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High-Dose Vitamin D: Without Benefit but Not Without Risk

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It is now 100 years since deficiency of vitamin D was identified as the cause of rickets and osteomalacia (see Figure). Since then, enormous amounts of work have been undertaken elucidating the synthesis and catabolism of vitamin D, the regulation of these processes, and the mechanisms of action of vitamin D metabolites on calcium and bone metabolism. The findings of the early studies, mainly in children, that vitamin D promotes the growth and mineralisation of the skeleton have been generalised to other contexts, and vitamin D has become widely used in many conditions associated with decreases in skeletal strength, particularly in the prevention and treatment of osteoporosis. In recent times, considerable effort has been invested in demonstrating its efficacy in this regard, with trials addressing its effects on bone mineral density (BMD) and fracture incidence.

In this issue of the *Journal*, Smith et al present a further randomised controlled trial in which daily doses of 400 - 4800 IU/day are compared with placebo in their effects on BMD at the spine, hip and total body over one year [1]. No significant differences from placebo were demonstrated at any site, and there was no evidence of a dose-response effect. BMD changes were not related to achieved levels of serum total 25-hydroxyvitamin D (25OHD), free 25OHD or change in serum 1,25(OH)2D, indicating that even when these variables are pushed to above normal levels there is no suggestion of bone benefit. Bone resorption (measured as circulating levels of N-terminal telopeptide) was also unaffected by vitamin D supplementation. This appears to suggest that vitamin D, across this broad range of doses, is without effect on BMD or bone metabolism.

This negative outcome is broadly consistent with the last major meta-analysis of vitamin D on BMD, which found no evidence of effects at the spine, total hip or total body, but a 0.8% increase at the femoral neck over a mean trial duration of 2 years, which is of doubtful clinical significance [2]. Subgroup analyses of this meta-analysis suggested that trials with baseline 25OHD < 40-50 nmol/L were more likely to find benefit. Since that meta-analysis several other studies have supported this possibility [3]. The BMD sub-study of the ViDA trial showed no clinically significant effects overall of a high monthly dose of vitamin D on BMD [4]. However, a pre-planned analysis in terms of baseline levels of 25OHD, demonstrated that those who started with winter 25OHD levels < 30 nmol/L had bone density benefits of up to 2%. This finding led to a secondary analysis of a large Scottish trial, which confirmed the ViDA finding that those with baseline winter 25OHD levels < 30 nmol/L did indeed show benefits in BMD, whereas those above this level did not [5]. These findings indicate that the threshold for vitamin D effects on bone is much lower than many had previously supposed, and it provides an explanation for the negative results of the Smith trial, in which the baseline 25OHD levels were 45 - 50 nmol/L.

The comparatively high baseline 25OHD levels in the Smith trial highlight another problem with vitamin D research – the variability between assays for this metabolite. The levels just quoted were measured by liquid chromatography/mass spectrophotometry (LCMS), and contrast with the intention of the trial which was to recruit individuals with 25OHD levels < 50 nmol/L. That was done, but using the Diasorin assay which reported values about 10 nmol/L lower. Appreciation of these differences is critically important, both when using clinical trials to define vitamin D deficiency and when evaluating patients in the clinic and judging whether vitamin D

supplements are indicated. These judgements are further complicated by the seasonal variation in 25OHD levels, which can be up to 40 nmol/L between the winter nadir and the summer peak.

The negative findings for vitamin D supplementation on BMD (except in those with very low 25OHD levels) are mirrored by the absence of fracture prevention with this intervention [6]. An exception to this was the study of Chapuy, in which fracture risk was reduced by 30-40% as a result of supplementation with calcium and vitamin D [7]. Of note, baseline 25OHD levels in this study, after adjustment for assay calibration, were about 13 nmol/L. Thus, the Chapuy trial results are consistent with the evidence from BMD studies, that bone health is improved with vitamin D supplements when there is demonstrable vitamin D deficiency. This responsiveness to vitamin D is most graphically demonstrated in individuals with osteomalacia, in whom BMD increases of up to 50% over 12 months have been reported following vitamin D repletion [8].

An important aspect of the Smith study is that it used a wide range of vitamin D doses, some sufficient to push D metabolite levels to values well above normal. There is no suggestion from these data that these supra-normal levels of vitamin D metabolites confer any benefits. Indeed, other reports from this study have indicated that the highest doses of vitamin D increased the risk of falls [9], a finding supported by other studies (reviewed in reference 3). Increased fracture rates following high-dose vitamin D have also been reported (reviewed in reference 3). The mechanism of these adverse effects of high vitamin D doses remains to be determined, but may result from both increased bone resorption and impaired bone mineralization caused

by hypervitaminosis D [10] (Figure). While some preclinical studies have suggested that high vitamin D levels increase bone formation, clinical evidence is lacking that this occurs without of stimulation of bone resorption, and vitamin D supplements only benefit bone density in those who have unequivocal vitamin D deficiency before treatment. Muscle function appears to be impaired by high doses of vitamin D [11], possibly mediated by factors released from bone, such as TGF-β [12]. Thus, vitamin D doses > 2000 IU/day are not without risk, but do seem to be without benefit. They should be abandoned, other than in individuals with malabsorption, in whom monitoring of 25OHD levels is required.

While the last 100 years have seen an explosion in knowledge regarding the physiology of the vitamin D endocrine system, its proven clinical role has changed little. It remains a safe and highly efficient therapy for the rickets and osteomalacia that result from vitamin D deficiency, but once satisfactory levels of circulating 25OHD have been established (winter nadir >30 nmol/L) pushing levels higher does not result in demonstrable improvements in bone or non-bone health, based on current trial evidence. Thus, vitamin D is not a tonic for bone or other tissues but it is an effective way of treating and preventing osteomalacia. Therefore, the use of vitamin D supplements should be targeted at those at risk of this problem (i.e. those with dark skin living at high latitudes, veiled women, the frail elderly, and other sunlight-deprived groups) using vitamin D doses of 400-800 IU/day, which have been shown to safely maintain 25OHD levels in the appropriate range. This approach is effective, inexpensive, and removes the need for expensive (and often unreliable) 25OHD measurements in most clinical situations.

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Legend to Figure

Physiological and clinical associations of high, normal, and low circulating concentrations of 25-hydroxyvitamin D (25OHD). The concentrations of 25OHD at which the various changes occur vary between studies so inidcatoin on the figure are only approximate, and the y-axis is not linear. Secondary hyperparathyroidism is reported when 25OHD is <25-40 nmol/L, and clinical osteomalacia is usually only reported when 25OHD is <25 nmol/L. The trials which have suggested that vitamin D supplements increase falls and fractures have achieved 25OHD concentrations >120 nmol/L. Hypercalcaemia is generally only found at very much higher 25OHD levels. sCa = serum calcium concentration