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High dose vitamin D supplementation does not alter bone mass or muscle function over one year

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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 mineralization 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 randomized, double-blind, placebo-controlled trial setting, whether maintenance of 25(OH)D>30ng/ml for one year would lead to improvements in total fractional calcium absorption (TFCA), bone density and muscle function at one year. The investigators went to great lengths to mitigate confounding effects of calcium intake and PTH levels and the trial was well designed in terms of methodology and analysis. At baseline, 25(OH)D ranged from 14 to 27ng/ml amongst the 230 postmenopausal women (aged 75 years) enrolled. They were randomised to either 800IU vitamin D₃ daily (n=75), twice monthly 50,000IU vitamin D₃ (n=79) or placebo (n=76). The high-dose group received initial loading at 50,000IU/day for 15 days with sham loading in the other 2 groups.

Findings

Importantly the mean baseline 25(OH)D was similar in all groups (21ng/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%; 10mg/day) in

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Commentary on: Treatment of Vitamin D Deficiency in Postmenopausal Women: A Randomised Clinical Trial.

contrast to a 2% decrease in the low dose group ($p=0.005$ versus 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 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 amongst the other biochemical indices at baseline. However, the relationship between 25(OH)D, parathyroid hormone concentrations and fractional calcium absorption is a vexed one, with previous studies suggesting optimal 25(OH)D anywhere between 25-125nmol/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 the that achieved at one month after 500,000IU vitamin D₃ given as an oral (not intramuscular as Hanson et al incorrectly state) dose in the Sanders trial[6]. Indeed, in a UK trial, 300,000IU 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 fifteen 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 800IU daily or 50,000IU twice per month vitamin D₃ has no benefits for bone or muscle outcomes in this age group when baseline concentrations are an average of 21ng/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 anti-osteoporosis therapy[2].

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