Osteoporosis International (2023) 34:1531–1533
https://doi.org/10.1007/s00198-023-06802-x

EDITORIAL

Evaluating benefit from vitamin D supplementation: defining the area for treatment

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Received: 26 January 2023 / Accepted: 19 May 2023 / Published online: 27 May 2023

Editorial

Despite the availability of effective treatments, a substantial proportion of osteoporotic patients still do not receive specific treatment for osteoporosis post fracture. In addition, the failure or inadequate supplementation with vitamin D in these patients elevates the risk of re-fracture and mortality [1]. The measurement of serum 25-hydroxyvitamin D (25(OH)D) is used in clinical practice to assess the so-called vitamin D status, and the 25(OH)D form is relatively stable in serum with a half-life of 2–3 weeks [2].

The Institute of Medicine has defined a serum 25(OH) D concentration of 30 nmol/L (12 ng/mL) as the threshold below which clinical vitamin D deficiency may occur [3]. This report also defined 30–50 nmol/L (12–20 ng/mL) indicating "risk of inadequacy," greater than 50 nmol/L (>20 ng/mL) indicating "sufficiency," and greater than 125 nmol/L (>50 ng/mL) indicating "risk of harm" [3]. This definition has also recently been adopted by European government agencies [4, 5] and in line with the European Calcified Tissue Society which favours a lower 25(OH)D threshold of >50 nmol/L (>20 ng/mL) for sufficiency [6]. However, scientific societies, such as the Endocrine Society, the National Osteoporosis Foundation, and the International Osteoporosis Foundation, suggest that sufficiency levels should be based on values of >75 nmol/L (30 ng/mL) [7, 8].

Several recent meta-analyses and trials have generated debate with regard to the interpretation of results from these studies and in turn our understanding of the "true" role of vitamin D and its potential benefit in a range of skeletal and extraskeletal diseases [9–14]. In this Editorial, we discuss key design issues from studies evaluating the benefit afforded from vitamin D supplementation using as examples the recent Vitamin D and Omega-3 Trial (VITAL) study [15] and the Nonlinear Mendelian Randomization Study [16].

Considering these issues, the aim of this Editorial is to reinforce some key concepts in clinical study design related to studies evaluating the benefit afforded from vitamin D supplementation. Etiological research aims to establish the causal role of risk factors in the pathogenesis of a specific disease or event [17]. Once a given risk factor-outcome link is demonstrated to be independent of potential confounders and has biological plausibility, the functional form of this relationship is next assessed. Evaluating the functional form of the risk factor-outcome link is a hallmark of etiological research because (1) it allows us to identify the range of values of a given biomarker that is associated with a steeper increase or decrease of the risk of the event of interest and (2) it is useful to define the clinical phenotype that could specifically benefit from an intervention, as in RCTs representing the last step in etiological research to confirm causality.

In the Nonlinear Mendelian Randomization Study [16], the relationship between 25(OH)D and mortality was investigated in a large, prospective cohort based in the UK. The authors considered 307,601 individuals (aged 37–73 years) with available measurements of 25(OH)D and genetic data. Genetically predicted 25(OH)D was also calculated by using 35 variants of 25(OH)D. Information on all-cause and cause-specific (cardiovascular disease, cancer and respiratory) was also collected. To assess the relationship between 25(OH) D and the study endpoints, two analytical approaches were applied: (1) an analysis adjusting for potential confounders and (2) an analysis using as instrumental variable, the

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genetically predicted 25(OH)D. The main finding that emerged from this analysis revealed a non-linear relationship between 25(OH)D levels (adjusted for confounders) and the odds ratio of all-cause death. Of note, the risk of mortality steeply increased with decreasing 25(OH)D levels below 50 nmol/L (<20 ng/mL), therefore highlighting values of 25(OH)D below 50 nmol/L (<20 ng/mL) as a potential area of intervention and values of 25(OH)D above 50 nmol/L (>20 ng/mL) as a futile area of intervention. The same analysis carried out by genetically predicted 25(OH)D and accordingly to other endpoints (cancer, cardiovascular and respiratory-related mortality) provided similar results [16].

In a meta-analysis including 15 prospective cohort studies comprising a total of 51,239 participants and 3386 hip fractures [18], individuals with low 25(OH)D concentration were observed to have an increased risk of hip fracture. Furthermore, in a dose-response sub-analysis of the same study, the effect of low 25(OH)D concentration on the risk of hip fracture was evident when the 25(OH)D concentration was less than 60 nmol/L (<24 ng/mL) [18]. This cutoff is close to the critical threshold (50 nmol/L; 20 ng/mL) identified in the Nonlinear Mendelian Randomization Study [16], further emphasizing the notion that low 25(OH)D concentrations, mortality, and fractures at least in part share a common pathogenetic pathway, as also suggested by the strong link between mortality and fractures in the population [19].

Overall, these results indicate that interventions in patients with baseline 25(OH)D >50 nmol/L (>20 ng/mL) are unlikely to be effective because this cutoff represents the lower limit of the futile area of intervention for both mortality and fractures, as consistently suggested by observational studies [18, 19].

Possible examples on why it is of crucial importance to maintain scientific coherence between observational cohort-hypothesis generating studies and randomized controlled-hypothesis testing studies can be seen from results derived from an ancillary study of the VITAL trial [15], in which LeBoff et al. tested the hypothesis that vitamin D3 supplementation could lead to a reduction in the risk of fractures over placebo. Participants in this trial were not enrolled on the basis of vitamin D deficiency, low bone mass, or osteoporosis. The primary endpoints were incident total, non-vertebral, and hip fractures as reported by participants and validated by an independent scientific committee. Supplemental vitamin D3, compared with placebo, did not show a significant effect on total fractures ($p = 0.70$), non-vertebral fractures ($p = 0.50$), or hip fractures ($p = 0.96$) [15]. Of note, in a subgroup of 16,757 participants out of 25,871 (about 65%), baseline 25(OH)D concentrations were also available. Mean (SD) 25(OH)D concentrations were 76.6 ± 25 nmol/L (30.7±10 ng/mL) and 87% of patients had 25(OH)D levels >50 nmol/L (>20 ng/mL) [15]. This finding implies that about 9 patients out of 10 enrolled in this ancillary study of VITAL had a 25(OH)D concentration falling in the futile area for intervention, and for this reason, no effect of supplemental vitamin D3 would be expected to be observed on the incidence rate of fractures.

Our analysis of these two studies [15, 16] further confirms the need for etiological research to maintain consistency between its observational and interventional component. This is particularly relevant for the identification of phenotypes and biomarker cutoff values suitable for making the risk factor-outcome link clear and homogeneous, which will in turn facilitate clinicians and researchers to arrive at the most likely conclusions, in terms of evidence-based medicine.

Declarations

Conflicts of interest None.

References

1. Degli Esposti L, Girardi A, Saragoni S et al (2019) Use of anti-osteoporotic drugs and calcium/vitamin D in patients with fragility fractures: impact on re-fracture and mortality risk. Endocrine 64:367–377. https://doi.org/10.1007/s12020-018-1824-9
2. Tuckey RC, Cheng CYS, Slominski AT (2019) The serum vitamin D metabolome: what we know and what is still to discover. J Steroid Biochem Mol Biol 186:4–21. https://doi.org/10.1016/j.jsbmb.2018.09.003
3. Ross AC, Manson JE, Abrams SA et al (2011) The 2011 report on dietary reference intakes for calcium and vitamin D from the institute of medicine: what clinicians need to know. J Clin Endocrinol Metab 96:53–58. https://doi.org/10.1210/jc.2010-2704
4. EFSA Panel on Dietetic Products , Nutrition and Allergies (NDA) (2016) Dietary reference values for vitamin D. EFSA J 14:e04547. https://doi.org/10.2903/j.efsa.2016.4547
5. Cashman KD (2020) Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. Calcif Tissue Int 106:14–29. https://doi.org/10.1007/s00223-019-00559-4
6. Lips P, Cashman KD, Lamberg-Allardt C et al (2019) Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endocrinol 180:P23–P54. https://doi.org/10.1530/EJE-18-0736
7. Chun RF, Peercy BE, Orwoll ES et al (2014) Vitamin D and DBP: the free hormone hypothesis revisited. J Steroid Biochem Mol Biol 144:132–137. https://doi.org/10.1016/j.jsbmb.2013.09.012
8. Holick MF, Binkley NC, Bischoff-Ferrari HA et al (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1911–1930. https://doi.org/10.1210/jc.2011-0385
9. McKenna MJ, Flynn MAT (2023) Preventing type 2 diabetes with vitamin D: therapy versus supplementation. Ann Intern Med. https://doi.org/10.7326/M23-0220
10. Bilezikian JP, Formenti AM, Adler RA et al (2021) Vitamin D: Dosing, levels, form, and route of administration: does one approach fit all? Rev Endocr Metab Disord 22:1201–1218. https://doi.org/10.1007/s11154-021-09693-7

11. Bouillon R, Manousaki D, Rosen C et al (2021) The health effects of vitamin D supplementation: evidence from human studies. Nat Rev Endocrinol. https://doi.org/10.1038/s41574-021-00593-z
12. Cummings SR, Rosen C (2022) VITAL findings — a decisive verdict on vitamin D supplementation. New Engl J Med 387:368–370. https://doi.org/10.1056/NEJMe2205993
13. Pittas AG, Kawahara T, Jorde R et al (2023) Vitamin D and risk for type 2 diabetes in people with prediabetes. Ann Intern Med. https://doi.org/10.7326/M22-3018
14. Garland C, Kim J, Mohr S et al (2014) Meta-analysis of all-cause mortality according to serum 25-hydroxyvitamin D. Am J Public Health 104. https://doi.org/10.2105/AJPH.2014.302034
15. LeBoff MS, Chou SH, Ratliff KA et al (2022) Supplemental vitamin D and incident fractures in midlife and older adults. N Engl J Med 387:299–309. https://doi.org/10.1056/NEJMoa2202106
16. Sutherland JP, Zhou A, Hyppönen E (2022) Vitamin D deficiency increases mortality risk in the UK Biobank : a nonlinear Mendelian randomization study. Ann Intern Med 175:1552–1559. https://doi.org/10.7326/M21-3324
17. Stel VS, Chesnaye NC, Tripepi G et al (2021) Points of attention when conducting etiological research. Nephrology (Carlton) 26:701–707. https://doi.org/10.1111/nep.13875
18. Lv Q-B, Gao X, Liu X et al (2017) The serum 25-hydroxyvitamin D levels and hip fracture risk: a meta-analysis of prospective cohort studies. Oncotarget 8:39849–39858. https://doi.org/10.18632/oncotarget.16337
19. Ziadé N, Jougla E, Coste J (2010) Population-level impact of osteoporotic fractures on mortality and trends over time: a nationwide analysis of vital statistics for France, 1968-2004. Am J Epidemiol 172:942–951. https://doi.org/10.1093/aje/kwq215