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COMMENTARIES

Vitamin D – Let's Get Back to the Evidence Base

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Commentary on: Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010 May 12;303(18):1815-22.

Vitamin D was originally discovered as the factor that cured rickets in children and has subsequently been demonstrated to be vital to maintaining normal mineral homeostasis throughout life. Deficiency in adults results in osteomalacia, a condition characterized by impaired mineralization of bone, myopathy, and diffuse musculoskeletal pain. Vitamin D is a misnomer, since vitamins are regarded as required dietary constituents, whereas humans make most of their own vitamin D in the skin as a result of sunlight exposure, and this acts as a prohormone in a tightly regulated endocrine system. As a result, vitamin D deficiency is principally a marker of poor sunlight exposure, and levels are reduced in frailty and in a wide range of chronic illnesses, since such individuals spend less time exercising outdoors. Vitamin D levels are also inversely related to fat mass (1), since vitamin D is lipid soluble and thought to be sequestered in adipose tissue. This fact could further explain its associations with diabetes, hypertension and other cardiovascular diseases. Its receptors are widely distributed, leading to the proposal that it influences activity in a wide variety of organ systems, although direct clinical evidence for this is mostly lacking, at present.

Vitamin D, along with calcium, has long been a cornerstone of osteoporosis management. The rationale for this is that low levels of vitamin D are associated with increased parathyroid hormone levels and, therefore, increased rates of bone resorption. Vitamin D replacement reduces parathyroid hormone when baseline levels are <50 nmol/L (2;3), and bone loss is slowed (4). However, reductions in bone resorption have not been consistently demonstrated (5), and bone resorption may even increase after vitamin D supplementation (6), possibly as a result of vitamin D action on the osteoblast resulting in increased levels of RANKL and increased osteoclastogenesis. It has also been difficult to consistently demonstrate reductions in fracture numbers with vitamin D supplementation (7), with some large studies of vitamin D monotherapy showing no beneficial effect (8;9), although others have (10). The most positive fracture studies with vitamin D have co-administered calcium (11;12), which does not permit a determination as to whether it is calcium, vitamin D or their combination that is effective. Since calcium supplementation has been consistently demonstrated to reduce bone turnover (5;13;14) and to slow bone loss (13), studies of combined therapy would be consistent with much of the therapeutic benefit coming from the calcium.

Because severe vitamin D deficiency causes myopathy, vitamin D supplementation has also been suggested to reduce falls risk, and there is a body of clinical trials that demonstrate a variety of outcomes in this respect. Meta-analyses show the same mixture of findings, depending on which studies their authors choose to include (15;16).

In the light of continuing uncertainty regarding the efficacy of vitamin D supplementation for the prevention of either fractures or falls in the elderly, it is timely that Sanders *et al*. (17) have carried out a large (n=2256), randomized, controlled trial in community-dwelling women, aged 70

years or older, considered to be at high risk of fracture. Subjects received an annual dose of cholecalciferol 500,000 IU, or placebo, administered orally each autumn or winter for 3-5 years. The long half-life of vitamin D (18) has led to the use of such intermittent regimens in the past, and they are effective in bringing serum 25-hydroxyvitamin D (25OHD) levels into the target range, and keeping them there over many months (3). They were also effective in 'normalizing' 25OHD in the Sanders study, producing median values of 120 nmol/L at one month, 90 nmol/L at three months, and 70-80 nmol/L 12 months after the dose. In contrast, the placebo group had median 25OHD concentrations of 40-50 nmol/L. Despite the success of the intervention with respect to serum 25OHD levels, this intervention did not produce beneficial effects on falls and fractures. Quite the reverse, the incidence ratio for fracture in the vitamin D group was 1.26 (95% CI, 1.00–1.59) and that for falls was 1.15 (95% CI, 1.02–1.30). There was a temporal pattern in the increases of falls and fractures, with the incidence rate ratio for fractures being 1.53 in the 3 months after dosing, in comparison with 1.18 during the rest of the year. For falls, the respective figures were 1.31 after dosing, and 1.13 subsequently.

Thus, we are again in the situation of a huge investment having been made (in terms of the time and effort of volunteers and investigators, as well as financially) to provide definitive evidence of the efficacy of vitamin D, only to be met with a negative outcome. In this instance, however, the result is more negative than most, actually demonstrating an increased fracture risk. This is not without precedent – the Wessex study (9) also showed that fracture rates were increased by 21% (for non-vertebral fractures) to 80% (for hip fractures) in postmenopausal women given 300,000 IU intramuscularly each autumn. A number of trials using the potent vitamin D metabolite, calcitriol, have also shown adverse fracture outcomes (19;20). The similarity of outcomes between the Sanders and the Wessex studies suggests that annual high-dose vitamin D therapy in postmenopausal women should be abandoned.

The mechanism of the adverse effect on fractures is likely to be via stimulation of bone resorption, as noted above, though other explanations have been offered. It has been speculated that dosing with vitamin D actually induces deficiency in 1,25-dihydroxyvitamin D, through induction of the vitamin D 24-hydroxylase (21). This seems homeostatically improbable, and would suggest that vitamin D intoxication could never occur, which is clearly not the case. In fact, this explanation is ruled out by the measurements of 1,25-dihydroxyvitamin D from the Wessex study, where a 36% increase was demonstrated in the D-supplemented group (9). In the Sanders study, it is tempting to speculate that the increase in falls caused the increase in fractures, but the increase in fractures is numerically larger, and only a minority of falls result in fractures, so this explanation is not tenable. It does, however, pose the question as to how vitamin D increases falls risk. Since there are vitamin D receptors in muscle, a sudden increase in receptor occupancy could have an adverse effect on muscle function. There are also vitamin D receptors in the central nervous system (22) so an adverse effect on balance or co-ordination is also possible.

While the Sanders study tells us that annual dosing of vitamin D in postmenopausal women should be abandoned, it potentially has much wider implications. It establishes unequivocally that vitamin D supplementation has potential toxicities other than simply hypercalcemia. Reviews on the subject repeat the mantra that doses greater than 10,000 u/day are necessary to produce toxicity – this is no longer tenable. That statement was only ever based on isolated case reports, and the only toxicity being considered was hypercalcemia. Vitamin D is a powerful bioactive compound, and those taking it deserve more thorough assessment of its safety than the haphazard process of the clinical anecdote. The toxicity observed in the Sanders study occurred at serum levels of 25OHD that are commonly being advocated and achieved with regular oral dosing with vitamin D (23). This fact exposes the huge gulf that has developed, particularly in North America, between the evidence base and routine clinical practice.

Advocates of the widespread benefits of vitamin D supplementation have brought about a redefinition of the reference range for 25OHD that has created an artificial epidemic of vitamin D deficiency. This has lead to widespread supplementation in populations and using doses that have never been systematically evaluated in large-scale clinical trials. In many ways, this is reminiscent of the widespread adoption of hormone replacement therapy in the latter part of the last century, again without adequate trial evidence for its safety or efficacy. It is disturbing that therapeutic enthusiasm has caused us to overlook these lessons of the very recent past.

While it cannot be certain that the adverse effects seen in the Sanders study will follow from daily or weekly doses of vitamin D that consistently maintain 25OHD levels >100 nmol/L, this study places the burden of proof on those who would advocate such target levels, and suggests that we should revert to using vitamin D supplementation in an evidence-based manner. While a number of trials are underway to determine whether there are therapeutic benefits of vitamin D supplementation in extra-skeletal tissues, the only established justification for its use at the present time is in the musculoskeletal system, and multiple prospective studies have demonstrated that parathyroid hormone suppression is maximal at 25OHD levels >50 nmol/L. All of the cross-sectional associations of 25OHD levels with health outcomes are potentially confounded by associations between 25OHD and sunlight exposure, exercise and obesity and, in the absence of randomized trials, provide no basis for advocating supplementation for extra-skeletal benefit. Even enthusiasm for its use for fracture prevention needs to be tempered by the slimness of the evidence base. As discussed above, much of this evidence relates to co-administration with calcium. With mounting evidence that calcium supplements significantly increase the risk of myocardial infarction to an extent that overwhelms their potential skeletal benefit (24-26), we are likely to be administering vitamin D on its own in the future. The most recent Cochrane analysis indicates that monotherapy with vitamin D has no effect on fractures (27) and little effect on falls in the community (28). Thus, with vitamin D supplementation as in all other aspects of medicine, we should return to the evidence base and remember our obligation to 'first do no harm.'

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