option to improve bone health with possible beneficial pleiotropic extra-skeletal effects.*

Key words: *vitamin D, deficiency/insufficiency, supplementation, fractures, falls*

Introduction

Vitamin D is more than a vitamin – it is a real hormone with an intra-nuclear steroid receptor and a variety of genomic and non-genomic effects. Vitamin D came under scrutiny mainly due to advances in osteoporosis and metabolic bone disease. In the meantime a number of extra-skeletal actions came into focus and now are relatively well described. The vitamin D story received steeply growing interest around the millennium years and reached a peak around 2010-2012. Great hopes existed for the use of vitamin D as help in a great variety of diseases – cardio-vascular, oncologic, inflammatory ones and many others. Accumulating evidence more or less brought realism to these expectations with the skeletal effects being regarded as having firm proofs for benefit and the extra-skeletal effects remaining as a field for future research.

Many early studies described the clinical effects of vitamin D supplements on skeletal outcomes, such as falls and fractures [1, 2]. Unfortunately, none of those studies was powered enough to definitely resolve all the open questions. All these studies varied in the population included, the intervention used, the events reported and in the way of ascertainment. One possible way to correct for this heterogeneity was to perform meta-analyses in an attempt to increase statistical power also.

Beneficial effects of vitamin D supplements on falls and fractures – the decade of optimism

One of the first robust meta-analyses of the risks of falls was that of Bischoff-Ferrari et al. published in 2004 [3]. The primary analysis included 5 double-blind randomized studies (RCTs): 3 of them used 800 IU/day, while one applied 400 IU only and the fifth one – an active vitamin D metabolite. Four of the studies co-administered 1200 mg daily calcium. The study population was rather old – mean age of 70 years, the majority were women (81%). The treatment duration was also very variable – between 2 months and 3 years. However, the authors were able to register a reduction in the pooled odds ratio (OR) for falling by 22% and calculated the Number Needed to Treat (NNT) – 15 person-years to prevent one major fall [3]. The authors did an auxiliary (sensitivity) analysis by adding 5 additional studies and

increasing the number of participants to 10,001. The risk reduction was lower in this analysis – only 13%. The small sample sizes prevented any stratification based on sex, type or dose of vitamin D and calcium. In the end, the authors made the conclusion that vitamin D combined with calcium supplementation appeared to reduce the risk of falls among elderly people at stable health [3].

One year later (in 2005) Bischoff-Ferrari et al. published a similarly robust meta-analysis, focused on fracture prevention [4]. It combined 5 RCTs for hip fracture (n = 9294) and 7 RCTs for nonvertebral fracture risk (n = 9820). The vitamin D dose was 400 IU/d in 2 RCTs, while the other 5 RCTs used 700 to 800 IU/d. Four studies only used calcium supplements. The age of the participants was even higher – mean age 79 years, and 68% were female. The primary result was non-significant – a pooled relative risk of hip fractures of 0.88 with vitamin D (12% reduction). This was assigned to the heterogeneity of studies and those with higher vitamin D doses (700-800 IU/d) were pooled separately. Thus, in 3 such trials vitamin D reduced hip fracture risk by 26%, translating into NNT of 45 with treatment duration of 24 to 60 months. The authors suggested that 400 IU daily vitamin D did not reduce hip fracture risk and that higher risk reduction was seen in individuals with higher achieved serum 25(OH)D levels. Again, the final conclusion was that oral vitamin D supplementation between 700 to 800 IU/d appeared to reduce the risk of hip and any nonvertebral fractures in elderly persons [4].

The sufficient dose of vitamin D for fracture prevention was addressed in an exploratory review published 2 years later by Bischoff-Ferrari [5]. It plotted together 6 major studies and made a breakthrough by showing the exact matches between supplementation dose, achieved serum 25(OH)D levels and resulting hip fracture relative risk reduction. A dose of 600 IU vitamin D daily was the starting point for risk reduction. The author provided a clear guidance for supplementation based on those studies (see table 1.).

The author identified 2 main factors: sufficient vitamin D dose and adherence. It was clearly stated that the dose of vitamin D in the management of osteoporosis should be no less than 700-800 IU per day and the desirable range of serum 25(OH) D should be at least 75 nmol/l. 700 to 1,000 IU of vitamin D per day might bring 50% of younger and older adults up to 75-100 nmol/l, therefore higher doses are needed in older adults. In their article Bischoff-Ferrari highlighted the problem of poor adherence by citing figures from the RECORD study, showing 1-year adherence of 60% and 2-year adherence below 50% [6]. Giving larger intermittent doses was then thought to be one possible way to overcome poor adherence.

However, this same narrative analysis showed that large intermittent doses of vitamin D were no better than daily supplementation with 100,000 ergocalciferol every 4 months achieving similar results as 400 IU daily, while 300,000 IU once yearly did not have any effect on fractures and falls [5]. These findings were replicated in 2 studies almost 10 years later: the one giving 100,000 UI once monthly, the second one – 500,000 IU once per year [7, 8]. The first study (the ViDA trial) applied a bolus of 200,000 IU first followed by 100,000 IU vitamin D monthly but failed to prevent fractures [7]. On the contrary, in healthy volunteers with baseline serum 25(OH)D of 63 nmol/l there was a trend for higher fracture risk. In the second study the large annual bolus administered to elderly women with a baseline 25(OH)D of 50 nmol/l increased falls and fractures [8].

The efforts to describe the anti-fracture effect of vitamin D supplements better led to the next big meta-analysis by Bischoff-Ferrari [9]. It pooled together 11 double-blind RCTs with 31,022 people (mean age of 76 years; 91% women) receiving oral vitamin D supplementation (daily, weekly, or every 4 months), with or without calcium. The primary end points were the incidence of hip and any nonvertebral fractures as compared with placebo or calcium alone according to Cox regression analyses. This study provided further insight into optimal serum levels of 25(OH) D. The authors stratified the participants according to their baseline vitamin D status and found signif-

Table 1. What fracture reduction can be achieved by different doses of vitamin D – modified after Bischoff-Ferarri 2007 [5] (80% adherence was assumed)

	Expected mean 25(OH)D serum concentrations	Anti-fall efficacy	Anti-fracture efficacy
Oral daily 400 IU cholecalciferol	60-65 nmol/l	No	No
Oral daily 700-800 IU cholecalciferol	74-110 nmol/l	YES	YES
Oral 100,000 IU cholecalciferol every 4 months	74 nmol/l	?	YES
Annual 300,000 IU ergocalciferol	45-65 nmol/l	No	No

icant differences in individuals with serum levels ≥ 61 nmol/l compared to those with levels < 30 nmol/l. The observed risk reduction was 37% for hip fractures and 31% for non-vertebral fractures [9].

The overall effect of vitamin D supplementation on fracture risk was non-significant: 10% reduction in the risk of hip fracture and 7% in the risk of any non-vertebral fracture. Comparing quartiles of vitamin D intake, a fracture risk reduction was registered only at the highest actual intake of 792 to 2000 IU/d: 30% reduction in hip fractures and 14% – in non-vertebral fractures. The authors concluded that high-dose vitamin D supplementation (≥ 800 IU daily) was expected to be somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in people 65 years of age or older with more pronounced effect in institutionalized individuals [9].

These studies by Bischoff-Ferarri and coworkers marked the peak interest in the vitamin D story. In this time period a number of manuals and textbooks on vitamin D were published; among them are the books by Michael Hollick and the one edited by D. Feldmann and co-workers [10, 11]. The first decade of the 21st century might be regarded as the great rise of vitamin D popularity. What should not be omitted is that most robust data had come from meta-analyses of RCTs with great variety in desired vitamin D ranges, supplementation doses and regimens. It should also be noted that most of the trials analyzed the combined effects of vitamin D plus calcium versus calcium alone or placebo. In the second decade of the 21st century further RCTs accumulated with observational and retrospective studies in addition. This allowed more detailed testing of the vitamin D effects on falls and fractures based also on improved statistical methods.

The accumulation of less optimistic evidence about vitamin D – the decade of realism

A number of large analytical reviews and meta-analyses were published after 2010-2012. The association of serum vitamin D with hip fractures in the elderly was questioned in a meta-analysis summarizing 28 studies, 61,744 elderly subjects, 15.8% of whom had sustained of hip fractures [12]. Therefore, the study population was at rather high risk for fractures. In the lowest as compared to the highest categories of vitamin D in the elderly, pooled OR of hip fractures was 1.80 (P ≤ 0.001). The OR of a hip fracture was highest in case-control studies (2.16) followed by cohort and case-cohort studies (1.52 and 1.41, respectively; P ≤ 0.001). This analysis confirmed the notion that low serum vitamin D levels in the elderly were associated with an increase in the odds of hip fracture [12].

One of the less optimistic meta-analyses was a Cochrane review performed in 2014 by A. Avenel et al. [13]. It included 27,000 patients and showed that vitamin D alone was unable to reduce fractures or falls. In contrast, the combination of vitamin D plus calcium was associated with a fracture incidence reduction by 16% for hip fractures and 6% for any fracture. In addition to the importance of added calcium this study revealed a greater anti-fracture effect in institutionalized individuals, thus defining a patient profile that would be expected to benefit most from vitamin D supplementation [13]. The inability of vitamin D alone to significantly reduce fractures and falls was also replicated in the meta-analysis by Bolland et al. [14]. The pooled analysis included 81 studies with only 6% of the participants being vitamin D deficient. As a result, the supplementation with vitamin D alone did not reduce the incidence of fractures and falls [14].

Despite the emerging trend for vitamin D supplementation at higher dosages (> 2000 IU/d) the most recent publications advocated a rather moderate approach. A meta-analysis of RCTs tried to describe the effect of vitamin D supplementation on risk of fractures and falls according to dosage and interval [15]. The final analysis included 32 studies. The vitamin D dosage was stratified in 3 subgroups: below 800 IU/d, 800-1000 IU/d and > 1000 IU/d. The authors were able to show that the daily vitamin D dose of 800 to 1000 IU was able to reduce the risk of osteoporotic fractures and falls (OR 0.87 and 0.91 respectively, p < 0.05), while higher or lower doses were not. Daily dosing was better than intermittent one in the reduction of falls (Risk ratio 0.85 versus 1.01). The effect of vitamin D supplementation on falls was more pronounced in community-dwelling individuals (risk ratio 0.91, p < 0.05) and in participants with baseline serum vitamin D levels ≤ 20 ng/dl (50 nmol/l). Therefore, this analysis recommended moderate doses and daily supplementation with larger effect on falls in community-dwelling elderly and those with confirmed vitamin D insufficiency/deficiency [15].

A Bayesian network meta-analysis and meta-regression of randomized controlled trials examined 33 studies with 83,083 participants [16]. The authors tested different doses of vitamin D with/without different modes of calcium supplementation. They came to the conclusion that the best way to reduce total as well as hip fractures was the combined sup-

plementation with calcium and 700-800 IU vitamin D3 daily, while the impact of 700-800 IU vitamin D3 daily only (without calcium) was very slight. Of note, > 800 IU vitamin D per time (but not daily) showed statistically increased risk of fracture. In addition the authors looked at the confounding effect of the body mass index (BMI) on the effect of vitamin D supplements on fractures. Their meta-regression analysis of the association between BMI and relative risks of total fractures confirmed that if the same supplemental dose was used, individuals with lower BMI would be expected to get larger fracture protection [16].

All this accumulating data led to the conclusion that moderate supplementation with calcium and vitamin D was the best way to achieve anti-fracture and anti-fall effects. Accordingly, Anagnostis et al. published a review article focusing on the evidence of a U-shaped effect of vitamin D supplementation on fracture risk [17]. They advocated against high vitamin D doses (such as 60-100,000 IU once monthly or > 4000 IU per day) which might even increase the fracture risk. Their recommendation was to apply 800 IU/d plus 1000-1200 mg calcium daily in elderly populations and especially in vitamin D-deficient subgroups. The treatment duration was also addressed – at least 3-5 years with good compliance [17].

Recent Consensus Statements and Recommendations

This moderate approach has been the foundation of the Consensus Statement on vitamin D deficiency drafted by a group of experts from Central and Eastern Europe [18]. The skeletal effects of vitamin D were regarded as very well supported by current evidence and were in the center of the discussions. In addition many other important topics concerning the extra-skeletal effects of vitamin D had been addressed. Concerning falls and fractures a good level of agreement was reached and three main recommendations were issued (see Table 2).

This statement reflected the authors' view that all patients at risk for fractures and falls might benefit from daily supplementation with moderate doses of 800-2000 IU vitamin D3 [18]. Moreover, the treatment of osteoporosis might work better in vitamin D sufficient individuals indicating the need for selective screening and correction of possibly diagnosed vitamin D insufficiency/deficiency. Target levels were defined as serum 25(OH)D between 75 and 125 nmol/l [18].

A few months after the publication of the Central and Eastern European Expert Consensus the European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) published its 2022 Update on the role of vitamin D supplementation in the management of musculoskeletal diseases [19]. The Working Group focused on elderly subjects with levels of 25(OH) below 50 nmol/l as the best candidates for supplementation with vitamin D and calcium. It defined the oral regimen as the most beneficial one, preferably daily or weekly, and with moderate doses (1000 IU daily). They determined preferable serum 25(OH)D levels 50-100 nmol/L, with those up to 125 nmol/l being still possible [19].

We should also be familiar with the Bulgarian Guide on Good Clinical Practice in relation to Vitamin D, published in 2019 [20].

Vitamin D supplementation affects the osteoporosis medications

The question of vitamin D supplementation during osteoporosis treatment had been very well

Table 2. Main recommendations on musculoskeletal disorders of the Central and Eastern European Expert Consensus Statement on vitamin D deficiency [18]

Consensus statements	% agreement	
1. In osteoporosis patients, a supplementation of 800–2000 IU/day, with oral cholecalciferol (vitamin D3) is recommended in combination with calcium, if indicated.	9 (strongly agree)	30%
	8	10%
	7 (agree)	60%
	6	0%
2. Vitamin D deficiency may impair the response to the osteoporosis treatment, thus screening of the 25(OH)D level and correction of vitamin D deficiency before starting the osteoporosis treatment with antiresorptive medications is recommended.	5 (neutral)	0%
	4	0%
	3 (disagree)	0%
3. In patients with an increased risk of falls or fractures, a supplementation of 800–2000 IU/day is recommended.	2	0%
	1 (strongly disagree)	0%

reviewed in a Position Statement by Korean experts [21]. The difficulty lies in the fact that low serum vitamin D (< 15-20 ng/ml) had been used as an exclusion criterion in many randomized trials (e.g. with Denosumab or Romosozumab). However, clinical trials found abaloparatide effective in patients with serum 25(OH)D > 15 ng/mL at enrollment, while both teriparatide and romosozumab were effective in women with serum 25(OH)D ≥ 20 ng/mL and low bone mass or osteoporosis [22-24].

At the time the main clinical trials with antiresorptive drugs (bisphosphonates, raloxifene) were performed, serum levels were not routinely measured. However, a great number of ad hoc and post hoc analyses have provided evidence for a beneficial effect of vitamin D sufficiency and supplementation in this particular setting. Observational studies have indicated that baseline serum 25(OH)D > 20 ng/mL is associated with higher BMD and lower fracture risk in patients receiving bisphosphonate or raloxifene treatment [25]. In a set of clinical trials baseline serum 25(OH)D did not affect the efficacy of risedronate, denosumab, or raloxifene on BMD and fracture risk when provided with calcium and vitamin D supplements [26]. This means that the initial difference in the risk of fractures and falls due to low vitamin D status might be overcome by appropriate supplementation. On the other hand, the mode of action of bisphosphonates is highly dependent on secondary mineralization. Vitamin D plays a crucial role in bone mineralization and is therefore well needed in this scenario. It should also be noted that serum 25(OH)D < 30 ng/mL had been associated with a higher risk of acute-phase response after the first dose of intravenous nitrogen-containing bisphosphonates, compared to those with higher vitamin D status [27].

Based on this body of evidence the Korean experts concluded that “the target serum 25(OH)D levels of the patients on anabolic agents (such as teriparatide, abaloparatide, and romosozumab) may be > 20 ng/mL, whereas 30 ng/mL may be more beneficial for patients treated with antiresorptives (such as bisphosphonates, denosumab, and raloxifene) [21].

Vitamin D and frailty – the role of the bone-muscle unit

A very intriguing direction of research is the link of vitamin D insufficiency/deficiency with frailty and osteosarcopenia. The body system underlying this link is the muscle–bone unit [28]. Basic science has identified at least four central mechanisms causing frailty and osteosarcopenic obesity in vitamin D-deficient individuals: dysregulated immunity/inflammation, altered lipogenesis and lypolysis, altered bone-skeletal muscle crosstalk and finally – effects on calcium absorption/utilization and synthesis of PTH [29]. A great number of studies have examined different indicators of physical performance such as grip strength, gait speed, everyday activities, etc. [30, 31]. Results based on different quality of life questionnaires have been published. However, the study populations, the methods used and the final results differ substantially across trials. A recent systematic review and meta-analysis tried to summarize the effects of vitamin D monotherapy on indices of sarcopenia in community-dwelling older adults [32]. Ten studies were included in the final analysis. Vitamin D supplements as monotherapy had no effect on muscle mass, strength, or any other physical performance parameters. The only positive result was decreased short physical performance battery scores (indicating negative effects on physical performance) [32]. Detailed reviews have indicated that additional randomized controlled trials are required to better discern the synergistic effect of exercise, nutritional interventions, and drug compounds in osteosarcopenia . An even difficult situation is found in osteosarcopenic obesity, an epidemic in older population in the westernized world. To better define the role of vitamin D in the pathogenesis and treatment of this condition large observational and interventional studies representative of different sex, age and race are still needed [31].

Conclusion

The vitamin D story resembles actually the challenges facing the main characters in many novels – rises, falls, plateaus. These perturbations are quite well described in the article by Gallagher and Rosen [33]: “Clinical trials of vitamin D, aimed at clarifying its effect in the prevention of multiple diseases, […], disappointingly, […] have not fulfilled the expectations many had 10 years ago […] In almost every trial, various doses and routes of administration did not show efficacy of vitamin D in preventing fractures, falls, […]” [33].

As a matter of fact, the existing evidence shows a modest effect of the vitamin D supplements on fractures and falls, which may be comparable to that of some older antiresorptives (calcitonin, clodronate and etidronate). The pleiotropic (extra-skeletal) effects of vitamin D are achieved at much higher serum 25(OH)D levels (> 40-50 ng/ml) and are much less robustly documented. Current evidence identi-

fies the following subgroups that would benefit most from vitamin D supplements: the elderly, institutionalized people, those with vitamin D insufficiency/deficiency or secondary hyperparathyroidism, those at higher risk of fractures and falls (including OP). As fractures and falls seem to be dependent from the baseline levels of vitamin D, serum levels should be measured and supplementation should be tailored accordingly (800-2000 IU daily). A combination with daily calcium of 600-1200 mg is highly recommended. And in the end the clinician should be aware of the fact that the effects of vitamin D supplements are quite different in osteoporosis and vitamin D deficiency (as they are 2 distinct bone disorders).

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Библиография / References

1. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med. 1992; 327(23): 1637-42. doi: 10.1056/NEJM199212033272305.
2. Meunier P. Prevention of hip fractures by correcting calcium and vitamin D insufficiencies in elderly people. Scand J Rheumatol Suppl. 1996; 103: 75-8. doi: 10.3109/03009749609103753.
3. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA. 2004; 291(16): 1999-2006. doi: 10.1001/jama.291.16.1999.
4. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005; 293(18): 2257-64. doi: 10.1001/jama.293.18.2257.
5. Bischoff-Ferrari HA. How to select the doses of vitamin D in the management of osteoporosis. Osteoporos Int. 2007; 18(4): 401-7. doi: 10.1007/s00198-006-0293-9.
6. Grant AM, Avenell A, Campbell MK, et al; RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low – trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo – controlled trial. Lancet. 2005; 365(9471): 1621-8. doi: 10.1016/S0140-6736(05)63013-9.
7. Khaw KT, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol. 2017; 5(6): 438-447. doi: 10.1016/S2213-8587(17)30103-1.
8. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010; 303(18): 1815-22. doi: 10.1001/jama.2010.594.
9. 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. doi: 10.1056/NEJMoa1109617.
10. Hollick M (ed.). Vitamin D. Physiology, molecular biology and clinical applications. 2nd edition, Springer, 2011.
11. Feldmann DJ, Pike JW, Adams JS (eds.). Vitamin D – 2 volume – set. 3rd edition, Academic Press, 2011.
12. Habibi Ghahfarrokhi S, Mohammadian-Hafshejani A, Sherwin CMT, Heidari-Soureshjani S. Relationship between serum vitamin D and hip fracture in the elderly: a systematic review and meta- analysis. J Bone Miner Metab. 2022; 40(4): 541-553. doi: 10.1007/s00774-022-01333-7.
13. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014; 2014(4): CD000227. doi: 10.1002/14651858.
14. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018; 6(11): 847-858. doi: 10.1016/S2213-8587(18)30265-1.
15. Kong SH, Jang HN, Kim JH, Kim SW, Shin CS. Effect of Vitamin D Supplementation on Risk of Fractures and Falls According to Dosage and Interval: A Meta-Analysis. Endocrinol Metab (Seoul). 2022; 37(2): 344-358. doi: 10.3803/EnM.2021.1374.
16. Li S, Xi C, Li L, et al. Comparisons of different vitamin D supplementation for prevention of osteoporotic fractures: a Bayesian network meta-analysis and meta-regression of randomised controlled trials. Int J Food Sci Nutr. 2021; 72(4): 518-528. doi: 10.1080/09637486.2020.1830264.
17. Anagnostis P, Bosdou JK, Kenanidis E, Potoupnis M, Tsiridis E, Goulis DG. Vitamin D supplementation and fracture risk: Evidence for a U-shaped effect. Maturitas. 2020; 141: 63-70. doi: 10.1016/j.maturitas.2020.06.016.
18. Pludowski P, Takacs I, Boyanov M, et al. Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement. Nutrients. 2022; 14(7): 1483. doi: 10.3390/nu14071483.
19. 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): 2603-2623. doi: 10.1007/s40520-022-02279-6.
20. Ministry of Health, Bulgarian Society of Endocrinology. Recommendations for Good Clinical Practice in Vitamin D Deficiency/Insufficiency, Sofia, 2019.
21. Han A, Park Y, Lee YK, Park SY, Park CY. Position Statement: Vitamin D Intake to Prevent Osteoporosis and Fracture in Adults. J Bone Metab. 2022; 29(4): 205-215. doi: 10.11005/jbm.2022.29.4.205.
22. Miller PD, Hattersley G, Riis BJ, et al. ACTIVE Study Investigators. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA. 2016; 316(7): 722-33. doi: 10.1001/jama.2016.11136.

23. Cosman F, Dawson-Hughes B, Wan X, Krege JH. Changes in vitamin D metabolites during teriparatide treatment. Bone. 2012; 50(6): 1368-71. doi: 10.1016/j.bone.2012.02.635.
24. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med. 2016; 375(16): 1532-1543. doi: 10.1056/NEJMoa1607948.
25. Carmel AS, Bockman RS. Vitamin D and bisphosphonate response. Osteoporos Int. 2014; 25(8): 2155. doi: 10.1007/s00198-014-2711-8.
26. Sugimoto T, Matsumoto T, Hosoi T, et al. Efficacy of denosumab co-administered with vitamin D and Ca by baseline vitamin D status. J Bone Miner Metab. 2020; 38(6): 848-858. doi: 10.1007/s00774-020-01119-9.
27. Bertoldo F, Pancheri S, Zenari S, et al. Serum 25-hydroxyvitamin D levels modulate the acute-phase response associated with the first nitrogen – containing bisphosphonate infusion. J Bone Miner Res. 2010; 25(3): 447-54. doi: 10.1359/jbmr.090819.
28. Gunton JE, Girgis CM, Baldock PA, Lips P. Bone muscle interactions and vitamin D. Bone. 2015; 80: 89-94. doi: 10.1016/j.bone.2015.02.029.
29. Di Filippo L, De Lorenzo R, Giustina A, Rovere-Querini P, Conte C. Vitamin D in Osteosarcopenic Obesity. Nutrients. 2022; 14(9): 1816. doi: 10.3390/nu14091816.
30. Kim J, Lee Y, Kye S, Chung YS, Lee O. Association of serum vitamin D with osteosarcopenic obesity: Korea National Health and Nutrition Examination Survey 2008-2010. J Cachexia Sarcopenia Muscle. 2017; 8(2): 259-266. doi: 10.1002/jcsm.12154.
31. Polito A, Barnaba L, Ciarapica D, Azzini E. Osteosarcopenia: A Narrative Review on Clinical Studies. Int J Mol Sci. 2022; 23(10): 5591. doi: 10.3390/ijms23105591.
32. Prokopidis K, Giannos P, Katsikas Triantafyllidis K. Effect of vitamin D monotherapy on indices of sarcopenia in community – dwelling older adults: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2022; 13(3): 1642-1652. doi: 10.1002/jcsm.12976.
33. Gallagher JC, Rosen CJ. Vitamin D: 100 years of discoveries, yet controversy continues. Lancet Diabetes Endocrinol. 2023; 11(5):362-374. doi: 10.1016/S2213-8587(23)00060-8.

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