Nutrition and bone health: the case of selenium

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Bone health deteriorates with age, reflected in decreasing bone mineral density and increasing numbers of fractures. In women, the primary cause of this deterioration is the fall in circulating oestrogen concentrations at the time of the menopause, which results in increased osteoclast activity and an excess of bone resorption over bone formation. Several decades later, decreasing muscle strength with impaired balance and coordination contribute to a progressive increase in the frequency of falls, which further accelerates fractures in a weakening skeleton.

Observational studies of bone health find associations with age, but also with a range of nutrients. It has become a familiar situation to read that vitamin X or mineral Y is present in lower concentrations in those with osteoporosis compared with controls. Whether such dietary associations are causative is uncertain, since global food intake decreases as age and frailty advance, as does bodyweight, a further key determinant of skeletal health. Thus, bidirectional effects between advancing frailty and suboptimal diet are likely to occur. Inter-correlations between intakes of a wide range of nutrients have the potential to make it challenging to determine which nutrient–bone associations are causative. For many nutrients, so-called optimal intakes have been determined on the basis of simple observational studies, without rigorous proof that an observed association is causative. In some cases, this situation has resulted in waves of publications decrying the widespread inadequacy of diets with respect to specific nutrients.

Studies finding epidemiological associations of nutrients with health can be supported by laboratory investigations showing effects of a particular nutrient on cell function in vitro, or in profoundly deficient animals in vivo. Such studies require scrutiny to ensure that biological effects found occur at concentrations of nutrients present in various states of human nutrient deficiency. If in-vitro effects or those in animal studies occur at nutrient concentrations substantially different from those found in human populations they are unlikely to have relevance to human nutrition.

In this context, selenium is one of many nutrients which has been reported to be associated with bone health in some,[1,2] but not all studies.[3,4] Such observational studies could indicate that sub-optimal selenium intakes contribute to declining bone health. Selenium exerts its biological functions through selenoproteins, which contain the amino acid selenocysteine. There are 25 selenoproteins in the human genome, some of which act in anti-inflammatory and antioxidative pathways, such as the enzyme glutathione peroxidase that catalyses the degradation of organic hydroperoxides.

The possibility that selenium status affects bone health has now been tested for the first time in a randomised controlled trial, reported in this issue of *The Lancet Healthy Longevity* by Jennifer Walsh and colleagues.[5] In a 6-month study, 120 postmenopausal women were randomly allocated to receive placebo or sodium selenite 50 µg or 200 µg orally once per day. The primary endpoint was a biochemical marker of bone resorption (urine NTx, expressed as ratio to creatinine), with additional assessments of other markers of bone turnover, bone mineral density, physical performance, glutathione peroxidase, highly sensitive CRP, and IL-6. None of these were significantly changed by selenium supplementation, except for a approximately 1% improvement in spine density with the 50 µg dose, not seen with the higher dose. So, perhaps selenium has no role in bone health?

Ideally, dietary intervention studies should recruit a population that has borderline or deficient nutrient status, and provide a supplement which restores this status to optimal levels. Reference ranges for serum selenium vary between countries but the optimal range in adults has been suggested to be 120 µg/L, and reductions in glutathione peroxidase activity are found when the serum concentration is lower than 40 µg/L.[6] In the Walsh and colleagues' study, the mean serum selenium concentration at baseline was 79 µg/L (range 35–117 µg/L), indicating that most participants were below the optimal range before intervention, but only very few had concentrations associated with altered enzyme function. Consistent with this fact, there were no changes in glutathione peroxidase activity in the study following supplementation, despite the increases in serum selenium concentrations that were shown.

The negative results of the Walsh and colleagues' study need to be interpreted in the context of the baseline serum selenium concentrations of the study

participants. The study's findings indicate that selenium is not a general tonic for bone health. Selenium might still be a threshold nutrient affecting bone but that remains to be systematically explored. It is possible that individuals with serum selenium concentrations of less than 40 µg/L might have responded differently following supplementation. A comparison with vitamin D supplements is apt—in those with osteomalacia as a result of vitamin D deficiency, supplements increase bone density by as much as 50%, whereas in healthy community cohorts extra vitamin D produces no significant effect on density or fractures. The Walsh and colleagues' study is an important contribution to our understanding of the effects of selenium on bone, and indicates that there is no reason to consider general supplementation of this element in the older population. However, this study should not be interpreted as indicating that selenium has no role in skeletal biology and wellbeing.

I declare no competing interests.

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