JIM Editorial

Linked to: Sha Sha et al. J Intern Med 2023; https://doi.org/10.1111/joim.13578 doi: 10.1111/joim.13582

Low vitamin D is a marker for poor health and increased risk for disease: But causality is still unclear in most cases

It is almost 100 years since Adolf Windaus received the Nobel Prize in chemistry in 1928 for his studies' on the constitution of sterols and their connection with vitamins', including vitamin D and its role to prevent rickets [1]. The role of vitamin D to protect the bone has been well known since and has a central role in all medical textbooks. This part of vitamin D metabolism is generally known as the endocrine system, where the liver produces the storage form 25-hydroxyvitamin D (25OHD) and the kidney carries out the conversion into bioactive 1,25-dihydroxyvitamin D (1,25OHD), which mainly regulates calcium balance. In addition, the pro-form 25OHD can be activated locally in many different cell types, including monocytes, epithelial cells and even in neurons [2, 3]. Local production of the active form of vitamin D (1,25OHD) leads to activation of the vitamin D receptor and subsequent transcription of several hundreds of genes, depending on the cell type and physiological context [4]. This part of vitamin D metabolism is called the paracrine system and has been the focus of intense research during recent years [5]. In parallel with the molecular discoveries of vitamin D metabolism, there has been a rapid increase in observational studies that have found associations between low vitamin D levels and increased risk of many common diseases, including cancer, cardiovascular diseases, respiratory tract infections and Alzheimer's disease as well as all-cause mortality [6–9]. Combined, there has been a solid rationale to perform randomised controlled trials (RCTs) in many of these areas since there is a potential mechanism for beneficial effects and data from observational studies show an increased risk for disease with lower vitamin D levels in plasma. Randomised and placebo-controlled clinical trials of vitamin D supplementation in cancer, cardiovascular diseases and respiratory tract infections have shown both beneficial effects as well as null results [10, 11]. Interestingly, meta-analyses, where results from many RCTs are combined, have shown beneficial effects of vitamin D supplementation on cancer mortality and total mortality as well as reduced risk for respiratory tract infections [12–14]. In addition, Mendelian randomisation studies have shown an inverse association between genetically predicted 25OHD levels and all-cause mortality [15].

It is against this background that Sha et al. set out to obtain further information on the role of vitamin D in reduction of mortality from cancer and other causes, including cardiovascular and respiratory diseases [16]. They used data from the UK Biobank (n = 445,601 participants), including data on the use of vitamin D supplements (over-the-counter drugs or as part of a multivitamin product) and 25OHD levels defined as deficiency (<30 nmol/L) or insufficiency (30 to <50 nmol/L). The outcomes were all-cause and cause-specific mortality, with a focus on mortality due to cardiovascular disease, cancer and respiratory disease. Several covariates were also collected for the adjustment analyses, including demographic and socio-economic factors, which potentially could influence the outcome. The mean age of the cohort was 56.5 years, and a majority were overweight or obese. Interestingly, 21% of the cohort had vitamin D deficiency (<30 nmol/L) and 34.3% had insufficiency (<50 nmol/L). Only 4.3% reported a regular intake of vitamin D supplements, whereas 20.4% reported using multivitamin supplements on a regular basis. Consequently, users of vitamin D or multivitamin supplements had a higher level of 25OHD than nonusers.

Next, the authors analysed determinants associated with vitamin D deficiency. In general, worse health concomitant diseases, obesity, higher blood pressure, poor general health and the latitude of the test centre were factors associated with vitamin D deficiency or insufficiency, whereas the use of vitamin D or multivitamin supplements often had the reverse association, that is,

healthier people had a higher tendency to take supplements.

The authors found that both vitamin D deficiency and insufficiency were associated with all-cause mortality and mortality due to cancer, cardiovascular disease (CVD) and respiratory diseases. Five different adjustment models were employed, and the hazard ratios were attenuated with increasing adjustment. The excess mortality was most prominent for CVD, followed by respiratory disease mortality and cancer mortality.

Finally, the association between self-reported vitamin D intake and the outcomes was analysed. Notably, no effect was observed, but after considering concomitant diseases and general health status in the broadest adjustment model, users of vitamin D supplements had 10% lower all-cause mortality and 11% lower cancer mortality, whereas mortality for CVD did not reach statistical significance. The strongest effect was found for respiratory diseases, where self-reported vitamin D intake was associated with 29% decreased mortality.

How should these results be interpreted in the light of available evidence? First, there have been many studies before this one with a similar message, that is, low vitamin D levels are associated with many different diseases, including those discussed here. For example, there is evidence from a large European consortium that low vitamin D levels are associated with increased mortality [17]. We also know that vitamin D has several important functions in the body, apart from regulating calcium homeostasis. A recent example is from the covid area, where vitamin D was found to suppress inflammation in T cells, with potential implications for prevention and treatment of SARS CoV-2 infection [18]. However, despite ample evidence from experimental and observational studies, solid data from RCTs showing beneficial effects against any indication are scarce, with a few exceptions. For example, vitamin D did not prevent CVD or cancer in a large and well-designed RCT [19]. In contrast, in the field of respiratory tract infections, the team around Adrian Martineau has performed two large meta-analyses, one of which is an individual patient data meta-analysis, which found small but statistically significant effects of vitamin D supplementation against respiratory tract infections (RTIs) [13, 14]. However, two recent RCTs could not find any evidence of vitamin D supplementation (or cod liver oil supplementation) against covid-19 [20–22]. Thus, there is still a discrepancy between experimental and observational data on one side and data from RCTs on the other. Why is that? There are three models to consider at this point. The first of these implies that low levels of 25OHD are directly causing the disease. Supplementation would then be the solution and lead to reduced risk of the disease. The other explanation could be a reverse association, that is, that the disease causes low vitamin D levels; for example, if a chronic disease leads to immobilisation indoors without exposure to the sun. The final model is that there is a spurious or 'false' association where a third factor leads to both low vitamin D levels and increased risk for the disease. In the paper by Sha et al., for example, subjects with self-reported poor health status had 77% higher odds to have vitamin D deficiency and 19% lower odds of taking vitamin D supplements. Thus, there is a significant risk of the healthy user effect, that is, that healthier people tend to take more supplements, spend more time outdoors and simply avoid diseases to a higher extent than poor, fragile and sick people do. Sha et al. apply an ambitious adjustment approach to avoid this risk, but as the authors point out themselves, it is impossible to adjust for so-called hidden or residual confounders. This means that there could still be additional factors that we cannot adjust for, which could influence the observed associations. Thus, despite the impressive size of the study by Sha et al., we still cannot draw firm conclusions on causality and whether vitamin D supplementation can reduce mortality from CVD, cancer or respiratory diseases.

But which advice should we give to the public, physicians and policy makers about vitamin D deficiency and risk for disease? A pragmatic approach could be to focus on groups at the highest risk for vitamin D deficiency and supplement those <50 nmol/L with 1000–2000 IU/day. This would support the bone, improve immunity and potentially also reduce the risk of respiratory tract infections. Perhaps this strategy could also reduce mortality from CVD, cancer and respiratory disease, as suggested by Sha et al., but solid evidence from bona fide randomised and placebo-controlled clinical trials is still warranted.

Conflict of interest

No conflict of interest to report.

Peter Bergman
Department of Laboratory Medicine, Division of Clinical Immunology, Karolinska Institutet, Huddinge, Stockholm, Sverige

References

1 Wolf G. The discovery of vitamin D: the contribution of Adolf Windaus. *J Nutr.* 2004;**134**(6):1299–302.
2 Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. *JBMR Plus.* 2021;**5**(1):e10405.
3 Uthaiah CA, Beeraka NM, Rajalakshmi R, Ramya CM, Madhunapantula SV. Role of neural stem cells and vitamin D receptor (VDR)–mediated cellular signaling in the mitigation of neurological diseases. *Mol Neurobiol.* 2022;**59**(7):4065–105.
4 Carlberg C. Vitamin D and its target genes. *Nutrients.* 2022;**14**(7):1354.
5 Hewison M. Vitamin D and immune function: autocrine, paracrine or endocrine? *Scand J Clin Lab Invest Suppl.* 2012;**243**:92–102.
6 Berry DJ, Hesketh K, Power C, Hypponen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr.* 2011;**106**(9):1433–40.
7 Mahendra A, Karishma, Choudhury BK, Sharma T, Bansal N, Bansal R, et al. Vitamin D and gastrointestinal cancer. *J Lab Physicians.* 2018;**10**(1):1–5.
8 Mokry LE, Ross S, Morris JA, Manousaki D, Forgetta V, Richards JB. Genetically decreased vitamin D and risk of Alzheimer disease. *Neurology.* 2016;**87**(24):2567–74.
9 Zhang H, Wang P, Jie Y, Sun Y, Wang X, Fan Y. Predictive value of 25-hydroxyvitamin D level in patients with coronary artery disease: a meta-analysis. *Front Nutr.* 2022;**9**: 984487.
10 Ganmaa D, Enkhmaa D, Nasantogtokh E, Sukhbaatar S, Tumur-Ochir KE, Manson JE. Vitamin D, respiratory infections, and chronic disease: review of meta-analyses and randomised clinical trials. *J Intern Med.* 2022;**291**(2):141–64.
11 Grant WB, Boucher BJ, Al Anouti F, Pilz S. Comparing the evidence from observational studies and randomized controlled trials for nonskeletal health effects of vitamin D. *Nutrients.* 2022;**14**(18):3811.
12 Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev.* 2014;(1):CD007470.
13 Jolliffe DA, Camargo CA Jr, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol.* 2021;**9**(5):276–92.
14 Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ.* 2017;**356**:i6583.
15 Afzal S, Brondum-Jacobsen P, Bojesen SE, Nordestgaard BG. Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. *BMJ.* 2014;**349**:g6330.
16 Sha S, Nguyen TMN, Kuznia S, Niedermaier T, Zhu A, Brenner H, et al. Real-world evidence for the effectiveness of vitamin D supplementation in reduction of total and cause-specific mortality. *J Intern Med.* 2023;**293**:384–97.
17 Gaksch M, Jorde R, Grimnes G, Joakimsen R, Schirmer H, Wilsgaard T, et al. Vitamin D and mortality: individual participant data meta-analysis of standardised 25-hydroxyvitamin D in 26916 individuals from a European consortium. *PLoS One.* 2017;**12**(2):e0170791.
18 Chauss D, Freiwald T, McGregor R, Yan B, Wang L, Nova-Lamperti E, et al. Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. *Nat Immunol.* 2022;**23**(1):62–74.
19 Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* 2019;**380**(1):33–44.
20 Brunvoll SH. Prevention of covid-19 and other acute respiratory infections with cod liver oil supplementation, a low dose vitamin D supplement: quadruple blinded, randomised placebo controlled trial. *BMJ.* 2022. https://doi.org/10.1136/bmj-2022-071245
21 Jolliffe DA. Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomised controlled trial (CORONAVIT). *BMJ.* 2022. https://doi.org/10.1136/bmj-2022-071230
22 Bergman P. Can vitamin D protect against covid-19? *BMJ.* 2022. https://doi.org/10.1136/bmjo1822

Correspondence: Peter Bergman, Department of Laboratory Medicine, Division of Clinical Immunology, Karolinska Institutet, Alfred Nobels Allé 8, Huddinge, 14152 Stockholm, Sverige.
Email: peter.bergman@ki.se

