Vitamin D and Bone Health

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Abstract. Vitamin D is necessary to allow adequate absorption of calcium from the diet, which is necessary to maintain normal circulating calcium concentrations which, in turn, underpins normal bone mineralisation. When serum 25-hydroxyvitamin D is <25-30 nmol/L, bone density and/or mineralisation are reduced, and supplements of vitamin D are found to have measurable benefits to bone.

Discussion

The primary role of the vitamin D endocrine system is to maintain normocalcaemia and normophosphataemia, thus permitting normal skeletal mineralization. The principal way in which vitamin D does this is through regulation of intestinal absorption of these minerals. Loss of the vitamin D receptor (VDR) in mice or humans results in osteomalacia i.e. impaired mineralisation of the skeleton. This problem can be reversed either by provision of high intakes of calcium and phosphate sufficient to normalize serum concentrations, or by the selective expression of the VDR in enterocytes alone, indicating that the skeletal actions of vitamin D are principally mediated by its effects on intestinal calcium absorption. VDR is expressed in bone, where its main role is to stimulate bone resorption, consistent with the function of the vitamin D endocrine system to maintain circulating calcium levels. Vitamin D intoxication is associated with sustained increases in bone resorption.

While severe vitamin D deficiency results in osteomalacia, less marked reductions stimulate parathyroid hormone (PTH) secretion in some individuals, leading to bone resorption, activation of vitamin D, and renal retention of calcium, which together result in maintenance of serum calcium levels in the normal range. Bone mineralization is maintained but bone mass is reduced. Preventing secondary hyperparathyroidism is the principal rationale for using vitamin D in the management of osteoporosis.

In 2014 we published a systematic review of trials assessing the effects of vitamin D supplementation alone on BMD in adults (Reid et al., 2104). The study identified data from 23 trials, with a mean duration of 23.5 months, and involved 4082 participants, 92% women, with an average age of 59 years. Meta-analysis found no significant effect in the lumbar spine or total hip, there were non-significant negative effects in the total body and forearm, but in the femoral neck there was a positive treatment effect of 0.8% (95% confidence interval 0.2% to 1.4%, P = 0.005). The femoral neck data showed evidence of heterogeneity among the trials and also of publication bias. When the trials were grouped by mean baseline 25-hydroxyvitamin D, only those with starting levels <50 nmol/L showed a significant increase in femoral neck BMD. Treatment effects also differed by vitamin D dose: trials using a supplement of <800 units/day showed significant increases in both lumbar spine and femoral neck BMD but trials using higher doses did not.

Since that time, several more negative studies have been published, plus two studies in which the effect of baseline levels of 25-hydroxyvitamin D on the bone density response to vitamin D has been assessed. In the ViDA study, an exploratory analysis suggested that individuals with baseline 25-hydroxyvitamin D <30 nmol/L benefited from vitamin D supplementation, but those above this level did not (Reid et al., 2107). In a large study of postmenopausal women in Scotland, McDonald confirmed this finding, again demonstrating that supplementation only impacted positively on BMD when baseline 25-hydroxyvitamin D was <30 nmol/L (in press).

Analyses of vitamin D supplementation and fractures have produced similar outcomes. Bolland recently meta-analyzed these studies (Bolland et al., 2014). In trials involving >28,000 participants there were no demonstrable benefits in terms of either total fracture (relative risk 0·97 [0·88 to 1·08]) or hip fracture (relative risk 1·11 [0·97 to 1·27]. The findings of the Bolland meta-analysis are consistent with the results of the DIPART individual patient meta-analysis (Abrahamsen, et al., 2010) and a recent Cochrane review (Avenall, et al., 2014). Two trials merit specific mention in that they each showed statistically significant increases in fractures, either in the hip (Smith et al., 2007) or for total fractures (Sanders et al., 2010). Each study used annual administration of a high-dose supplement, so many authors have since concluded that infrequent bolus dosing is unsafe.

In contrast to the negative findings from vitamin D monotherapy, there is some evidence that combined supplementation with calcium plus vitamin D reduces fractures. This group of trials is heavily influenced by the positive findings from the Chapuy study, in which severely vitamin D-deficient French women in nursing homes were provided with combined supplementation. In contrast, when calcium plus vitamin D is provided to community-dwelling individuals, a reduction in fractures is not found. It is likely that the Chapuy study demonstrates the benefits from treating osteomalacia with calcium and vitamin D, rather than effects on osteoporosis.

Conclusions

- Vitamin D is essential to prevent osteomalacia
- 25OHD > 25 nmol/L (easily achieved with 400IU/d) prevents osteomalacia
- There is no evidence that pushing 25OHD higher has any bone benefits
- Very high vitamin D intakes (e.g. ≥4000 IU/day) increase falls and fractures

References

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