Randomised controlled trial

High-dose vitamin D supplementation does not alter bone mass or muscle function over 1 year in postmenopausal women

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Context

As recent systematic reviews have demonstrated, associations documented in observational studies between low vitamin D status and a wide range of disease outcomes have generally not been borne out by randomised control trials conducted thus far[1]; even for the traditional vitamin D-related outcomes of bone mineralisation and muscle function, such intervention studies have not provided a uniform message.[2] Indeed there is continued controversy regarding what constitutes an optimal serum 25-hydroxyvitamin D concentration [(25OH)D].[3]

Methods

Against this backdrop, Hanson *et al* aimed to test, in a randomised, double-blind, placebo-controlled trial setting, whether maintenance of 25(OH)D>30 ng/mL for 1 year would lead to improvements in total fractional calcium absorption (TFCA), bone density and muscle function. The investigators went to great lengths to mitigate confounding effects of calcium intake and parathyroid hormone (PTH) levels and the trial was well designed in terms of methodology and analysis. At baseline, 25(OH)D ranged 14–27 ng/mL among the 230 postmenopausal women (aged≤75 years) enrolled. They were randomised to either 800 IU vitamin D_3 daily (n=75), twice monthly 50 000 IU vitamin D_3 (n=79) or placebo (n=76). The high-dose group received initial loading at 50 000 IU/day for 15 days with sham loading in the other two groups.

Findings

Importantly the mean baseline 25(OH)D was similar in all groups (21 ng/mL), just above the concentration that the Institute of Medicine would view as sufficient.[4] After adjustment for baseline levels, TFCA increased marginally in the high-dose group (by 1%; 10 mg/day) in contrast to a 2% decrease in the low-dose group (p=0.005 vs high dose), and a 1.3% decrease in the placebo group (p=0.03 vs high dose). 25(OH)D rose substantially in the high dose and modestly in the low dose, compared with the placebo groups. No changes were observed in terms of Dual-energy X-ray Absorptiometry (DXA) indices or functional assessments.

Commentary

Overall then, this was not a population with frank vitamin D deficiency, a point borne out by the lack of perturbation among the other biochemical indices at baseline. However, the relationship among 25(OH)D, PTH concentrations and fractional calcium absorption is a vexed one, with previous studies suggesting optimal 25(OH)D anywhere between 25 and 125mnol/L.[3 5] Interestingly the high-dose group did achieve really quite high 25(OH)D at 30 days (mean 80 ng/mL) following loading, which is greater than that achieved at 1 month after 500 000 IU vitamin D_3 given as an oral (not intramuscular as Hanson *et al* incorrectly state) dose in the Sanders trial.[6] Indeed, in a UK trial, 300 000 IU ergocalciferol given annually intramuscularly, resulted in a greater incidence of hip fractures.[7] Reassuringly in the present study, falls and fractures did not differ across groups, but the population was on average 15 years younger than the Australian cohort and therefore at much lower baseline risk of these events. These results taken together do raise questions about intermittent dosing at high levels; as the authors suggest, the underlying mechanisms are not clear, but may involve excess calcitriol and increased bone turnover.[6] We can conclude, as did the study's authors, that supplementing women with either 800 IU daily or 50 000 IU twice per month vitamin D_3 has no benefits for bone or muscle outcomes in this age group when baseline concentrations are an average of 21 ng/mL.

Implications

The place of calcium and/or vitamin D supplementation as a population strategy remains uncertain, and overall the existing evidence base most strongly supports use of such treatments in those at high risk of deficiencies or who are on antiosteoporosis therapy.[2]

Competing interests None declared.

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