Vitamin D, bones and muscle: myth versus reality

AUTHOR(S)

G Duque, Robin Daly, K Sanders, D P Kiel

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Review Article

Vitamin D, bones and muscle: myth versus reality

Gustavo Duque
Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health; and Department of Medicine, Melbourne Medical School – Western Precinct, The University of Melbourne, St. Albans; Victoria, Australia

Robin M. Daly
Department of Medicine, Melbourne Medical School – Western Precinct, The University of Melbourne, St. Albans; Victoria, Australia and Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Burwood,Victoria, Australia

Kerrie Sanders
Department of Medicine, Melbourne Medical School – Western Precinct, The University of Melbourne, St. Albans; Victoria, Australia and Institute for Health and Ageing, Australian Catholic University, Melbourne, Victoria, Australia

Douglas P. Kiel
Institute for Aging Research, Hebrew SeniorLife; and Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

Objectives: *Evidence regarding the efficacy and dosing of vitamin D on fall and fracture prevention, with or without calcium, is characterised by uncertainty.*

Methods: *A panel of experts was organised at the First Australasian Conference on Sarcopenia and Frailty in Melbourne, Australia, in November 2016 to provide an interpretation of the current evidence and to give their opinions regarding the supplementation of vitamin D in three hypothetical cases.*

Results and Conclusion: *The authors conclude that (i) target serum 25(OH)D concentration should be 50 to 60 nmol/L year round, with a conservative upper limit <100 nmol/L; (ii) change in serum concentrations at any given dose is highly variable among individuals; (iii) dosing interval may need to be <2 months to have a continuous benefit; (iv) a loading dose can raise levels to target quickly, but there is no evidence yet that this has any positive effect on falls or fracture outcomes; and (v) a maintenance dose of 1000 IU/day, or given as an equivalent dose weekly or monthly, is sufficient for most individuals.*

Practice impact: Vitamin D supplementation and higher dietary calcium together are effective for fracture risk reduction. Vitamin D improves muscle strength and reduces the risk of falls. Frail older patients with low baseline levels of vitamin D (<30 nmol/L) show the highest therapeutic benefit.

Caution is needed with the use of high-dose vitamin D supplementation regimens.

Key words: *falls, fractures, osteoporosis, sarcopenia, vitamin D.*

Introduction

Evidence regarding the efficacy and dosing of vitamin D on fall and fracture prevention, with or without calcium, is characterised by uncertainty. International vitamin D experts Professor Robin Daly, Professor Douglas P. Kiel and Professor Kerrie Sanders participated in a panel discussion chaired by Professor Gustavo Duque at the First Australasian Conference on Sarcopenia and Frailty in Melbourne, Australia, in November 2016 to provide an interpretation of the current evidence and to give their opinions regarding the supplementation of vitamin D in three hypothetical cases.

An overview of evidence

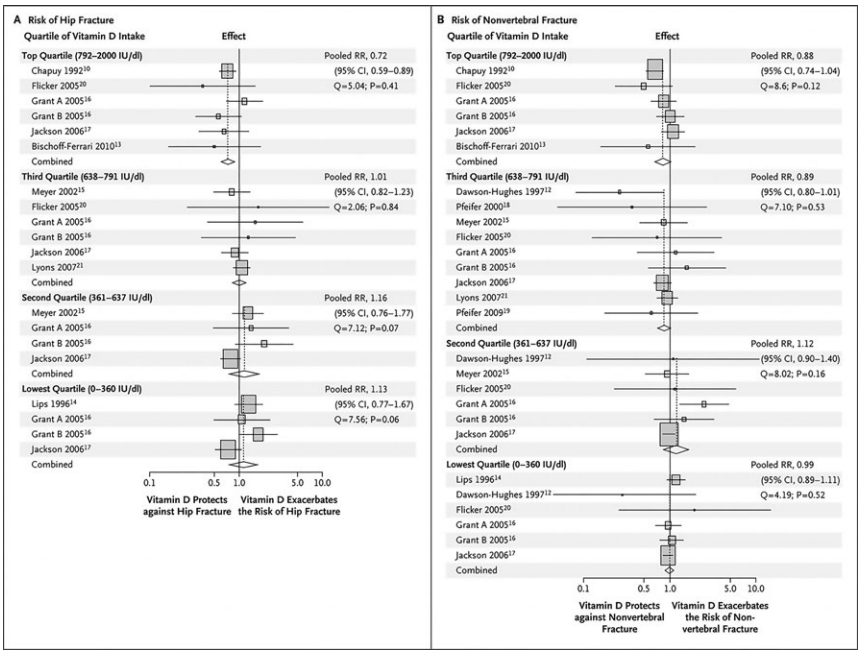
Vitamin D and fracture prevention

A recent Cochrane review of 53 trials with 91 791 participants from a range of community, nursing home or hospital populations assessed the evidence for vitamin D with or without calcium in fracture prevention [1]. The authors concluded there is high-quality evidence that vitamin D alone is unlikely to be effective in preventing hip fractures or fracture of any type. However, none of the trials included tested vitamin D3 at doses greater than 800 IU/day and the authors speculate that higher daily doses may be needed to raise serum 25-hydroxyvitamin D (25(OH)D) concentrations sufficiently [1].

In men and women aged ≥65 years living in the community, Trivedi et al. [2] demonstrated that 100 000 IU vitamin D3 administered orally every 4 months without calcium reduced the overall rate of fractures of the hip, wrist or forearm, or vertebrae by 33% compared with placebo over 5 years. A 2012 meta-analysis which analysed source data reported that a mean vitamin D intake ranging from 792 to 2000 IU/day (or a serum 25(OH) D > 61 nmol/L) reduced hip fractures by 30–37%

Correspondence to: Professor Gustavo Duque, Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health. Email: gustavo.duque@unimelb.edu.au

Figure 1: Results from a meta-analysis showing pooled analysis of relative risk, according to quartile of actual intake of vitamin D. A meta-analysis pooled participant-level data from 11 double-blind, randomised, controlled trials of oral vitamin D supplementation (daily, weekly or every 4 months), with or without calcium, compared with placebo or calcium alone in persons 65 years of age or older. The forest plots show the results of individual trials at each quartile of actual vitamin D intake. The Q-test shows homogeneity among trials with respect to quartiles of actual intake of vitamin D. The size of the symbol indicates the size of the individual trial and its representation in each quartile of vitamin D intake, the bars indicate 95% confidence intervals, and the dotted lines indicate the pooled effect across the individual trials within each quartile of vitamin D intake. RR denotes relative risk. Adapted with permission from Bischoff-Ferrari et al. [3].



(Figure 1) [3]. However, high-dose supplementation regimens may have some adverse effects. A double-blinded, placebo-controlled trial of 2256 community-dwelling women aged 70+ years receiving a large oral dose of 500 000 IU vitamin D3 annually found 15% more falls and 26% more fractures among people taking vitamin D [4]. Subsequent analysis showed a non-significant tendency for increased fractures in the first 3 months after dosing when 25(OH)D levels were at their peak [5].

For vitamin D plus calcium, the Cochrane review concluded there is high-quality evidence that this combination reduces hip fractures by 16% as well as the risk of any type of fracture [1]. A recent systematic review indicated that increasing calcium intake has no effect on fracture risk [6]. However, a beneficial effect from increased dietary calcium intake cannot be excluded. Conversely, an alternative meta-analysis found calcium plus vitamin D supplementation produced a significant 15% reduction in risk for total fractures and a 30% reduced risk for hip fracture [7]. Overall, the benefit of oral vitamin D supplementation was independent of additional calcium supplementation among seniors age 65 and older – in both institutionalised and community-dwelling seniors [8]. Collectively, the current evidence supports the use of calcium plus vitamin D supplements as an intervention to reduce fracture risk in both community-dwelling and institutionalised middle-aged to older adults. It should be noted that pharmacologic treatment of individuals with osteoporosis and/or a history of fragility fractures is the most effective way to prevent future fractures.

Role of vitamin D on muscle health and falls risk

While there are many observational and cross-sectional studies looking at the association between serum 25(OH)D status and physical function, a meta-analysis of 29 randomised controlled trials showed a positive effect of vitamin D supplementation on muscle strength, with the greatest benefit seen in those with the lowest baseline serum 25(OH)D levels [9]. Others have reported that vitamin D can improve sway and mobility [10,11], although these findings are not universal [9]. In terms of falls, at least 10 meta-analyses of intervention trials published in the last decade have found an overall reduction following vitamin D supplementation [12]. However, a Cochrane review reported a reduced rate of falls only in those with low baseline vitamin levels [13] and another meta-analysis only observed a significant reduction in falls (19–23%) at a dose of 700–1000 IU/day or an achieved serum 25(OH)D level ≥60 nmol/L [14]. While a recent meta-analysis reported no effect of vitamin D on falls, issues related to the inclusion criteria for trials that were analysed make it difficult to interpret these findings [15]. There is some evidence that high-dose supplementation may be associated

with an increased risk of falls [4], which may be related in part to the possibility that an increase in serum 25(OH)D is associated with an increase in muscle strength up to a certain level, after which the relationship becomes inverse, with higher levels associated with decrease in muscle strength [5].

Optimal dosing and administration of vitamin D supplements in fall and fracture prevention

There is considerable variation in the individual response to a fixed dose of vitamin D_3 supplementation, with a wide range of serum 25(OH)D levels achieved [16]. While individual baseline serum 25(OH)D levels have an important influence on the response, as shown in Table 1 there are a number of other factors that can influence changes in circulating 25(OH)D concentrations following treatment.

Globally, there is considerable heterogeneity in the recommendations for vitamin D for musculoskeletal health benefits. Guidelines for Australia and New Zealand and the US Institute of Medicine recommend a target serum 25(OH)D of 50–60 nmol/L year round, which are based on a population model to prevent vitamin D deficiency in 97.5% of the general population. In contrast, the Endocrine Society (and the International Osteoporosis Foundation) suggests a target of at least 75 nmol/L, and these guidelines are targeted to prevent vitamin D deficiency and avoid other risks related to inadequate vitamin D status in clinic patients [17,18].

Secondary analyses from two meta-analyses suggest that doses of ~800–2000 IU/day reduce fracture risk and falls in community-dwelling individuals and nursing home residents, while lower doses have no effect [3,19]. It should be noted that nearly all the trials reporting positive effects also provided calcium supplements. Fracture risk reduction is significantly greater when compliance is high [20].

Several trials using high-dose, intermittent vitamin D report an increase rather than a decrease in both falls and fractures [21]. This negative effect was observed in patients taking 500 000 once a year [4], and even 60 000 IU once a month [22].

Table 1: Factors influencing dose response to vitamin D supplementation [17,18]

Baseline serum 25(OH)D levels
Age
Race/ethnicity
Body composition (obesity)
Renal function
Geographic locations
Sex
Calcium/phosphorus status
Genetics
Oestrogen use
Supplement use of vitamin D_2 or D_3

A loading dose may be required in those with levels <50 nmol/L and a loading dose of 500 000 IU vitamin D3 has been shown to rapidly normalise 25(OH)D levels in frail elder persons [23]. Nevertheless, there is no evidence of the effect of loading doses on falls and fracture efficacy.

Case discussion

The panel of experts gave their views on the management of three hypothetical cases to consider how this evidence could apply in practice.

Case 1

Sophie, an otherwise well, active 38-year-old woman, presents to discuss a recent blood test showing serum vitamin D of 40 nmol/L. She is concerned because she has heard there are health implications of having low vitamin D. She has a history of chronic hypothyroidism, on thyroxine 50 μg/day, and she does not smoke, drinks one glass of wine a day and attends a regular outdoor exercise program twice a week. Her diet is well balanced, and her main source of dietary calcium is milk on her breakfast cereal. Her physical examination is normal with the exception of mild osteoarthritis.

Professor Kerrie Sanders

As her hypothyroidism may put her at increased risk of low vitamin D levels, I would prefer her level to be 50–60 nmol/L so I would recommend a supplement of about 1000 IU a day. The exercise is probably of insufficient frequency per week and the type of exercise would be important in relation to bone health. It is unlikely that she is meeting the requirements for calcium for a 38-year-old woman with just milk on cereal. The recommendation would be 4 serves a day, and she is getting at most 1 serve so that should be also addressed.

Professor Robin Daly

It is important to know the time of year her 25(OH)D levels were measured, and also what time of day she is undertaking the regular outdoor exercise; the amount of effective UVB rays is reduced in the morning/evening which limits the capacity to produce vitamin D. I agree with a supplement of around about 1000 IU per day, but I would encourage her to do some outdoor exercise, perhaps 10 minute during the middle of the day depending on the time of year, then to cover up to reduce her risk of skin cancer. If she had dark coloured skin, she would need 3–6 times more UVB exposure to get the same effective dose of vitamin D.

Professor Douglas Kiel

If you send a single blood test to 10 laboratories, you will get variability in the assay. In addition, there is increasing evidence that vitamin D levels are age dependent and that the amount of 25(OH)D required to maintain a specific PTH-level increases substantially with age. Therefore,

40 nmol/L is probably adequate for a 38-year-old woman. Other than ensuring adequate thyroid replacement and making sure her diet is well rounded in terms of protein, fruits and vegetables and calcium, I would not place this patient on supplements and I would encourage her doctor not to order vitamin D assays for young healthy patients.

Case 2

Edith, an otherwise well, active 78-year-old woman, presents to emergency after suffering a fall at home. A pelvic fracture is documented, and she is admitted for pain management and rehab under aged care. Her mother sustained a fracture to her neck of femur at the age 85. Edith smokes ten cigarettes and drinks three glasses of wine a day. Her main source of dietary calcium is 'some' cheese about three times a week. She is on amitriptyline 10 mg/d for depression and metoprolol to control her blood pressure. Medical history includes depression, hypertension and chronic pain. Edith is 165 cm tall and weighs 58 kg. Her blood tests report serum vitamin D of 16 nmol/L, and her serum calcium, renal function and PTH are normal.

Professor Kerrie Sanders

It is very likely that she has fallen more frequently than this one case and that might influence further decisions. She has risk factors, her mother had a hip fracture, she smokes 10 a day, and her alcohol is above what is recommended. Her calcium intake is low, and I would encourage her to increase her dietary calcium. If she is resistant, I would consider starting a calcium supplement of 500 mg/day. Her BMI is around 21, which is within normal but at the lower end of the spectrum which may indicate she could benefit from additional dietary protein. A serum 25OHD of 16 nmol/L is very low and she would definitely qualify for supplements, but I would only start her at 1000 IU vitamin D and if necessary 500 mg of calcium a day. She would require other interventions to look at her falls and fracture risk.

Professor Robin Daly

I would disagree with a dose of 1000 IU a day because with a current 25(OH)D levels of 16 nmol/L, 1000 IU a day would probably only get her to around 30–40 nmol/L. The Australian and New Zealand guidelines published in 2012 recommended 3000–5000 IU/day for more severe deficiency until levels reached 50–60 nmol/L. Check levels 3 months after the initial dosing regimen and then drop down to 1000–2000 IU/day if she was above 50–60 nmol/L. I would agree that vitamin D with calcium is needed. A targeted exercise/rehab program for fall and fracture prevention is required to improve her mobility and function to reduce her risk of future falls.

Professor Douglas Kiel

This woman had a fragility fracture and her FRAX score is around 43–47% so she is at high risk. I would say she needs to have 2000 IU vitamin D daily at least. The American Geriatric Society recommends a daily dose of 4000 IU a day from all sources; sun exposure, plus diet and supplements. In this case, 2000 IU is reasonable for about 3 months, but she also needs an osteoporosis drug once her vitamin D levels are at 50 nmol/L. A multifactorial geriatric assessment is needed to identify other fall prevention interventions. This is a classical geriatric patient who would benefit from a full assessment to target fall risk factors and treat bone fragility.

Case 3

Steve is an 89-year-old man living in a residential aged-care institution. He is brought to emergency by ambulance after suffering a fall in his nursing home and is unable to stand by himself due to pain and external rotation of his left leg. His previous medical history includes severe osteoarthritis with right total knee replacement, moderate dementia (MMSE 19/30), hypertension, type 2 diabetes, congestive cardiac failure and mild chronic renal failure. His record at the nursing home reports four falls in the last 6 months. He is partially dependent in his activities of daily living (ADLs) and instrumental ADLs, he uses a walker to go to the dining area, and he occasionally participates in the local exercise program. Current medications include paracetamol 1gm/td, perindopril 4 mg/day, metformin 1 g/days, hydrochlorothiazide 25 mg/mane. Blood test results include vitamin D concentration of 15 nmol/L, serum PTH of 6.9 pmol/L, creatinine 112 μmol/L, eGFR 39 mL/min, calcium 2.30 mmol/L and albumin 28 g/L. The patient was started on vitamin D 50 000 IU/month for 3 months.

Professor Douglas Kiel

This man living in residential care has multiple comorbidities and many fall risk factors and now has likely broken his left hip. If confirmed, he would benefit from geriatric/orthopaedic co-management during his hospitalisation for fracture repair. I would increase the vitamin D dose to 50 000 per week for at least a couple of months and then cut back to a reduced daily dosing. His medications may need to be changed to lower his risk of falls. Treating nursing home residents with osteoporosis medications is based on clinical judgement because there is only one study with zoledronic acid in nursing home residents.

Professor Robin Daly

I would ask about his exercise program and what is involved. It might be dictated by what he is capable of undertaking, but just because he has comorbidities does not mean he should not exercise; anyone can exercise but it needs to be targeted, individualised and supervised. I agree that a dose of 50 000 IU vitamin D once a month is too low and probably would not be effective. I would also consider his diet; his protein intake may need to be addressed.

Professor Kerrie Sanders

This man is in a nursing home and he has lots of comorbidities, if he has suffered a hip fracture then the statistics

are against him. I would make his time left comfortable without much active or expensive intervention.

Summary and Conclusion

The balance of evidence supports the use of vitamin D and higher dietary calcium together for fracture risk reduction. Vitamin D also appears to improve muscle strength and reduce the risk of falls. The greatest benefit to muscle function/falls risk is likely to be in those who have low baseline levels (<30 nmol/L) and impaired function, and caution is needed with the use of high-dose supplementation regimens.

The evidence for vitamin D dosing suggests:

1 Target serum 25(OH)D concentration 50–60 nmol/L year round, conservative upper limit <100 nmol/L.
2 Change in serum concentrations at any given dose is highly variable among individuals.
3 Dosing interval may need to be <2 months [24] to have a continuous benefit although others estimate 21 days coinciding with the half-life of 25(OH)D [25].
4 A loading dose can raise levels to target quickly, but there no evidence yet that this has any positive effect on falls or fracture outcomes.
5 A maintenance dose of 1000 IU/day, or given as an equivalent dose weekly or monthly, is sufficient for most individuals. Monthly bolus doses of vitamin D among seniors with a prior fall are safe and most effective at 24 000 IU/month.

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