

Vitamin D supplementation: bones of contention



The discovery of vitamin D as an essential nutrient for skeletal development a century ago was a major public health victory. Supplementation, whether solar or dietary, prevented the devastating effects of rickets in children. Five decades later, the molecular mechanisms of the vitamin's active form (1,25-dihydroxyvitamin D) and its receptor (vitamin D receptor [VDR]), were elucidated, and subsequently clinical investigators linked vitamin D deficiency or insufficiency with osteoporosis. This finding seemed logical because osteomalacia (ie, the softening of bone in adults due to impaired mineralisation) can cause fractures and often coexists histologically with osteoporosis. Slowly, vitamin D supplementation became established for prevention of osteoporosis. But, as shown in a meta-analysis in *The Lancet*,¹ the story is more complex, both from an epidemiological and mechanistic perspective.

Ian Reid and colleagues¹ did a systematic review of the effects of vitamin D supplements on bone mineral density that included 23 randomised controlled trials encompassing more than 4000 participants, with a mean age of 59 years. The authors found that vitamin D supplementation for 2 years resulted in no change in bone mineral density at four major skeletal sites (spine, total hip, radius, and total body), with a significant increase (0.8%, 95% CI 0.2–1.4) only at the femoral neck. Surprisingly, any benefit reported in bone mineral density was independent of calcium supplementation, baseline concentration of 25-hydroxyvitamin D, duration of treatment, or age. The investigators conclude that widespread vitamin D prophylaxis in healthy community dwelling adults to prevent osteoporosis is unwarranted.

How can these surprising findings be reconciled with clinical practice and public health strategies to prevent osteoporosis? First, bone mineral density was the primary outcome in the present analysis and is widely used as a surrogate measure of fracture risk. However, changes of bone mineral density in this age group are a modest predictor of subsequent fractures.^{2,3} Even with bisphosphonate treatment in high-risk elderly patients (older than 70 years), the bone mineral density increase with bisphosphonates accounts for less than 50% of the effect on fractures.⁴ Thus, the absence of a positive relation between vitamin D supplementation and change in bone mineral density

could be dismissed as the findings having few clinical implications. However, the results are consistent with those of two recent meta-analyses of randomised trials with vitamin D supplementation alone that recorded no efficacy in fracture prevention, nor in another meta-analysis of vitamin D with an intention-to-treat design.⁵⁻⁷

Second, it is difficult to distinguish between the effects of calcium versus those of vitamin D on skeletal integrity, because the main mechanism of action for vitamin D is promotion of calcium absorption in the gut and not direct incorporation of calcium in bone.⁸ In the present meta-analysis, only half of the trials used both calcium and vitamin D supplementation.¹ In trials in which vitamin D was given simultaneously with calcium, a significant reduction of 11% in hip fractures and a very modest increase in hip bone mineral density was reported.^{9,10} This finding formed the basis of the recommendation by the US Institute of Medicine that 1200 mg of calcium and 800 IU of vitamin D were optimum intakes for skeletal health in elderly people.¹⁰ The inclusion of more studies with calcium plus vitamin D in the present report could have resulted in greater increases in bone mineral density, but confounding by calcium supplementation would not have clarified the role of vitamin D alone in supporting bone mass.

Third, mechanisms of vitamin D action on the skeleton have recently been re-examined leading to a new appreciation of the vitamin's biological role; these findings also

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lend further support to the present meta-analysis. For example, 1,25 dihydroxyvitamin D has been shown to inhibit mineralisation in bone cell cultures. To reconcile this paradoxical finding, Lieben and colleagues¹¹ used mice in which the VDR in intestine or bone was deleted. In mice with the intestine-specific knockout of VDR, secondary increases in 1,25-dihydroxyvitamin D concentrations stimulated bone resorption while simultaneously inhibiting mineralisation in vivo. By contrast, VDR ablation in bone cells only resulted in increased bone mass and enhanced mineralisation.¹¹ Lieben and coworkers surmised that, over the long run, maintenance of normocalcaemia takes precedence over skeletal integrity, hence bone is lost and mineralisation is suppressed at the expense of circulating concentrations until calcium sufficiency is restored.

If correct, these findings support the data presented by Reid and colleagues.¹ During states of adequate calcium intake and normal skeletal homeostasis, vitamin D supplementation might have little or no role in strengthening bone mass since calcium status is adequate. However, with severe vitamin D deficiency (eg, 25-hydroxyvitamin D concentrations <40 nmol/L) or low calcium intake or both, skeletal micro-architecture (but not necessarily areal bone mineral density) is disrupted leading to micro-cracks, skeletal fragility, defects in mineralisation, and increased bone resorption from high concentrations of 1,25-dihydroxyvitamin D.¹² Replacement with vitamin D and calcium would restore skeletal homeostasis. In Reid and coworkers' analysis,¹ the predominantly female population in middle age is almost certain to be in a state of calcium sufficiency.

Reid and colleagues' meta-analysis is consistent with our understanding of vitamin D: supplementation to prevent osteoporosis in healthy adults is not warranted.

However, maintenance of vitamin D stores in the elderly combined with sufficient dietary calcium intake (800–1200 mg per day) remains an effective approach for prevention of hip fractures.

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I declare that I have no conflicts of interest.

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