Update of a systematic review of vitamin D for preventing osteoporotic fractures

Osteoporotic fractures are a major and growing healthcare problem in many industrialised societies. An epidemiological study of fracture data between 1988 and 1998 for England and Wales found that one in two women and one in five men over the age of 50 had suffered a fracture.[1] Most of these fractures would have occurred after low-energy trauma, such as a fall from standing height or less, in bone weakened by osteoporosis. Of the fractures primarily associated with osteoporosis, hip fracture is the most disabling and is often fatal. Mainly old (mean age ~80 years), female (~80% are women) and often frail people sustain hip fractures. Characteristically such people have insufficient vitamin D, which is a key agent for building bone. An update of a comprehensive systematic review that examines the effects of vitamin D and vitamin D analogues for preventing osteoporotic fractures in older people has been published in the *Cochrane Database of Systematic Reviews*.[2]

This review by Avenell and colleagues includes 45 trials, of which, 42 were individually randomised trials, one was a large cluster randomised trial, and two were quasi-randomised. On the basis of predefined objectives established in previous versions of the review, the authors present the results for fractures separately for different comparisons and overall for adverse effects (hypercalcaemia, renal disease, gastrointestinal symptoms and death). Subgroup analyses by residential status (community dwelling versus institutional care) and history of previous osteoporotic fracture were also performed. The results for the two main comparisons, vitamin D alone versus control and vitamin D plus calcium versus control, are summarised below.

Pooled data from nine trials, and 24 749 participants, consistently showed that vitamin D alone did not prevent hip fracture (relative rate (RR) 1.15, 95% CI 0.99 to 1.33). A similar lack of protective effect was evident from the available data for non-vertebral fracture (all fractures except those of the vertebrae), vertebral fracture (clinically evident fracture or new vertebral deformity on a radiograph) and any new fracture (fractures from studies that did not report by fracture location).

In contrast, pooled data from eight trials, and 46 658 participants, showed that vitamin D with calcium significantly reduced hip fracture (RR 0.84, 95% CI 0.73 to 0.96). These results were statistically homogeneous. In their subgroup analysis by residential status, Avenell *et al* reported that, although these showed a significant reduction of hip fractures in people in institutional care (data from two trials conducted by the same investigators in France), the difference between this and a community-dwelling subgroup was not significant ($p = 0.15$). Thus a greater effect in the institutional subgroup is not proven. Nonetheless, as the authors reflect, a greater benefit from administration of vitamin D and calcium would be consistent with data from clinical biochemistry and epidemiology that reveal that many frail institutionalised older people are vitamin D deficient, especially in the winter months. The pooled results for non-vertebral and vertebral fractures were not significant.

Avenell *et al* found that vitamin D or vitamin D analogues, with or without calcium, significantly increased hypercalcaemia (high blood calcium), gastrointestinal symptoms and renal disease. Although these risks were relatively small, the risk of hypercalcaemia was particularly high with calcitrol, a vitamin D analogue. Although vitamin D did not reduce overall mortality, the authors observed that the marginal reduction in risk of death in people receiving vitamin D with calcium is consistent with the reduction in hip fracture risk.

On the basis of the available evidence, the authors concluded that taking vitamin D alone is unlikely to prevent fracture. However, vitamin D taken with additional calcium supplements does appear to reduce hip fracture, particularly in people living in institutional care. The authors advised caution for some people, such as those with kidney disease or high blood calcium, and emphasised that there was a particularly high risk of hypercalcaemia with calcitrol. The full review, which also presents results for other comparisons tested involving vitamin D and vitamin D analogues, is available in the *Cochrane Database of Systematic Reviews*.[2]

The maintenance of Cochrane reviews in the light of new evidence and developments is one of the key attributes of and aspirations for these reviews. The citation of an updated Cochrane review may remain unchanged, as for this review, because the criteria for citation change, including substantively changed conclusions, have not been met. It remains an important observation, however, that there were no important changes to the conclusions regarding fracture prevention despite the addition of eight new trials, contributing data from 44 827 participants who were mainly community dwellers. This brought the total to 84 585 participants for the review.

As the authors make clear, this abundance of evidence does not preclude the need for further primary research or, indeed, another review update in due course. In particular, a case could be made for large multi-centre placebo-controlled randomised trials of vitamin D with calcium in institutional settings in different countries. Such trials need to be informed by vitamin D dose-finding studies.

The review highlighted in this article is registered with the Cochrane, Bone, Joint and Muscle Trauma Group (www.bjmtg.cochrane.org). The work of this group involves preparing, maintaining and promoting the accessibility of systematic reviews on different aspects of the prevention, treatment and rehabilitation of musculoskeletal injuries. People interested in contributing to this work can contact Lindsey Elstub, the Review Group Coordinator, at lindsey.elstub@manchester.ac.uk.

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