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EDITORIALS

Vitamin D and fracture prevention—treatment still indicated but clarification needed

The publication of Chapuy's 1992 paper, 'Vitamin D3 and calcium to prevent hip fractures in elderly women', was a turning point in fracture prevention in older adults. It was the first large-scale study to demonstrate that simple, oral, daily administration of calcium and vitamin D supplements could cause a substantial reduction in hip fractures with a relative risk of 0.74 over 3 years [1]. The mechanism for the reduction in fracture risk is probably a combination of improved bone health and neuromuscular changes. The latter may reduce falls risk or improve neuroprotective reflexes, so a fall is less likely to result in a serious injury. Chapuy's study included 3,270 women aged over 70 years, living in residential care. This paper was followed by a number of others, which reinforced the view that vitamin D alone, or with calcium, could reduce peripheral fractures in older adults. These studies extended the populations likely to benefit including men as well as women, those living in their own homes as well as in residential care and slightly younger adults, down to the age of 65 years [2–5]. The apparent benefits, cost effectiveness (numbers needed to treat 17 to prevent one hip fracture of women living in residential care) and relative safety have meant that many national and local guidelines advocate the widespread prescription of calcium and vitamin D supplements to prevent fractures in adults aged 65 years and over.

However, not all studies of the effects of calcium and vitamin D supplementation on fracture rates in older people have had positive findings [6–8]. The publication of three high-profile, negative studies within the past year calls these recommendations into doubt [9–11]. Two of these were primary prevention studies. The Wessex fracture prevention study was a population-based study of 9,440 men and women, aged over 75, who received an annual injection of vitamin D (ergocalciferol 300,000 IU) for 3 years [12]. The study by Porthouse and colleagues [9] looked at 3,314 women aged over 70 years who were treated with calcium (1 g/day) and vitamin D (cholecalciferol 800 IU/day). The third study (RECORD) investigated secondary prevention of fractures in 5,292 men and women, aged over 70 years, who had suffered a fragility fracture within the previous 10 years. In a factorial design, they were given calcium (1 g/day), vitamin D (cholecalciferol 800 IU/day), both or neither [10]. It is unlikely that the conclusions of the studies demonstrating benefit were wrong, so what is it about the populations studied, the nature of the interventions or the ascertainment of outcomes that can explain these differences?

The variables that are likely to be significant in altering the outcome of such studies are the likelihood of vitamin D deficiency or insufficiency in the population being studied, the calcium intake of subjects, the rate of fracture in that population (in turn related to the duration of follow-up) and the dose and type of vitamin D administered. Furthermore, adherence to treatment may differ depending on the setting and the treatment regime, so that studies in care homes or those using intermittent bolus vitamin D may have higher adherence rates and, therefore, be more likely to have positive results compared to population-based studies such as RECORD where compliance may have been as low as 45%. Finally, self-selection of study subjects, particularly in population-based studies [9–11], may bias the sample towards fitter and more active older people, so the studies may be missing frailer, housebound people, the very group who are at higher risk of vitamin D deficiency, falls and fractures.

The likelihood of vitamin D deficiency in the populations studied and the dose and type of vitamin D supplements administered warrant further discussion.

Increasing age and housebound lifestyle are important determinants of vitamin D status [13]. High rates of vitamin D deficiency have been demonstrated in community-based samples of older people [14] and high-risk groups such as people with falls [15] or fractures [16]. The majority of studies looking at the efficacy of vitamin D in fracture prevention, particularly those with a large sample size, have not ascertained vitamin D status in all subjects, presuming that the population under study will have a high prevalence of vitamin D deficiency. Vitamin D and parathyroid hormone (PTH) levels (since PTH is an important mediator of bone loss and osteoporosis in later life), before and during supplementation, were either measured in small subgroups [1, 4, 10, 12] or not measured at all [9]. Scrutiny of this data shows a wide range of levels of vitamin D with improvements with treatment which still leave many subjects in the deficient/insufficient range and modest changes in PTH (if measured). Furthermore, the vitamin D status of the vast majority of subjects is unknown.

Since the publication of the papers by Chapuy [1] and then by Dawson-Hughes [3], 7–800 IU of cholecalciferol/day with or without calcium has been widely accepted as an appropriate dose of vitamin D for supplemental use; however, these doses may not be sufficient. Useful guidelines on interventional studies with vitamin D suggest that doses of 3,000–10,000 IU cholecalciferol/day are necessary [17, 18] and can be safely administered without toxicity. Ergocalciferol

(vitamin D2) is at least threefold less potent than cholecalciferol (vitamin D3) [19], which may account for the negative findings in the Wessex hip fracture prevention study [12] in which an ergocalciferol injection was used. Finally, it is not known whether activated vitamin D would be a more effective supplement for widespread use in older adults. Calcitriol can reduce vertebral fractures in postmenopausal women with osteoporosis [20], and alpha-calcidol has been shown to reduce falls in frail older adults with low calcium intake or renal impairment [21]. Given that many older adults have low calcium intake and low glomerular filtration rate, activated vitamin D has theoretical advantages in this respect, although the major disadvantage is the risk of hypercalcaemia. In contrast, supplementation with cholecalciferol and ergocalciferol is unlikely to lead to hypercalcaemia due to homeostatic regulation of activation of vitamin D. If calcitriol were used on a routine 'whole population' basis, the need for monitoring of calcium levels would lead to increased cost and inconvenience.

Where does the current body of literature leave us with regard to using calcium and vitamin D supplements for peripheral fracture prevention in older adults?

The situation is best summarised as follows:

(i) For older women, aged over 70 years, living in residential or nursing care, the evidence for population-based supplements is good. This could still reasonably be extrapolated to frail, housebound adults of both genders. Oral supplements of cholecalciferol 800 IU with calcium 1 g a day are preferable to an injection, and intermittent oral dosing of cholecalciferol may aid compliance.

(ii) For secondary fracture prevention, since the publication of National Institute of Clinical Excellence (NICE) guidance on the secondary prevention of osteoporotic fracture [22], all women over 75 and postmenopausal women under 75 who meet criteria based on bone densitometry should now be treated with bone-strengthening drugs, usually a bisphosphonate. The guidance specifically says that all patients should have adequate calcium and vitamin D levels before treatment, and it is important that patients treated with bisphophonates are calcium and vitamin D replete, so it is good practice to co-prescribe calcium and vitamin D supplements to this group too. Although NICE does not address osteoporosis treatment in men, this recommendation also applies to men being treated for osteoporosis.

(iii) In postmenopausal women under 75 who have fractured, but do not meet bone densitometry criteria for specific treatment, there is no evidence at present to give vitamin D supplements. However, between 20 and 50% will be vitamin D deficient and, given that they have already fractured, it would be good practice to check vitamin D levels and replace if deficient or insufficient.

(iv) For primary prevention of fractures in 'younger' older adults, there is currently no evidence to support population-based administration of calcium and vitamin D.

It is clear that there is a need for more research on this subject, particularly using higher doses of vitamin D or activated vitamin D. Whether vitamin D needs to be combined with calcium supplements is also not clear. It should be remembered that vitamin D deficiency is common, and untreated vitamin D deficiency has adverse effects throughout the body, including an increased risk of falls, increased vascular risk and a higher incidence of cancer. So, reducing fracture rates is not the only desirable outcome of vitamin D supplementation in older adults.

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Reversible dementia—the implications of a fall in prevalence

When I took my oral exams in geriatric medicine in the mid 1980s, according to the literature which we then parroted, the percentage of dementias considered to be reversible was at least 20% [1]. However, only a few years later and in the same month, two separate reviews were published pointing out that the prevalence was in fact much lower, that is, just over 11% [2, 3]. By the mid-1990s, [4] and again just over 8 years later in 2003 in an update to the 1988 meta-analysis [5], the prevalence of reversibility was reported to have decreased to less than even 1%.

What can explain such a rapid fall and what are the clinical implications? Firstly, it is possible that some of the conditions which make up most of the underlying causes of reversibility such as the use of drugs which can cause reversible cognitive decline (benzodiazepines, alcohol, etc.), metabolic causes (such as B_{12} deficiency or hypothyroidism) or cognitive decline secondary to depression, have fallen for reasons not entirely clear to us. Secular trends often confound our understanding of disease processes. On the other hand, the prevalence may have stayed the same but these conditions are now being diagnosed earlier and treated more effectively. Finally, there may have been changes in reporting.

To begin with the possibility of a change in the natural history of the reversible dementias, there is little evidence that the prevalence of the underlying diseases has fallen. It is, however, possible that the elderly are indeed better cared for today. For example, Weytingh *et al.* [4] adduce some indirect evidence that improvements in primary care may have contributed to fewer patients with reversible dementia being referred to the relevant diagnostic frameworks. In support of this proposition, if one compares the data from the 2003 study [5] which updates the 1988 meta-analysis [3], in the more recent study there is evidence of less selection bias in that far fewer studies now emanate from inpatient units. Many more patients were examined either in outpatient settings or in the community where Alzheimer's disease [AD] (the most common cause of dementia and to date still irreversible) is much more likely to be found [6]. As well, patients who made it into the more recent meta-analysis were both older and more likely to be female than those reported earlier, more clearly reflecting the dementia seen in the community, almost all of which will turn out to be AD [6].

There is also some evidence that better general education for primary care physicians in the principles of geriatric pharmacology has had a positive effect. For example, while medication as a cause of dementia (not necessarily reversed) was reported in 1.5% of all cases of dementia in 1988, by 2003 this particular aetiology had dropped almost to zero.

Perhaps a more careful use of standardised assessment instruments, consensus diagnosis and sufficient follow-up as a positive spin-off from the increasing number of drug trials for dementia has increased our diagnostic accuracy, both of dementia and of reversibility. Again, support for