

Clinical effects of vitamin D supplementation

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Extended Abstract.

Vitamin D is a standard part of osteoporosis management in many parts of the world and used for prevention of a number of other conditions by some. However, the evidence for efficacy for these indications is weak.

In recent decades vitamin D supplementation has become a standard part of the prevention and treatment of osteoporosis. In the last few years, many people have started to take vitamin D in the hope that it might reduce the risk of other conditions, including cardiovascular disease and cancer. Therefore, it is timely to review the evidence supporting both of these possibilities. There is no question that very low levels of vitamin D ($\ll 25$ nmol/L) cause osteomalacia, which is a failure of bone to mineralise normally as a result of reduced concentrations of calcium ions in the extracellular fluid. In adults this presents with bone and muscle pain, and in children it presents as rickets – reduced longitudinal growth and bowing of weight-bearing bones. This is almost always as a result of low sunlight exposure, since the diet provides only a trivial quantity of vitamin D, and exposure of the skin to ultraviolet light is the source of the great majority of vitamin D supplies. In older individuals at risk of osteoporosis there has been concern that reductions in vitamin D result in secondary hyperparathyroidism, as a normal homeostatic response for the maintenance of serum calcium concentrations, and that this accelerates postmenopausal bone loss. Indeed, there are some observational studies which show that low vitamin D levels on their own are not associated with accelerated bone loss but low vitamin D levels plus elevation of parathyroid hormone are (Arabi et al. 2012). The landmark study of Chapuy in the early 1990s demonstrated a substantial reduction in hip fracture risk in frail, malnourished, elderly women randomised to calcium together with vitamin D, or to placebo (Chapuy et al. 1992). Enthusiasts from both the calcium and vitamin D camps attributed this benefit to one or other of the components of the intervention, and that study certainly increased the general acceptance of vitamin D supplementation as a key part of the management of postmenopausal osteoporosis. However, more recent systematic reviews have not supported this contention and meta-analyses from the Cochrane group (Avenell et al. 2009), from the American Endocrine Society (Murad et al. 2012), and from the DIPART group (Abrahamsen et al. 2010), have all failed to show that vitamin D alone reduces fracture risk. In contrast, a meta-analysis of medication compliers from studies of vitamin D with or without calcium did suggest a reduction in fracture (Bischoff-Ferrari et al. 2012), but only to the same extent as has been demonstrated when compliers within the placebo group of the FIT Study are compared with those who were not compliers (Curtis et al. 2011). Therefore, this analysis is likely to be flawed and not represent a therapeutic effect of vitamin D itself.

In light of the recent failure of vitamin D supplement studies to demonstrate fracture prevention, we have undertaken a systematic review of studies of vitamin D supplementation which measured bone mineral density. The rationale for this was that there are a larger number of such studies with a greater diversity of populations and vitamin D dosing regimens. Also, bone density is a more sensitive endpoint than fracture, so it was possible that therapeutic benefits could be demonstrated by some studies in this context, and might give guidance for the better design of future fracture prevention studies. Restricting ourselves to adults, we identified 23 studies with over 4,000 participants. The mean duration of the studies was two years and the age of participants covered the full adult age range. We failed to find any overall benefit on bone density from the use of vitamin D supplements, though five studies did show benefits at one skeletal site, failing to support this at the other skeletal sites measured. Two studies showed detrimental effects in total body scans. In the meta-analysis, there was a 0.8% benefit in bone density at the femoral neck, but only a non-significant 0.2% benefit at the closely related total hip site. Thus, we conclude that vitamin D supplements probably confer no clinically significant benefit in individuals at risk of osteoporosis, and the main indication for their use is for the prevention of osteomalacia. This only requires the achievement of vitamin D levels above 25 nmol/L, and is likely to be easily achievable with a small dose of only 400 iu/day.

Many studies have been published in recent years which document inverse associations between serum 25-hydroxyvitamin D levels and incidence or severity of a diverse range of conditions, which covers almost every disease known to man. Some have interpreted these associations as being causative, though there is an implausibility related to the diversity of conditions that could be attributed to low vitamin D levels. This is illustrated by a recent two-month survey of the literature which we undertook, in which 92 papers were published linking vitamin D levels to 53 different conditions. However, tens of thousands of people have already been studied in randomised, controlled trials of vitamin D supplements, usually with bone outcomes or falls as the primary endpoints. However, many of these studies have documented other adverse effects including cancers and cardiovascular disease. We have recently published trial sequential meta-analyses of these data demonstrating that there is no overall effect of vitamin D supplementation on either of these endpoints (Bolland et al. 2014). Furthermore, the number of subjects already studied, makes it extremely unlikely that further studies will in fact change the outcome of these meta-analyses since subject numbers are already well in excess of the futility boundaries defined by these analyses. Therefore, it is likely that the substantial sums of money currently invested in trials of vitamin D supplementation will bear no useful fruit.

On the basis of these findings we suggest that vitamin D supplementation should not be widely used, except in those who are at significant risk of very low vitamin D levels. This includes those who are permanently indoors, permanently veiled, or have very dark skin and are living in regions of low sunlight intensity. The reason for supplementation in these groups is osteomalacia prevention. Thus, one hundred years after vitamin D was discovered as the cause and cure of osteomalacia, that remains its only clearly established clinical use.

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