

Invited commentary

Calcium and osteoporotic fractures

Ca is a main component of bone and 99% of body Ca is found in the skeleton. In addition to being of great importance for the structural properties of bone, bone Ca is the major reservoir for body Ca. Ca is essential for numerous metabolic functions, and to maintain these, serum Ca is strictly regulated. Ca balance is determined by the amount of Ca in the diet (supplements included), the efficiency of absorption and the amount lost in urine, faeces and sweat. In negative Ca balance Ca homeostasis can be maintained by mobilisation from the skeleton, and in positive balance Ca can be deposited in the skeleton. It thus seems plausible to assume that a high Ca intake is good for skeletal health. In spite of this, the association between Ca intake and osteoporosis is highly debated, and studies have given conflicting results (Kanis, 1994; Heaney, 2000a,b; Specker, 2000).

In the current issue of *British Journal of Nutrition*, Xu *et al.* (2004) assess whether Ca at physiological doses in a normal diet affects fracture risk. In their carefully conducted meta-analysis, they do not find any association between dietary Ca and bone fractures in women. The only exception is a suggested protective effect of dietary Ca in a population of Chinese women with a very low habitual Ca intake.

To study the association between dietary intake of Ca and fracture in observational studies is, however, a challenging task. The measurement of Ca intake is subject to misclassification, which at least in prospective studies is expected to be non-differential; i.e. independent of whether the individuals fracture later or not. The imprecision of Ca intake as reported by the study participants will thus dilute a possible association between Ca and fracture.

In case-control studies and cross-sectional studies additional differential misclassification might occur with patients with fractures (cases) reporting their Ca intake systematically different from persons without fracture.

In addition, numerous other factors may affect the complex regulation of Ca balance and may obscure the effect of Ca intake in epidemiological studies. For example, a person with a high Ca intake and a reduced absorption or an increased excretion may not be in a better situation than a person with a low Ca intake. Of key importance for intestinal Ca absorption is vitamin D. The true impact of dietary Ca intake on fracture rate can only be assessed if vitamin D status is satisfactory. Vitamin D is provided both by the diet and by cutaneous production during exposure to sunlight. The reliable way to determine vitamin D status is thus via serum analysis of 25-hydroxy vitamin D; this has rarely been done in epidemiological studies of the type included in the meta-analysis.

The situation might also be complicated by possible interactions between Ca and other factors affecting bone

mass, including physical activity (Specker, 2000) and vitamin D receptor genotype (Specker, 2000).

The optimal design to study the effect of dietary Ca would be a randomised controlled trial with fracture endpoints. Randomising participants to a diet rich in Ca or a control diet would control for all other factors affecting Ca balance and fracture risk. However, to perform such a study would be very demanding.

Even when it comes to studying the effect of Ca supplementation as tablets, surprisingly few randomised controlled trials have been performed. The authors of a meta-analysis published in 2002 could only identify five randomised controlled trials including 576 women reporting fracture outcome (Shea *et al.* 2002). It was concluded that due to few endpoints, no conclusion concerning the effect on fracture risk could be made based on available controlled trials. On the other hand, a combination of Ca and vitamin D has proven effective in the prevention of fragility fractures in the elderly (Chapuy *et al.* 1992; Dawson-Hughes *et al.* 1997).

Concerning the effect on bone density, more data exist. During growth, a high Ca intake probably enhances peak bone mass. For example, in a randomised controlled trial in 8-year-old Swiss girls, 1 year of supplementation with calcium phosphate extracted from milk led to a greater increase in bone density in the intervention group compared with the control group (Bonjour *et al.* 2001). An effect of the intervention was still present 3.5 years after the supplementation had been discontinued.

A high Ca intake can decrease bone loss in the elderly. Bone remodelling takes place in bone remodelling units and is a sequential process, involving bone resorption by the osteoclasts followed by bone formation by the osteoblasts. Bone loss occurs when bone resorption is greater than bone formation in each remodelling unit, as in postmenopausal osteoporosis. Ca decreases bone turnover (the number of bone remodelling units), thus leading to a reduction in bone loss, as there will be fewer bone remodelling units to lose bone from. The association between Ca supplementation and postmenopausal osteoporosis has recently been evaluated in a meta-analysis of randomised controlled trials (Shea *et al.* 2002). A total of fifteen trials with 1806 participants were included. At all skeletal sites (hip, lumbar spine, total body and distal radius), a small, beneficial effect of Ca supplementation was found. For example, the pooled estimate after 2 years of treatment showed that women not supplemented with Ca had a 1.64% greater bone loss at the hip compared with women supplemented with Ca. It should be noted that the average habitual dietary Ca intake in these women was about 700 mg/d. The dose of supplemented Ca

ranged from 500 to 2000 mg, i.e. much greater than the common variation in habitual dietary Ca intake in the observational studies included in the current meta-analysis. In other words, in postmenopausal women with a relative high habitual dietary Ca intake, supplementation with Ca had an effect on bone density.

In conclusion, although observational studies in sum do not demonstrate an association between dietary Ca (within normal range) and fracture in women, it cannot be concluded that such an association does not exist. On the other hand, based on the modest effect of large doses of Ca supplementation on bone density, a potential effect is probably small and dependent on the sum of factors affecting Ca homeostasis, rather than Ca intake alone. A larger effect in populations with very low habitual Ca intake is plausible.

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