



# Vitamin D and Bone Health 2022: Is the Evidence Pendulum Switching Backward on Its Benefits?

Hussein F. Saadi<sup>1,2,3</sup>

<sup>1</sup>Medical Subspecialties Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

<sup>2</sup>Department of Medicine, College of Medicine and Health Sciences, Khalifa University, Abu Dhabi, United Arab Emirates

<sup>3</sup>Department of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Ohio, United States

Address for correspondence Hussein Saadi, MD, FACP, Professor, Chair, Medical Subspecialties Institute, Cleveland Clinic Abu Dhabi, UAE (e-mail: saadih@clevelandclinicabudhabi.ae).

J Diabetes Endocrine Practice 2022;5:138–144.

## Abstract

### Keywords

- ▶ review
- ▶ vitamin D
- ▶ bone health
- ▶ vitamin D deficiency
- ▶ osteoporosis
- ▶ bone density
- ▶ fractures
- ▶ narrative non-systematic review
- ▶ optimal vitamin D level
- ▶ osteomalacia

**Objectives:** This concise article aims to (a) review the role of vitamin D in bone health, (b) discuss the consequences of vitamin D deficiency, (c) analyze the use of vitamin D to prevent and treat osteoporosis and (d) explore if the evidence pendulum is switching back on the beneficial effects of vitamin D.

**Materials and Methods:** A narrative nonsystematic review of the literature was done thematically to answer the questions stated in the objectives above.

**Results:** A literature review suggests that vitamin D deficiency can be a real clinical condition that warrants recognition and management, particularly in high-risk groups. The optimal vitamin D level is likely more than or equal to 50 nmol/L (20 ng/mL). The established consequences of vitamin D deficiency in adults include osteomalacia and osteoporosis. Moreover, whether vitamin D supplementation reduces falls and fractures in subjects with baseline vitamin D more than 50 nmol/L (20 ng/mL) is not confirmed. However, vitamin D supplementation is still needed for patients with osteoporosis and those at increased risk of vitamin D deficiency. Finally, there is no justification for measuring 25-hydroxyvitamin D in the general population.

**Conclusions:** For patients at increased risk for osteoporosis, those with vitamin D deficiency, or both, it remains reasonable to consider vitamin D supplementation (800–1,000 IU/d or more), consistent with recommendations of multiple societies.

## Introduction

Vitamin D is a delightful hormone. It impacts several aspects of bone health, metabolic function, neuromuscular function, and possibly other functions.<sup>1</sup> Vitamin D plays three key roles in the bone; it helps with calcium absorption from food in the intestine, ensures the correct renewal and minerali-

zation of bone, and helps to keep muscles strong, reducing the risk of falling.<sup>1</sup> In this concise review, we aim to review the role of vitamin D in bone health, discuss the consequences of vitamin D deficiency and the use of vitamin D to prevent and treat osteoporosis, and explore if the evidence pendulum is switching back on the beneficial effects of vitamin D supplementation on bone density and fractures.

DOI <https://doi.org/10.1055/s-0043-1763273>.  
ISSN 2772-7653.

© 2023. Gulf Association of Endocrinology and Diabetes (GAED). All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

## Vitamin D Production

The synthesis, metabolism, and regulation of vitamin D are shown in ►Fig. 1.<sup>2</sup> A detailed discussion of these is beyond the scope of this communication. The consequences of vitamin D deficiency were recognized a long time ago, and there are several early attempts at the prevention and treatment of vitamin D deficiency and eradication of rickets. These included supplementation with cod liver oil and ultraviolet radiation in 1910.<sup>3</sup> In sunless Lovozero, Russia, children used to bathe in ultraviolet light to produce vitamin D for their bones.<sup>4</sup>

## Assessment of Vitamin D Status

Various methods are available for the assessment of vitamin D status. This includes the measurement of total 25-hydroxyvitamin D (25-OHD), bioavailable 25-OHD [25-OHD not bound to vitamin D binding protein (VDBP)], free 25-OHD (circulating 25-OHD bound to neither DBP nor albumin), and vitamin D metabolite ratio (25-OHD /24,25-dihydroxy vitamin D). In clinical practice, vitamin D status can be assessed by measuring the serum concentration of 25-OHD, which is the best indicator of vitamin D status. It has a circulating half-life of 2 to 3 weeks [compared to 4 hours for 1,25 (OH)<sub>2</sub>D] and 1000x higher concentration.<sup>5</sup> Free 25-OHD measurement may prove useful when there is an alteration of VDBPs

such as pregnancy, cirrhosis, acute illness, hypoalbuminemia, sex hormone use, or genetic polymorphisms.<sup>6</sup>

Different authorities have debated the optimal 25-OHD level. There is less disagreement about what constitutes significant vitamin D deficiency (25-OHD level below 30-nmol/L). ►Table 1 illustrates the cutoff points and criteria for different vitamin D statuses as defined by the Institute of Medicine (now named the National Academy of Sciences). The Institute of Medicine Report of 2011<sup>7</sup> defines vitamin D sufficiency at more lenient levels than the Endocrine Society Clinical Guidelines in the same year (2011).<sup>5</sup> Also, the latter categorizes the deficiency subgroup into two subclasses: deficiency and moderate-to-severe deficiency. An interesting observation was made on vitamin D levels in traditionally living populations in East Africa<sup>8</sup>—35 pastoral Maasai (age 34 ± 10 years; 43% male) and 25 Hadzabe hunter-gatherers (age 35 ± 12 years, 84% male) living in Tanzania. They have skin type VI, have a moderate degree of clothing, and spend most of the day outdoors but avoid direct exposure to sunlight when possible. Their overall mean 25-OHD concentration was 115 nmol/L with a range of 58 to 171 nmol/L.

## Causes of Vitamin D Deficiency

25-OHD deficiency can result from decreased formation or abnormal metabolism. Abnormal vitamin D metabolism

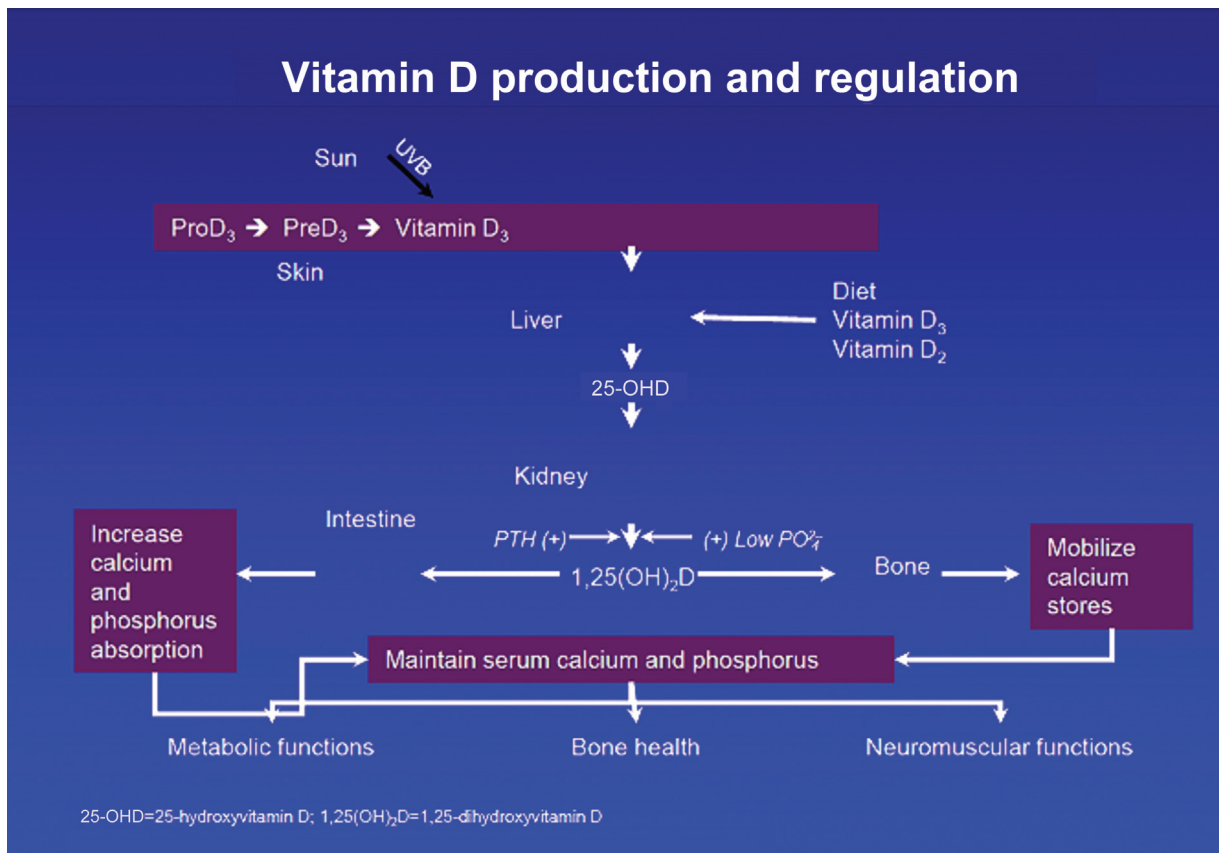


Fig. 1 Production and regulation of vitamin D.

**Table 1** Cutoff points and criteria for different vitamin D statuses as defined by the Institute of Medicine and Endocrine Society (2011).

Status	Institute of Medicine Report 2011	Endocrine Society Clinical Guidelines 2011
Moderate-to-severe Deficiency	–	<25 nmol/L (10 ng/mL)
Deficiency	<30 nmol/L (12 ng/mL)	<50 nmol/L (20 ng/mL)
Insufficiency	30–50 nmol/L (12–20 ng/mL)	50–75 mol/L (20–30 ng/mL)
Sufficiency	above 50 nmol/L (20 ng/mL)	75–250 nmol/L (30–100 ng/mL)

could be due to defective 25-hydroxylation due to biliary cirrhosis, alcoholic cirrhosis, and chronic use of anticonvulsants. In adults, osteomalacia can be caused by abnormal vitamin D metabolism, defective 1- $\alpha$  25-hydroxylation, or inadequate target organ response to calcitriol, such as Vitamin D-dependent rickets, type 2 (hereditary vitamin D-resistant rickets), phosphate deficiency, and mineralization defects.<sup>9,10</sup>

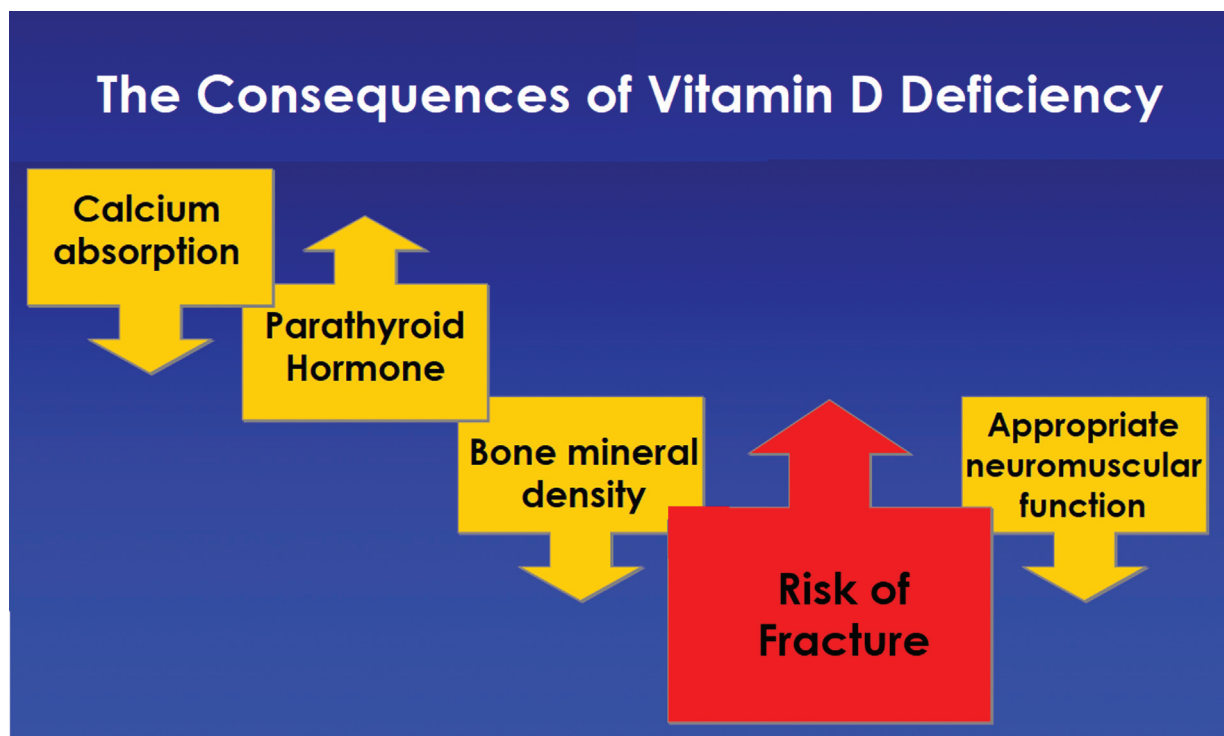
Decreased formation of vitamin D may result from low dietary intake, inadequate sunlight exposure, and decreased absorption. Vitamin D absorption can be impaired in all malabsorption syndromes, postgastrectomy, small bowel disease, and pancreatic insufficiency. On the other hand, natural sources of vitamin D come from cutaneous production and dietary intake. However, besides fatty fish and cod liver oil, natural food contains a small amount of vitamin D. Indeed, in comparison to sunlight, the diet provides less than 10% of the body's vitamin D requirements in the best circumstances.<sup>9,10</sup>

### Consequences of Severe Vitamin D Deficiency

The impact of vitamin D deficiency depends on the maturation stage of the skeleton. Whereas it results in rickets in the growing skeleton of children, it causes osteomalacia and osteoporosis in adults. In general, vitamin D deficiency has important consequences (►Fig. 2). The decreased calcium absorption stimulates increased parathyroid hormone (PTH) production, which results in decreased bone mineral density and impaired neuromuscular function, which jointly lead to an increased risk of fracture and its acute and long-term consequences, as illustrated in ►Fig. 2.<sup>2,10–14</sup>

### Clinical Presentation of Osteomalacia

Osteomalacia may present with diffuse bone pain and tenderness, and muscle weakness. Alternatively, it may be

**Fig. 2** Consequences of vitamin D deficiency.

asymptomatic and present radiologically as osteopenia (or low bone density).<sup>15</sup> Radiologic findings in osteomalacia include reduced bone density with thinning of the cortex, loss of radiologic distinctness of vertebral body trabeculae, looser zones, or pseudofractures. On the other hand, laboratory findings in osteomalacia include low or low-normal serum calcium and phosphate, variable increase in serum alkaline phosphatase, elevated serum PTH, markedly decreased serum 25-OHD, and variable levels of serum 1,25 (OH)2-D.<sup>16</sup>

**Treatment of Osteomalacia**

The primary course of action is to correct the underlying cause. In addition, calcium supplementation is empirically given in a dose of about 2.0 gm of elemental calcium. The type and dose of vitamin D supplements depend on the underlying etiology.<sup>17,18</sup> Prevention of osteomalacia is generally easily achieved through adequate calcium and vitamin D intake by fortifying milk and other food items with vitamin D and adequate exposure to sunlight.<sup>19</sup>

**Vitamin D Supplements Controversy**

There are some differences in the recommended dietary allowance (RDA) for vitamin D in the recommendation of the Institute of Medicine and Endocrine Society RDA for vitamin D<sup>5,7</sup> (→ **Table 2**). In contrast, the Institute of Medicine suggested that supplementation with their recommended doses has been shown to achieve the target above 50 nmol/L.<sup>7</sup> However, the Endocrine Society argued for a higher cutoff of 75 nmol/L for vitamin D sufficiency based on the observation that PTH levels begin to plateau at 25-OHD levels of 75 to 100 nmol/L.<sup>20</sup> Also, the efficiency of intestinal calcium absorption increases by 45 to 67%, with increasing 25-OHD levels from 50 to 80 nmol/L,<sup>21</sup> and achieving this level reduces major osteoporotic fractures by 33%.<sup>22</sup>

**Impact of Oral Vitamin D Supplementation**

Several studies addressed this question.<sup>22–28</sup> The effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in older men and women living in the community was evaluated in a randomized, double-blind controlled trial (100 000 IU oral vitamin D3 or placebo every 4 months over 5 years). Vitamin D (nmol/L) reached 74.3 ± 20.7 in the treatment group versus

53.4 ± 21.1 in the controls. The cumulative probability of any first fracture according to treatment with vitamin D (*n* = 1345) or placebo (*n* = 1341), based on Cox regression, was lower by 22% in the treatment group; risk ratio 0.78 (95% confidence interval: 0.61–0.99, *p* = 0.04).<sup>22</sup>

Later similar studies failed, however, to show such beneficial effects. In the ViDA trial in New Zealand, the effect of monthly high-dose vitamin D supplementation on falls and nonvertebral fractures was examined (secondary and post-hoc outcomes) in 5,108 community-resident adults aged 50 to 84 years who were randomized to receive vitamin D3 or placebo.<sup>23</sup> The baseline mean 25-OHD concentration was 63 nmol/L. Oral vitamin D3 was given in an initial dose of 200,000 IU, followed a month later by monthly doses of 100 000 IU or placebo for a median of 3.3 years (range, 2.5–4.2 years). They found that high-dose vitamin D supplementation of 100 000 IU cholecalciferol monthly over 2.5 to 4.2 years did not prevent falls or fractures in this healthy, ambulatory adult population.<sup>23</sup>

Similarly, the DO-HEALTH randomized clinical trial looked at the effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in 2,157 adults aged 70 years or older. Three-year treatment with vitamin D3 (2000 IU/day), with omega-3 fatty acids (1 g/day), or with a strength-training exercise program did not result in statistically significant differences in improvement in systolic or diastolic blood pressure, nonvertebral fractures, physical performance, infection rate, or cognition.<sup>24</sup> The mean baseline serum 25-OHD concentration was 56 ± 21 nmol/L in the vitamin D treatment group, and 40% had levels below 50 nmol/L (12% had levels below 30 nmol/L). At year 3, participants who were randomized to receive vitamin D had higher mean serum concentrations of 25-OHD than the placebo group (94 vs. 61 nmol/L, respectively). The number of observed fractures in the 1,076 participants who were randomized to receive vitamin D was (129 or 12%), which was not significantly different from that in the 1,081 controls (127 or 11.7%).<sup>24</sup>

Finally, the Vitamin D and Omega-3 Trial (VITAL) investigated whether supplemental vitamin D3 (2000 IU/day), *n* – 3 fatty acids (1 g/day), or both would prevent cancer and cardiovascular disease in men aged 50 years or more and women 55 years of age or older in the United States.<sup>25</sup> Vitamin D supplementation did not prevent cancer or cardiovascular disease, prevent falls, improve cognitive function, reduce atrial fibrillation, change body composition,

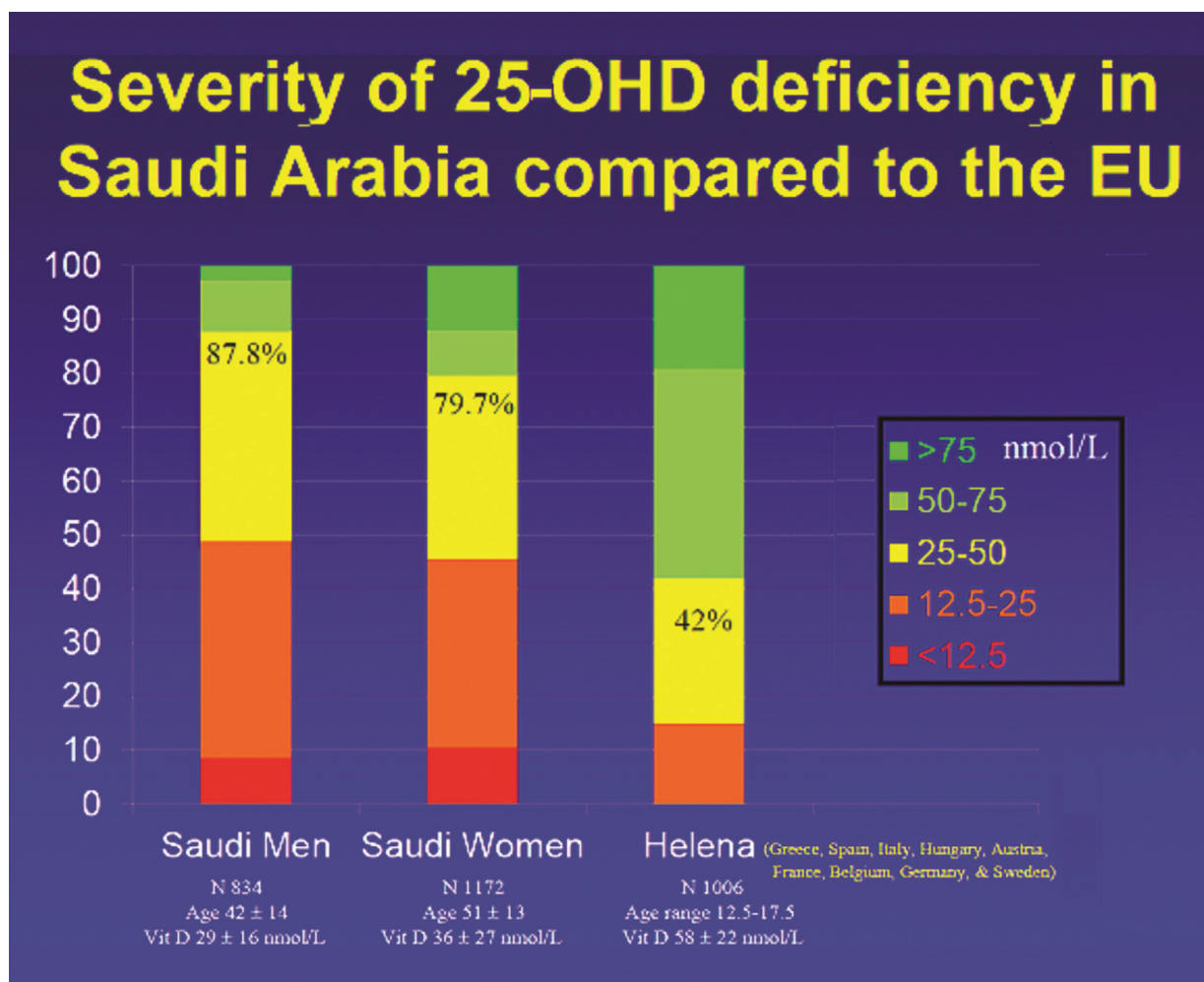
**Table 2** The differences in the recommended dietary allowance (RDA) for vitamin D suggested by the Institute of Medicine (2010) and the Endocrine Society (2011)

Institution	Institute of Medicine (2010)	Endocrine Society (2011)
Children	400 IU	400–1000 IU
Adults < 50	600 IU	1500–2000 IU
Adults 51–70	600 IU	
Adults 71 +	800 IU	800 IU

reduce migraine frequency, improve stroke outcomes, decrease age-related macular degeneration, or reduce knee pain. There was, however, a significant 22% reduction in autoimmune conditions (rheumatoid arthritis and psoriasis)<sup>26</sup> and a significant 17% reduction in advanced cancers (metastatic or fatal).<sup>27</sup>

In the VITAL and Fracture Ancillary Study, incident fractures were reported by participants on annual questionnaires and adjudicated by centralized medical-record review. The primary end points were incident total, non-vertebral, and hip fractures. Participants were not recruited based on vitamin D deficiency, low bone mass, or osteoporosis.<sup>28</sup> This ancillary study revealed that supplemental vitamin D3 did not result in a lower risk of incident total, nonvertebral or hip fractures than placebo among generally healthy midlife and older adults who were not selected for vitamin D deficiency, low bone mass, or osteoporosis. In an accompanying commentary, Cummings and Rosen<sup>29</sup> wrote that “in this ancillary study and other VITAL studies, no subgroups defined according to baseline 25-OHD level, even below 50nmol/l (20 ng per milliliter), benefited from supplements. Vitamin D3 did not reduce the risk of fractures over a median follow-up of 5.3 years. The finding was evident even in the 20% of the participants taking supple-

mental calcium at a dose of up to 1200 mg per day. Thus, there is no justification for measuring 25-OHD in the general population or treated to a target serum level.”<sup>29</sup> They also added, “A 25-OHD level might be a useful diagnostic test for some patients with conditions that may be due to or that may cause severe deficiency. For example, persons living in residential settings with little or no sunlight exposure or malabsorption or those receiving treatments for osteoporosis that might cause hypocalcemia may benefit from vitamin D supplementation; the need for measuring serum 25-OHD levels in these groups remains uncertain. Otherwise, the use of the terms vitamin D ‘insufficiency’ and ‘deficiency’ should now be reconsidered.” Similarly, Reid notes that “Current evidence suggests that there is little reason to prescribe calcium and that vitamin D should be targeted at those at risk of 25-OHD levels less than 30 nmol/L (12 ng/mL).<sup>30</sup> The threshold for bone benefits occurs at a 25-OHD level above 30 nmol/L (12 ng/mL), which is easily exceeded with doses of vitamin D of 400 to 1,000 IU/day. At these levels, vitamin D supplements have no known adverse effects and can be widely endorsed for individuals at risk of deficiency. Supplement doses greater than 2,000 IU/day should be used only in exceptional circumstances and with appropriate monitoring.”<sup>30</sup>



**Fig. 3** Severity of vitamin D deficiency in Saudi Arabia compared to European Union (EU) countries based on references.<sup>32-34</sup>

Although VITAL, DO-HEALTH, and ViDA trials provided a decisive verdict on the issue of vitamin D supplementation in the populations studied,<sup>23–27</sup> we need to be careful in extending the results to other populations where moderately severe vitamin D deficiency is highly prevalent such as in the Arabian Gulf countries.<sup>31</sup> For example, **Fig. 3** demonstrates that moderately severe 25-OHD deficiency (25-OHD below 25nmol/L) was more than 40% in Saudi Arabian men and women compared to less than 15% in the European Union (from the Helena Study with participants from Greece, Spain, Italy, Hungary, Austria, France, Belgium, Germany, & Sweden).<sup>32–34</sup> Additionally, the respective proportion of participants with serum vitamin D between 25 and 50 nmol/L were 87.8, 79.7, and 42%, respectively.<sup>32–34</sup>

## Conclusions

For patients at increased risk of osteoporosis, those with vitamin D deficiency, or both, it remains reasonable to consider vitamin D supplementation (800–1,000 IU/day or more), consistent with recommendations of the Endocrine Society and National Osteoporosis Foundation as well as Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases.<sup>35</sup> The literature is also supportive of the benefit of vitamin D supplementation for fall prevention in vulnerable populations, such as those with vitamin D deficiency, older adults living in institutions, other older adults at high risk of fracture (such as a previous history of falls and problems with mobility, gait, or balance).<sup>36</sup>

### Authors contribution

Single authorship

### Compliance with Ethical Problems

No ethical approval is required.

### Ethics

No ethical approval is required

### Funding and Sponsorship

None.

### Conflict of Interest

None declared.

## References

- Holick MF. Vitamin D: a d-lightful solution for health. *J Investig Med* 2011;59(06):872–880
- Holick MF. Vitamin D requirements for humans of all ages: new increased requirements for women and men 50 years and older. *Osteoporos Int* 1998;8(Suppl 2):S24–S29
- Harding JS. A history of cod liver oil therapy. *Sci Mon* 1928;26(04):338–341
- Hernigou P, Auregan JC, Dubory A. Vitamin D: part II; cod liver oil, ultraviolet radiation, and eradication of rickets. *Int Orthop* 2019;43(03):735–749
- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96(07):1911–1930
- Aloia J, Dhaliwal R, Mikhail M, et al. Free 25(OH)D and calcium absorption, PTH, and markers of bone turnover. *J Clin Endocrinol Metab* 2015;100(11):4140–4145
- Institute of Medicine (U.S.) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Ross AC, Taylor CL, Yaktine AL, et al., editors. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (D.C.): National Academies Press (U.S.); 2011. Accessed January 16, 2023 at: <https://www.ncbi.nlm.nih.gov/books/NBK56070/> Doi: 10.17226/13050
- Luxwolda MF, Kuipers RS, Kema IP, Dijck-Brouwer DA, Muskiet FA. Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l. *Br J Nutr* 2012;108(09):1557–1561
- Chauhan K, Shahrokhi M, Huecker MR, Vitamin D. 2022 Sep 9. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–
- Allain TJ, Dhese J. Hypovitaminosis D in older adults. *Gerontology* 2003;49(05):273–278
- Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD. Vitamin D and bone health in the elderly. *Am J Clin Nutr* 1982;36(05, Suppl):1014–1031
- DeLuca HF. Osteoporosis and the metabolites of vitamin D. *Metabolism* 1990;39(04, Suppl 1):3–9
- Pfeifer M, Minne HW. Vitamin D and hip fracture. *Trends Endocrinol Metab* 1999;10(10):417–420
- Lips P. Suboptimal vitamin D status: a risk factor for osteoporosis? In: Draper HH, ed. *Advances in Nutritional Research*. New York: Plenum Press; 1994:151–165
- Maricic M. Osteomalacia. *Curr Osteoporos Rep* 2008;6(04):130–133
- Scharla S. Diagnosis of disorders of vitamin D-metabolism and osteomalacia. *Clin Lab* 2008;54(11-12):451–459
- Dobson R, Cock HR, Brex P, Giovannoni G. Vitamin D supplementation. *Pract Neurol* 2018;18(01):35–42
- 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
- Parfitt AM, Frame B. Treatment of rickets and osteomalacia. *Semin Drug Treat* 1972;2(01):83–115
- Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998;338(12):777–783
- Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. *Osteoporos Int* 2010;21(07):1121–1132
- Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;326(7387):469. Doi: 10.1136/bmj.326.7387.469
- 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(06):438–447
- Bischoff-Ferrari HA, Vellas B, Rizzoli R, et al; DO-HEALTH Research Group. Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH Randomized Clinical Trial. *JAMA* 2020;324(18):1855–1868
- Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019;380(01):33–44
- Hahn J, Cook NR, Alexander EK, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune

- disease: VITAL randomized controlled trial. *BMJ* 2022;376:e066452
- 27 Chandler PD, Chen WY, Ajala ON, et al; VITAL Research Group. Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. *JAMA Netw Open* 2020;3(11):e2025850
  - 28 LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental vitamin D and incident fractures in midlife and older adults. *N Engl J Med* 2022;387(04):299–309
  - 29 Rosen CJ, Cummings S. Vitamin D and incident fractures. Reply. *N Engl J Med* 2022;387(17):1627–1628
  - 30 Reid IR. Calcium and vitamin D: to supplement or not? *Cleve Clin J Med* 2018;85(09):693–698
  - 31 Saadi H. Comment on Wahl et al.: A global representation of vitamin D status in healthy populations. *Arch Osteoporos* 2013;8:121. Doi: 10.1007/s11657-013-0121-8
  - 32 Cashman KD, Dowling KG, Škrabáková Z, et al. Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr* 2016;103(04):1033–1044
  - 33 Ardawi MS, Sibiany AM, Bakhsh TM, Qari MH, Maimani AA. High prevalence of vitamin D deficiency among healthy Saudi Arabian men: relationship to bone mineral density, parathyroid hormone, bone turnover markers, and lifestyle factors. *Osteoporos Int* 2012;23(02):675–686
  - 34 Ardawi MS, Qari MH, Rouzi AA, Maimani AA, Raddadi RM. Vitamin D status in relation to obesity, bone mineral density, bone turnover markers and vitamin D receptor genotypes in healthy Saudi pre- and postmenopausal women. *Osteoporos Int* 2011;22(02):463–475
  - 35 Weaver CM, Gordon CM, Janz KF, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos Int* 2016;27(04):1281–1386
  - 36 Bischoff-Ferrari HA, Bhasin S, Manson JE. Preventing fractures and falls: a limited role for calcium and vitamin D supplements? *JAMA* 2018;319(15):1552–1553