

Z Gerontol Geriatr

<https://doi.org/10.1007/s00391-019-01573-9>

Received: 30 April 2019

Accepted: 7 June 2019

© Springer Medizin Verlag GmbH, ein Teil von Springer Nature 2019



Heike A. Bischoff-Ferrari

Dept. of Geriatric Medicine and Aging Research, University Hospital Zurich and University of Zurich, Zurich, Switzerland

Should vitamin D administration for fracture prevention be continued?

A discussion of recent meta-analysis findings

Introduction

Recent meta-analyses on vitamin D and fracture reduction have led physicians and patients to question current guidelines on vitamin D. Vitamin D and calcium are key nutrients for bone health and vitamin D deficiency is an established risk factor for falls and fractures among adults aged 65 years and older. In 2016–2018 efforts were undertaken in 4 meta-analyses to review the benefit of vitamin D on fracture prevention. This article summarizes the findings of these meta-analyses and discusses their potential impact on current guidelines on vitamin D. Of these meta-analyses two focused on primary prevention of fractures among adults aged 50 years and older, who are not at risk of fracture or vitamin D deficiency [1, 2], which has not been established before: one focused on the combination of vitamin D plus calcium only [3] and one on the individual effect of vitamin D without calcium [4]. Only the meta-analysis that focused on the combined effects of vitamin D and calcium [3] targeted primarily adults aged 65 years and older living in the community or in institutions.

Individual summary and brief discussion of the four meta-analyses

Fracture prevention in adults aged 65+ years for combined vitamin D plus calcium

The first meta-analysis published in 2016 by Weaver et al. [3] aimed to investigate the combined effect of vitamin D with calcium compared with placebo. With this selection, this meta-analysis included approximately 40% of high-quality data on fracture reduction that contributed to the current guidelines recommending 800 IU vitamin D. In total, the authors summarized 8 randomized-controlled trials ($n = 30,970$ older adults) [3] and found a significant 15% reduction of total fractures (relative risk [RR] = 0.85; 95% confidence interval, CI 0.73–0.98) and a significant 30% reduction of hip fractures (RR = 0.70; 95% CI 0.56–0.87) [3]. Notably, the benefit observed in this meta-analysis may be explained by the fact that most of the trials tested 800 IU vitamin D and that the majority of the study population was comprised of more adults aged 65 years and older, vulnerable to both vitamin D deficiency and fracture risk. Also, the authors included both community-dwelling and institutionalized older adults, and given the combination of calcium and vitamin D, the dose administration was daily and did not include trials with large bolus doses of vitamin D that have been shown to be detrimental [5, 6].

Primary fracture prevention in community-dwelling adults aged 50+ years

The second meta-analysis published in JAMA in 2017 by Zhao et al. [1] aimed at assessing the effect of calcium and vitamin D individually as well as their combination on the primary prevention of fractures among community-dwelling adults aged 50+ years. The authors included 33 trials that recruited a total of 51,145 community-dwelling participants aged 50 years and older [1]. The primary endpoint was hip fracture and secondary endpoints included non-vertebral fractures, vertebral fractures, and total fractures. Regarding trial quality, the authors included any randomized clinical trial with a placebo or no treatment in the control group. The authors found no significant association of calcium or vitamin D with risk of hip fracture compared with placebo or no treatment (calcium: RR 1.53, 95% CI 0.97–2.42; vitamin D: RR 1.21, 95% CI 0.99–1.47). Furthermore, the authors found no significant association of combined calcium and vitamin D with hip fracture compared with placebo or no treatment (RR 1.09, 95% CI 0.85–1.39). Also, no significant associations were found between calcium, vitamin D or combined calcium and vitamin D supplements and the incidence of non-vertebral, vertebral or total fractures. The authors performed several subgroup analyses and documented that the results were generally consistent regardless of the calcium or vitamin D

Table 1 Summary of the four recent meta-analyses on vitamin D and fracture prevention

Author of meta-analysis and trials	Intervention tested	Target population and limitations	Result fractures
Weaver et al. 2016 [3] 8 randomized-controlled trials (RCTs) (n = 30,970)	Combined effect of daily vitamin D with calcium compared with placebo	Mostly adults age 65+ years – Excluded studies that tested vitamin D without calcium – Included 40% of the literature that contributed to current guidelines on vitamin D	– 15% reduction of total fractures (RR = 0.85; 95% CI 0.73–0.98) – 30% reduction of hip fractures (RR = 0.70; 95% CI 0.56–0.87)
Zhao et al. 2017 [1] 33 RCTs (n = 51,145)	Calcium and vitamin D individually as well as the combination	Community-dwelling participants age 50+ years for primary prevention without a prior fracture – Exclusion of older adults living in institutions, most vulnerable to low calcium intake, vitamin D deficiency and fracture risk – 11 out of 33 with follow-up of ≤12 months with little potential to show benefit on fracture reduction, 4 trials had an open study design without a treatment in the control group, and 1 study had an incorrect fracture report [8] – No adjustment for adherence – For vitamin D alone 8 of the 12 trials gave vitamin D in bolus doses (orally or intramuscular administration), which has repeatedly raised concerns in the literature about promoting both falls and fractures [5, 12]	No significant effect of calcium or vitamin D on risk of hip fracture compared with placebo or no treatment: – Calcium: RR = 1.53; 95% CI 0.97–2.42 – Vitamin D: RR = 1.21; 95% CI 0.99–1.47 No significant association of combined calcium and vitamin D with respect to hip fracture compared with placebo or no treatment: RR = 1.09, 95% CI 0.85–1.39 No significant benefit on any intervention on the incidence of non-vertebral, vertebral, or total fractures
US Preventive Task Force 2018 [2] 11 RCTs (N = 51,419)	Calcium and vitamin D individually as well as the combination	Community-dwelling adults age 50+ years not at risk for osteoporosis or vitamin D deficiency Panel acknowledged limited trial data for primary prevention	For vitamin D doses greater than 400 IU (according to current recommendations), the panel concluded that there is insufficient evidence to assess a benefit
Bolland et al. 2018 [4] 81 unblinded and blinded randomized trials among (n = 44,790)	Vitamin D compared to untreated controls, placebo or another dose of vitamin D	Adults age 50+ years – Authors excluded trials that combined vitamin D with calcium and thereby 40% of the literature that contributed to current guidelines – Authors included large bolus doses that have consistently increased the risk of falls and fractures [5, 6] – Biased reporting on dose assessment combining low-dose vitamin D with 800 IU vitamin D trials – Biased reporting on BMD findings	– The authors report no benefit for BMD although, in 3 of 5 BMD locations, benefits of vitamin D were significant, with 0.34% on total hip BMD (p = 0.002), 0.76% on femoral neck (p < 0.001), and 0.25% on lumbar spine (p = 0.05) – Authors report no benefit on falls and fractures – Re-analysis of 800–1000 IU vitamin D trials of this meta-analysis and excluding bolus trials suggests a significant 14% reduction in total fractures and 12% reduction in falls [16]

BMD bone mineral density, RR relative risk, CI confidence interval, RCT randomized controlled trial

dose, sex, fracture history, dietary calcium intake and baseline serum 25-hydroxyvitamin D concentration. The authors concluded that the routine use of calcium, vitamin D and the combination in community-dwelling older people is not supported by the findings. In a review of the meta-analysis by Zhao et al. [1], four aspects of their approach were identified that may affect the validity of their conclusions and implications for public health [7]:

– First, with the inclusion of trials among middle-aged adults age 50+ years and exclusion of older adults living in institutions, the authors selected a target population less vulnerable to low calcium intake,

vitamin D deficiency and fracture risk. Notably, this led to exclusion of many relevant data on the overall efficacy of calcium and vitamin D.

– Second, the authors included many studies that had little chance to demonstrate a benefit of the interventions. In one third of the trials follow-up was too short to demonstrate a benefit on fracture risk by the interventions as skeletal benefits cannot be expected to occur immediately (11 of 33 with follow-up of ≤12 months), 4 trials had an open study design without a treatment in the control group, and 1 study had an incorrect fracture report [8].

– Third, adherence to supplements was not addressed. While the authors acknowledged this limitation with their argument that assessment of adherence substantially differed between included trials, this was achieved in two prior meta-analyses demonstrating its significance [9, 10]. Notably, in the heavily weighted Record trial in the Zhang meta-analysis, only about half of the participants were taking any of the vitamin D or calcium supplements at the halfway point in the 5-year trial [11].

– Fourth, for vitamin D alone 8 of the 12 trials gave vitamin D in bolus doses (orally or intramuscular

administration), which has repeatedly raised concerns in the literature about promoting both falls and fractures [5, 12]. While it may be hard to make an a priori case to exclude all bolus studies of vitamin D, the Sanders trial [5] made a fairly convincing case that high dose bolus supplementation annually is bad, and so it is very possible that high monthly boluses are also bad; however, the authors have failed to address this concern in a subgroup analysis.

Primary prevention in community-dwelling adults aged 50+ years without osteoporosis and without vitamin D deficiency

The US Preventive Task Force panel [2] performed a careful review of the evidence in 2018 if and to what extent supplements containing vitamin D or calcium individually and in combination contribute to the primary prevention of fractures among community-dwelling adults age 50+ years not at risk for osteoporosis or vitamin D deficiency [13]. Acknowledging the limited data available for primary prevention, the panel recommended against daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures among community-dwelling adults. For vitamin D doses greater than 400 IU and calcium doses greater than 1000 mg, the panel concluded that there is insufficient evidence to assess a benefit. For example, for the higher dose of vitamin D, the panel identified one large trial with 4-monthly 100,000 IU vitamin D with a benefit on fracture risk [14] and one large trial with monthly 100,000 IU vitamin D without a benefit on fracture risk [15].

Fracture prevention with vitamin D without a combination with calcium

The authors [4] identified 81 unblinded and blinded randomized trials among 44,790 adults that compared vitamin D to untreated controls, placebo or another dosage of vitamin D. The authors reported no effect of vitamin D supple-

Z Gerontol Geriat <https://doi.org/10.1007/s00391-019-01573-9>
© Springer Medizin Verlag GmbH, ein Teil von Springer Nature 2019

H. A. Bischoff-Ferrari

Should vitamin D administration for fracture prevention be continued? A discussion of recent meta-analysis findings

Abstract

In consideration and critical review of four recent meta-analyses on vitamin D and fracture prevention, vitamin D supplementation with or without calcium is supported among older adults age 65 years and older at risk of vitamin D deficiency and fractures if given in daily or equivalent weekly or monthly doses of 800 to 1000 IU and with good adherence. Vitamin D supplementation might not be effective in primary prevention among adults age 50 years and older without vitamin D deficiency and osteoporosis; however, clinical

trials on primary prevention are limited. Notably, large annual bolus administration of vitamin D is detrimental with regard to falls and fractures among older adults at risk of fractures and should not be continued in clinical care. Larger monthly doses of 100,000 IU need further evaluation with respect to efficacy and safety.

Keywords

Review · Deficiency · Guidelines · Vitamin D · Old age

Sollte die Frakturprävention mit Vitamin D fortgesetzt werden? Eine Betrachtung aktueller Metaanalysen

Zusammenfassung

Nach kritischer Überprüfung von vier aktuellen Metaanalysen zu Vitamin D und Frakturprävention ist die Vitamin-D-Supplementierung mit oder ohne Kalzium bei ≥ 65 -jährigen Erwachsenen mit Risiko eines Vitamin-D-Mangels und von Frakturen zu befürworten, wenn bei guter Adhärenz täglich oder äquivalent wöchentlich bis monatlich Dosen von 800 bis 1000 IU pro Tag gegeben werden. Eine Vitamin-D-Supplementierung ist in der Primärprävention bei ≥ 50 -jährigen Erwachsenen ohne Vitamin-D-Mangel und Osteoporose möglicherweise nicht wirksam; allerdings ist die klinische

Studienlage zur Primärprävention beschränkt. Anzumerken ist, dass die Applikation hoher jährlicher Vitamin-D-Boli bei älteren Patienten mit Frakturrisiko negative Effekte auf das Sturz- und Frakturrisiko hat und in der Klinik keine Anwendung mehr finden sollte. Höhere monatliche Dosen von 100.000 IU müssen bezüglich ihrer Wirksamkeit und Sicherheit weiter untersucht werden.

Schlüsselwörter

Übersicht · Mangel · Leitlinien · Vitamin D · Hohes Alter

mentation on fractures and falls. They also reported no benefit for bone mineral density (BMD) given the subjectively defined futility boundary of 0.5% improvement. Notably, in 3 out of 5 BMD skeletal locations the benefits of vitamin D were significant, with 0.34% on total hip BMD ($p=0.002$), 0.76% on femoral neck ($p<0.001$) and 0.25% on lumbar spine ($p=0.05$), in fact suggesting that vitamin D does have a benefit on BMD and especially so at the hips. Also, with respect to fracture risk this meta-analysis has several limitations according to a review and re-analysis of this meta-analysis [16]:

- First, the authors excluded a significant portion of the literature on vitamin D, namely all trials that

combined vitamin D with calcium and compared to placebo. Such trials constitute approximately 40% of high-quality data on fracture reduction and contributed to the current guidelines recommending 800 IU vitamin D. The extent of this bias is documented by the 2016 meta-analysis by Weaver et al. described above, who documented a significant 15% reduction of total fractures and a 30% reduction of hip fractures [3].

- Second, the authors suggest that current recommendations on vitamin D should be revised according to their results; however, current guidelines refer to a daily dose of 800–1000 IU vitamin D, while lower doses are considered ineffective [17, 18]. Also,

large annual bolus applications have consistently increased the risk of falls and fractures [5, 6] and are not reflected by current guidelines on vitamin D. A re-analysis of 8 of the authors' randomized placebo-controlled trials for total fractures and 11 for falls [16], that tested 800–1000 IU vitamin D with more than 50% adherence, and excluding the large annual dosing trials, suggests a significant 14% reduction in total fractures (RR = 0.86; 95% CI 0.75–0.98) and a significant 12% reduction in falls (RR = 0.88; 95% CI 0.81–0.95).

Next to these limitations that raise questions regarding the conclusions by Bolland et al. [16], and relevant to clinical care, the re-analyses of the subset of studies included by Bolland et al. that reflect current guideline practice [16], suggest that vitamin D supplementation in a daily dose of 800–1000 IU does reduce the risk of both falls and fractures.

Discussion

Among the four recent meta-analysis discussed individually above and summarized in **Table 1**, only the meta-analysis by Weaver et al. found a significant 15% reduction of total fractures (RR = 0.85; 95% CI 0.73–0.98) and a significant 30% reduction of hip fractures (RR = 0.70; 95% CI 0.56–0.87) for a daily combination of vitamin D plus calcium [3]. The other three meta-analyses suggested that there is no benefit of vitamin D. In order to transfer these findings to clinical care, it is important to understand the goals and target groups of these recent meta-analyses.

Regarding the meta-analyses by Zhao et al. [1] and the US Preventive Task Force [2], both teams of authors stated that the recommendations only apply to community-dwelling adults who are not known to have osteoporosis or vitamin D deficiency, or are not at high risk of falling. The results therefore do not apply to a large segment of older adults that have these risk factors.

The fourth meta-analysis by Bolland et al. [4] included trials of primary and secondary prevention among adults aged

50 years and older. The findings regarding no benefit of vitamin D has been questioned based on the exclusion of approximately 40% of high-quality trials on the combined effect of vitamin D and calcium, and concern about the biased results by vitamin D dose [16]. In fact, a re-analysis of the Bolland et al. meta-analysis for trials that tested the currently recommended dose of 800–1000 IU vitamin D with more than 50% adherence, and excluding the large annual dosing trials, suggested a significant 14% reduction in total fractures (RR = 0.86; 95% CI 0.75–0.98) and a significant 12% reduction of falls (RR = 0.88; 95% CI 0.81–0.95) [16].

Practical conclusions

Based on the limitations of the Bolland et al. meta-analysis, the primary prevention target group of Zhao et al. [1] and the US Preventive Task Force [2] it may be too early to recommend the cessation of vitamin D with or without calcium for the prevention of fractures among all community-dwelling adults. Notably, for older adults at increased risk for fractures and/or vitamin D deficiency it is still reasonable to take 800–1000 IU vitamin D per day, following recommendations by the International Osteoporosis Foundation [19], the US Endocrine Society [20] and National Osteoporosis Foundation (NOF) [21] guidelines. Reducing the risk of fractures among vulnerable older adults age 65 years and older, who sustain 75% of all osteoporotic fractures [22], remains a major public health target. Also, in view of the small risk and cost it is believed that it is essential not to discourage older adults from receiving daily 800–1000 IU vitamin D and to further study the optimal dose and application of vitamin D.

Corresponding address

Prof. Dr. Dr. Heike A. Bischoff-Ferrari
Dept. of Geriatric Medicine and Aging Research, University Hospital Zurich and University of Zurich
Rämistrasse 100, 8091 Zurich, Switzerland
heike.bischoff@usz.ch

Compliance with ethical guidelines

Conflict of interest H.A. Bischoff-Ferrari has received speaker fees from Nestlé, Roche, Pfizer, WILD, Sandoz, and Vifor, and received investigator initiated and independent research funding from DSM Nutritional Products, WILD, Pfizer, and Besins.

For this article no studies with human participants or animals were performed by the author. All studies performed were in accordance with the ethical standards indicated in each case.

References

- Zhao JG et al (2017) Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA* 318(24):2466–2482
- Force USPST et al (2018) Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US preventive services task force recommendation statement. *JAMA* 319(15):1592–1599
- Weaver CM et al (2016) Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int* 27(1):367–376
- Bolland MJ, Grey A, Avenell A (2018) Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol* 6(11):847–858
- Sanders KM et al (2010) Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 303(18):1815–1822
- Smith H et al (2007) Effect of annual intramuscular vitamin D on fracture risk in elderly men and women—a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatol* 46(12):1852–1857
- Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC (2018) Issues of trial selection and subgroup considerations in the recent meta-analysis of Zhao and colleagues on fracture reduction by calcium and vitamin D supplementation in community-dwelling older adults. *Osteoporos Int* 29(9):2151–2152
- Bischoff-Ferrari HA et al (2008) Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. *Am J Clin Nutr* 87(6):1945–1951
- Bischoff-Ferrari HA et al (2009) Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 169(6):551–561
- Bischoff-Ferrari HA et al (2012) A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med* 367(1):40–49
- Grant AM et al (2005) 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* 365(9471):1621–1628
- Bischoff-Ferrari HA et al (2010) Effect of high-dosage cholecalciferol and extended physio-

- therapy on complications after hip fracture: a randomized controlled trial. *Arch Intern Med* 170(9):813–820
13. Bischoff-Ferrari HA, Bhasin S, Manson JE (2018) Preventing fractures and falls: a limited role for calcium and vitamin D supplements? *JAMA* 319(15):1552–1553
 14. Trivedi DP, Doll R, Khaw KT (2003) 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* 326(7387):469
 15. Khaw KT et al (2017) 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* 5(6):438–447
 16. Bischoff-Ferrari HA et al (2019) Vitamin D supplementation and musculoskeletal health. *Lancet Diabetes Endocrinol* 7(2):85
 17. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, Flicker L, Wark J, Jackson RD, Cauley JA, Meyer HE, Pfeifer M, Sanders KM, Stähelin HB, Theiler R, Dawson-Hughes B (2012) A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med* 367(1):40–49. <https://doi.org/10.1056/NEJMoa1109617>
 18. Foundation IO Guideline on vitamin D. <https://www.iofbonehealth.org/osteoporosis-musculoskeletal-disorders/osteoporosis/prevention/vitamin-d>. Accessed 17 Oct 2018
 19. Dawson-Hughes B et al (2010) IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* 21(7):1151–1154
 20. Holick MF et al (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96(7):1911–1930
 21. Cosman F et al (2014) Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 25(10):2359–2381
 22. Melton LJ 3rd, Crowson CS, O'Fallon WM (1999) Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. *Osteoporos Int* 9(1):29–37