Vitamin D deficiency—can old age learn from childhood?

Adequate vitamin D status is essential for musculoskeletal health throughout life as it promotes calcium absorption from the bowel, mediates the mineralisation of osteoid tissue within bone and plays an important role in bone turnover and muscle function [1, 2]. The impact of vitamin D deficiency on bone health was first recognised in children, where rickets were commonly seen among the poor of growing urban conurbations. In the early 20th century, vitamin D was identified as a component of cod liver oil which was found to cure rachitic beagle puppies [3, 4]. Subsequently, ultraviolet radiation from a mercury vapour lamp was successfully used to treat rickets in four children in 1919 [5]. Untreated childhood rickets results in widening of the epiphyseal growth plates and bowing of the long bones, and the latter may persist into adult life. Classically, vitamin D deficiency in adults results in osteomalacia which presents with bone pain, skeletal deformity, proximal myopathy and propensity to low trauma fractures. Osteomalacia due to vitamin D deficiency is most common in older people, occurring in up to 4% of patients in this age group admitted to hospital [6]. Patients with vitamin D deficiency osteomalacia generally, have a serum 25 hydroxyvitamin D (25 OHD) below 20 nmol/l and elevated parathyroid hormone (PTH) concentrations reflecting secondary hyperparathyroidism, but other biochemical findings may include hypocalcaemia, hypophosphatemia and raised alkaline phosphatase.

In recent years, it has become apparent that less severe vitamin D deficiency or insufficiency may also lead to secondary hyperparathyroidism which contributes to PTH induced bone loss, the development of osteoporosis and an increased risk of low trauma fractures [7–9]. There is no universal consensus on what constitutes vitamin D insufficiency, but Lips has suggested a threshold serum 25 OHD of 50 nmol/l [9]. Holick advocates a higher optimal serum 25 OHD above 75 nmol/l [1], but few older people living in the United Kingdom achieve this concentration [10]. The prevalence of vitamin D insufficiency depends on the criteria used, but this increases with advancing age, particularly in care home residents [10]. Vitamin D insufficiency is also more common in patients with low trauma fractures than age-matched control subjects [7, 8].

Calcium and vitamin D supplementation has been shown to correct vitamin D insufficiency, secondary hyperparathyroidism and reduce the risk of hip and other non-vertebral fractures in care home residents [11]. However, recent studies of calcium and vitamin D supplementation in non-institutionalised settings have shown no reduction in fractures, falls or mortality [12–14], although the participants in these studies were less likely to have vitamin D insufficiency and secondary hyperparathyroidism than care home residents. Nevertheless, other studies of vitamin D supplementation without calcium have also failed to show any benefit in care home residents [15–17].

In this edition of Age and Ageing, a well-designed study reports on the effects of vitamin D supplementation in nursing home residents [18]. The authors report a high prevalence of vitamin D insufficiency at baseline, with 98% of the participants having a serum 25 OHD below 50 nmol/l, but only found a raised PTH in 23% of the study population. They then compared the effects of two doses of vitamin D3 (400 and 1200 IU daily) with placebo on calcium regulating hormones and biochemical markers of bone turnover. Serum 25 OHD levels increased in a dose response manner, but a higher dose was required to increase serum 25 OHD above 50 nmol/l in the majority of participants. There was only a modest reduction in serum PTH with vitamin D supplementation. The observation of an unexpectedly low PTH in the presence of vitamin D insufficiency was reported previously in old people with hip fractures where it has been described as functional hypoparathyroidism [19]. Similar findings have been observed in adults with learning disability where increased bone resorption may lead to the release of calcium into the circulation and the suppression of PTH [20]. Recent work suggests that functional hypoparathyroidism in patients with established osteoporosis may be due to magnesium deficiency, as assessed by a magnesium loading test [21]. Important potential sources of magnesium deficiency include drug therapy, especially with loop diuretics, malabsorption and renal disease with magnesium wasting. This is clearly an area worthy of further study.

There are a number of limitations to the present study. Due to the exacting eligibility criteria, the sample size is quite small and the statistical power of the study is probably too low to reach firm conclusions. The exclusion of subjects with renal impairment makes the population studied less representative of the majority of frail older patients we treat, particularly those who live in nursing homes, where renal impairment is highly prevalent. However, there are some important scientific and clinical implications for current treatment and future research. First, we need to recognise that vitamin D
status in this group of subjects is difficult to evaluate. A low serum 25OHD does not necessarily predict that treatment with vitamin D supplements alone will result in a reduction in bone turnover markers or increased bone density. Moreover, the appropriate dose of vitamin D supplementation is not clear. Part of the problem is the inadequacy of PTH to act alone as a biological marker of vitamin D status, as there may be co-existent PTH resistance, occult primary hyperparathyroidism as well as the confounding effect of renal disease on vitamin D metabolism and parathyroid function.

Almost 100 years ago, vitamin D deficiency presented problems of diagnosis and treatment in poor, undernourished infants and children in our large cities. Now, vitamin D deficiency in poor, frail older people living in care homes presents a major clinical and public health challenge. Despite the encouraging results of calcium and vitamin D supplementation in care home residents, blanket supplementation with vitamin D does not appear to work consistently. However, with large-scale trials there is a fundamental methodological deficiency [due to] deliberate reduction of experimental control in order to maximise recruitment and compliance of subjects [22]. Such studies estimate the size of the effect of an intervention, but tell us nothing about its mechanisms or why it may be ineffective. Thus to prevent future large trials from failing, we may benefit from the approach of the researchers of the early 20th century and the authors of paper in this issue [18], in performing clinical scientific studies of the nature of vitamin D deficiency and the effects of its treatment. Once we can define who to treat, with what therapy and at what dose, we may have an adequate hypothesis to test in a randomised controlled trial.

T. J. Aspray1, R. M. Francis2*
1Sunderland Royal Hospital, Kayll Road, Sunderland, Tyne and Wear, UK
2School of Clinical Medical Sciences, University of Newcastle upon Tyne, UK
*To whom correspondence should be addressed: Muscular Skeletal Unit, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK

References

Editorials