The Vitamin D Paradox

Vitamin D is essential for musculoskeletal health, as it promotes calcium absorption from the bowel, mediates the mineralization of osteoid tissue within bones and plays an important role in bone turnover and muscle function [1, 2]. The most obvious consequence of vitamin D deficiency is the development of vitamin D deficiency osteomalacia, where a failure of mineralization leads to the accumulation of unmineralized osteoid within the skeleton. This is generally only seen when the serum 25-hydroxyvitamin D (25OHD) concentration falls below 20 nmol/l. It has become increasingly apparent that less severe vitamin D deficiency or insufficiency may lead to secondary hyperparathyroidism that contributes to parathyroid hormone (PTH)-induced bone loss, development of osteoporosis and an increased risk of low-trauma fractures [2–4].

There is no universal consensus on what constitutes vitamin D insufficiency [2]. Lips [5] has classified vitamin D insufficiency as mild (serum 25OHD 25–50 nmol/l), moderate (serum 25OHD 12.5–25 nmol/l) and severe (serum 25OHD <12.5 nmol/l) [5]. North American experts suggest that higher levels of 25OHD are essential not only to maintain bone health [6] but also for mental health, prevention of cancers, cardiovascular health and prevention of skin and autoimmune disorders [1]. Holick [1] suggests that an optimal serum 25OHD exceeds 75 nmol/l [1], but few older people living in the UK achieve this concentration [7].

The prevalence of vitamin D insufficiency depends on the criteria used, but this increases with advancing age and is particularly common in care home residents [7]. Vitamin D insufficiency is also more common in patients with low-trauma fractures than in age-matched control subjects [3, 4]. The study of Chapuy et al. [8] demonstrated that calcium and vitamin D supplementation in French care home residents corrected vitamin D insufficiency and secondary hyperparathyroidism, improved bone density and reduced the incidence of hip and other non-vertebral fractures.

Given the low cost of vitamin D, there has been interest in the role of supplementation in the prevention of fractures in older people. A meta-analysis of vitamin D supplementation published in 2005 concluded that doses of 700–800 IU daily decreased the risk of hip and other non-vertebral fractures, whereas lower doses were ineffective [9]. A number of recent pragmatic randomized controlled trials have shown no benefit of vitamin D, either with or without calcium supplementation, as public health measures to prevent fractures [10–14]. The latest study published in this issue also shows no reduction in fracture incidence with an annual i.m. injection of vitamin D2 in community-dwelling older people [15].

Given the high prevalence of vitamin D insufficiency in older people, why does vitamin D supplementation appear to be ineffective in fracture prevention? Clinical trials of vitamin D supplementation have shown poor long-term compliance and persistence with medication, particularly when co-administered with calcium [10–12]. Although the Women’s Health Initiative Study showed no overall reduction in fractures with vitamin D and calcium, the investigators were able to demonstrate a decrease in fractures among participants who remained compliant with medication [12]. Compliance and persistence with treatment was not a major problem in the present study, as study medication was administered by i.m. injection.

As the authors acknowledge, there is evidence that the metabolism of vitamin D2 may be less effective than that of vitamin D3. In a study in 20 normal healthy men, a single oral dose of 1.25 mg (50 000 IU) of either vitamin D2 or vitamin D3 was administered, following which the change in serum 25OHD was monitored over a 28-day period [16]. Although there were similar increases in serum 25OHD in the first 3 days after the administration of vitamin D2 and vitamin D3, at the end of the study, the serum 25OHD was 50 nmol/l above baseline after vitamin D3 administration but was 5 nmol/l lower than the initial value in the vitamin D2-treated group [16].

The authors also highlight in the discussion that i.m. vitamin D may be less bioavailable than when administered orally [15]. There is also the potential problem that vitamin D may be adsorbed on to the inner surface of plastic syringes, but the magnitude of this effect is unclear. Although venepuncture was only performed in a small number of the study participants, this showed a non-significant 20% increase in serum 25OHD above the baseline concentration of 56.5 nmol/l, four months after the first injection of vitamin D. The increases in serum 25OHD and the final level achieved in the present study and in other negative trials of vitamin D supplementation [13–15] are more modest than in the study of Chapuy et al. [8], where the serum 25OHD increased from 40 to 100 nmol/l with oral calcium and vitamin D supplementation. Nevertheless, the proportion of study participants undergoing measurement of serum 25OHD and PTH measurement in the anti-fracture studies of vitamin D has been small at less than 1% and it is generally unclear what if any selection of subjects has occurred, making it difficult to extrapolate the results to the whole study population.

Another limitation of many of the anti-fracture studies of vitamin D supplementation is the lower than expected fracture rate, because of the recruitment of relatively healthy participants, that decreases the statistical power to detect significant effects of treatment. This was not the case in the study of Chapuy et al. [8], where the fracture rate in elderly care home residents was particularly high. In the light of the potential problem of statistical power and the conflicting results of individual trials of vitamin D supplementation, it is appropriate to examine the results of meta-analyses. The latest Cochrane review [16] that includes some [10, 11, 15] but not all [12–14] of the recent studies suggests that vitamin D used alone has no significant effect on hip fracture [seven trials, 18 668 participants, relative risk 1.17, 95% confidence interval (CI) 0.98–1.41]. In contrast, combined supplementation with vitamin D and calcium marginally reduced the risk of hip fractures (seven trials, 10 376 participants, relative risk 0.81, 95% CI 0.68–0.96), but the effect appeared to be restricted to those living in institutional care. Another recent meta-analysis also shows a similar reduction in hip fractures with calcium and vitamin D (relative risk 0.82, 95% CI 0.71–0.94), with no beneficial effect of vitamin D alone on fracture incidence [17].

What then should be our reaction to the latest study and other recent trials of vitamin D supplementation? Routine vitamin D supplementation as a public health measure appears ineffective, apart from older care home residents, where there is a high prevalence of vitamin D insufficiency. In this situation, combined vitamin D and calcium supplementation should be used, as vitamin D alone appears ineffective [13, 14, 18]. Although other older people may benefit from vitamin D and calcium supplementation, this should be targeted on those with more marked vitamin D insufficiency who are willing to comply with treatment. The National Institute for Health and Clinical Excellence (NICE)
advocates that patients receiving osteoporosis treatment should also be given vitamin D and calcium, unless the clinician is confident that the patient is vitamin D replete and has an adequate dietary calcium intake [19]. This could be used to justify more extensive measurement of serum 25OHD in patients with osteoporosis and fractures, but there remains the problem of more precisely defining vitamin D insufficiency and repletion. Given the paradox of the high prevalence of vitamin D insufficiency and yet the apparent lack of consistent benefit of vitamin D supplementation in fracture prevention, future studies of supplementation should include more extensive measurement of serum 25OHD and PTH. This would help to establish optimal vitamin D status and address this apparent paradox.

Disclosure statement: R.M.F. has served as an adviser to Shire, Nycomed and ProStraken, who market calcium and vitamin D supplements. He is also a Co-Principal Investigator in two of the anti-fracture studies of calcium and vitamin D mentioned in this Editorial [10, 11].

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