

## Is nutrition important in osteoporosis?

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Osteoporosis is a crippling disease that affects millions of people worldwide. It is characterized by loss of bony tissue from the skeleton and deterioration of bone structure, and is associated with enhanced bone fragility and increased risk of fracture (Consensus Development Conference, 1991). Fragility fractures are most common at the wrist, spinal vertebrae and hip, although they can occur throughout the skeleton. The incidence of vertebral and hip fractures increases exponentially with advancing age while that of wrist fractures levels off after the age of 60 years (Compston, 1993).

Osteoporosis can be divided into two main categories (Melton & Riggs, 1988; Compston, 1993). Type I (postmenopausal) typically occurs between ages 50–75 years and is more common in women than men (women:men 6:1 approximately). Fractures occur predominantly in trabecular bone, especially the distal radius (Colles' fracture) and the spinal vertebrae (crush fracture). Bone loss is accelerated, parathyroid hormone and 1,25-dihydroxycholecalciferol levels are reduced and Ca absorption is decreased. Oestrogen deficiency is regarded as the main pathogenetic factor of Type I osteoporosis, and hormone-replacement therapy is effective in reducing the bone loss and fracture risk associated with the menopause (Compston, 1993; Lindsay, 1993). Type II (senile) affects women and men over the age of 70 years (women:men approximately 2:1). Fractures occur in both cortical and trabecular bone, most commonly in the proximal femur (hip) and the spinal vertebrae (wedge fracture). Unlike Type I, bone loss in senile osteoporosis is not accelerated, and parathyroid hormone levels may be raised. There is increasing evidence that this hyperparathyroidism plays an important role in the pathogenesis of Type II osteoporosis and is secondary to vitamin D insufficiency (Compston, 1993; Khaw & May, 1995).

Osteoporosis is a major public health problem in the UK, affecting one in three women and one in twelve men (National Osteoporosis Society, 1996). There are currently over three million sufferers in the UK, where approximately 60 000 hip fractures, 50 000 wrist fractures and at least 40 000 vertebral fractures occur each year. Approximately one-third of orthopaedic beds in the UK are occupied by hip-fracture patients and treatment of osteoporosis costs the National Health Service in excess of £750 million per annum. Osteoporosis is often associated with considerable pain, disability and disfigurement, and can lead to premature death. Approximately 50 % of elderly hip-fracture patients do not regain full independence, and 20 % die within 6 months through complications connected with the fracture. Internationally, more than 1.5 million fractures occur annually, and this number is projected to increase 4-fold by the year 2050 (Cooper *et al.* 1992).

### RISK FACTORS FOR OSTEOPOROSIS

Low bone mineral mass is the main factor underlying osteoporotic fracture. The World Health Organization (1994) uses the following diagnostic criteria for the disease, based on bone mineral status expressed either as bone mineral content (BMC) or bone mineral density (BMD): normal, within 1 SD of young adult reference mean for the population; osteopenia, between  $-1$  and  $-2.5$  SD of the young adult mean; osteoporosis, more than

–2.5 SD below the young adult mean. Assessments of bone mineral status are readily performed by techniques based on absorptiometry, such as dual-energy X-ray absorptiometry (DXA), quantitative computer tomography and ultrasound (World Health Organization, 1994). Other facets of bone quality, such as microarchitecture and turnover, are also likely to be important determinants of bone strength, but since, at present, they are less amenable to systematic study, their role in the pathogenesis of osteoporosis is unclear (Cooper & Aihie, 1994).

Most osteoporotic fractures result from a fall, often from standing height (Compston, 1993; Cooper & Aihie, 1994). A history of falls or dizziness, use of certain medications, alcohol abuse, poor eyesight, inadequate domestic lighting, dependency and immobility, are examples of factors that can increase the likelihood of falling and, hence, contribute to fracture risk. Age-related changes in neuromuscular function alter the way in which people respond during a fall, and this may account for the rise in hip fractures relative to wrist fractures among the elderly (Cooper & Aihie, 1994). Measures to minimize the risk of falls, such as handrails and regular eyesight checks, or to reduce the impact of falls, such as floor coverings and hip protectors, can be useful in the prevention of osteoporotic fractures (Lauritzen *et al.* 1993).

#### DETERMINANTS OF BONE MINERAL MASS

Bone mineral status in later life is the net outcome of lifelong influences on skeletal mineral accretion and loss. Bone mineral is laid down throughout childhood, with the most rapid increase occurring during puberty, and deposition continues, at a slower rate, after growth in height has stopped (British Nutrition Foundation, 1989; Parsons *et al.* 1996). Peak bone mineral mass is achieved in early adult life (25–35 years of age), although the exact timing is not certain and may vary between different regions of the skeleton (Sowers & Galuska, 1993). At older ages, bone is gradually lost from the skeleton in both men and women. For women, there is also a period of about 10–15 years when bone loss is accelerated due to oestrogen withdrawal at the menopause, when more than one-third of bone is lost from the skeleton (Compston, 1993).

Bone is a living tissue, and is constantly undergoing breakdown and formation as part of the natural process of renewal and repair. As a result, any factor that influences the development of peak bone mineral mass or the loss of bone mineral in middle-age will affect later fracture risk. Many factors are thought to influence bone mineral status, including genetic inheritance, body build, hormonal concentrations, especially those of the sex hormones and calciotropic hormones, and lifestyle factors such as physical activity and diet.

Heritability studies have demonstrated that about 80 % of the variation in bone mineral status is due to genetic factors (Eisman, 1995; Peacock, 1995). Allelic variations have been identified in a number of candidate genes that may be important in bone health, such as the vitamin D-receptor (VDR) gene, parathyroid-hormone-receptor gene, oestrogen-receptor gene, collagen genes, interleukin-6 gene, and apolipoprotein E (ApoE) gene. However, at present the degree to which polymorphism in any of these genes affects bone mineral status, bone turnover or fracture risk is unclear and controversial (Eisman, 1995; Peacock, 1995). There is some recent evidence that gene–nutrient interactions may influence the importance of nutrition to bone health. For example, response at the lumbar spine to Ca supplements and vitamin D analogues has been related to VDR genotype (Ferrari *et al.* 1995; Matsuyama *et al.* 1995) and lipoprotein transport of vitamin K to bone is affected by ApoE genotype (Saupe *et al.* 1993).

## NUTRIENTS AND BONE

A large number of dietary components have been proposed as possible determinants of bone health and osteoporosis risk. In some instances, such as in the case of vitamin K, vitamin C, Mg, Cu and F, the biological action of the dietary constituent is at the level of bone itself; vitamin K is discussed later (p. 364) as an example of this type of nutrient. However, the putative importance of the majority of nutrients lies in their observed effects on the excretion or absorption of Ca.

The adult human body contains about 1 kg Ca, and all but 1–2 % is contained in bone (British Nutrition Foundation, 1989). In consequence, any factor that affects the amount of Ca retained by the body must alter total bone mineral mass. Nutrients that increase urinary Ca excretion, such as S-rich proteins, salt and caffeine, or that reduce net Ca absorption, such as fat, phytates and oxalates, are regarded as having a negative effect on bone. Conversely, nutrients that decrease Ca excretion, such as B, or increase Ca absorption, such as sugars and Ca, are regarded as beneficial. However, the situation is highly complex and the impact of these dietary constituents on long-term Ca balance and fracture risk is unclear. Some nutrients, phosphate for example, affect both net Ca absorption and excretion in such a way that there is little overall effect on Ca balance (Heaney & Recker, 1994; Heaney *et al.* 1995). In addition, some dietary components, such as fat and phosphate, are digested or absorbed in the small intestine at a faster rate than Ca, minimizing the potential negative effect on Ca absorbability (Heaney *et al.* 1995). Where measurable effects on Ca balance are observed, the magnitude is often small and can be compensated for by small increases in Ca intake. Caffeine, for example, reduces Ca retention by increasing Ca excretion and decreasing Ca absorption, but the small effect, equivalent to approximately 3 mg Ca per cup of brewed coffee, is offset by the increased Ca intake associated with adding milk to the beverage (Barrett-Connor *et al.* 1994; Heaney *et al.* 1995). This may account for the observation that high caffeine intake is associated with greater post-menopausal bone loss only in women with low Ca intake (Harris & Dawson-Hughes, 1994).

## ADAPTATION TO DIETARY CHANGES

Interpretation of data relating diet composition to Ca balance is complicated by the likelihood that the body adapts to dietary changes by adjusting the amount of Ca absorbed from the gut and excreted in urine, sweat and gastrointestinal secretions. In general, only a proportion of the Ca in the diet is absorbed (about 30–40 %), some of the endogenous Ca secreted into the gut is re-absorbed, and only a very small proportion of the Ca filtered each day by the kidneys is excreted (approximately 2 %; Schaafsma, 1988). This provides considerable scope for the 'fine-tuning' of net absorption and excretion to ensure that the body retains sufficient Ca to meet its needs. Long-term control of Ca balance appears to occur primarily in the gastrointestinal tract rather than in the kidney. This is indicated by the fact that large increases in Ca intake produce only modest changes in urinary Ca excretion, equivalent to approximately 6 % of the dose (Lemann *et al.* 1979; Prentice *et al.* 1995).

Adaptation to sustained dietary change can take several months to accomplish and the capacity to respond may vary between individuals. This was demonstrated by the detailed studies of Malm in the 1950s, where negative Ca balance associated with a decrease in Ca intake from 1000 to 500 mg Ca/d gradually attenuated over the succeeding months, but zero balance, when Ca excretion had diminished to match intake, was restored only after a

considerable period and was not achieved in some subjects by the end of the study (Malm, 1958; Kanis, 1991).

Ca release and uptake by the skeleton is a key aspect in the short-term control of Ca homeostasis. A rise in blood ionized-Ca concentration following a recent meal prompts a reciprocal response in circulating parathyroid hormone concentration (Lobaugh, 1996). This initiates changes in the renal and gastrointestinal handling of Ca. In addition, the hormone elicits rapid uptake of Ca into a readily-exchangeable skeletal pool, followed by a second, slower phase of uptake into a skeletal compartment that turns over less rapidly (Lobaugh, 1996). The converse scenario occurs when blood ionized-Ca concentration falls.

The skeletal pool of slowly-exchangeable Ca corresponds to the Ca released and laid down during bone remodelling. Remodelling is the process whereby the skeleton undergoes continual renewal by a phased sequence of bone resorption and formation (Frost, 1973; Parfitt, 1980; Kanis, 1991). In the adult, 95 % of bone turnover occurs by remodelling and approximately 10–15 % of skeletal surfaces are in the process of being remodelled at any one time. Osteoclasts, the cells responsible for bone resorption, dissolve away a small, discrete portion of the surface. The resulting resorption cavity is refilled by the action of osteoblasts, the bone-forming cells. These lay down bone matrix (osteoid) which gradually becomes mineralized to form new bone. There is a strict chronological sequence of events, with recruitment of osteoblasts occurring some time after resorption, and with newly-formed bone mineralizing rapidly in the initial stages but more slowly thereafter. As a result, it takes many weeks for the entire process to be completed. During this time, there is a temporary net deficit of mineral in the volume of bone undergoing remodelling and, hence, in whole-body bone mineral (Parfitt, 1980; Kanis, 1991). It is estimated that, in normal adults, the reversible Ca deficit represents about 1.3 % of total body bone Ca, equivalent to approximately 14 000 mg Ca (Table 1). Since bone turnover is greater in trabecular bone, the reversible Ca deficit is greatest in trabecular regions (about 4 %; Table 1). When resorption conditions vary, there is a transition period where the number or size of new resorption cavities is modified but restoration of existing resorption pits is maintained at the previous rate. This produces a quantitative change in the remodelling space, a corresponding alteration in the reversible Ca deficit, and results in a rise or fall in the total amount of mineralized tissue per unit volume of bone until a new steady-state is established (Kanis, 1991).

Table 1. *Typical reversible calcium deficit associated with adult bone turnover* (Based on Parfitt, 1980)

	Cortical bone	Trabecular bone	Whole body
Total bone Ca (mg)	840 000	210 000	1 050 000
Reversible Ca deficit			
Remodelling space*: mg	3360	4200	7650
% total bone Ca	0.4	2.0	0.7
Osteoid space†: mg	840	2100	2940
% total bone Ca	0.1	1.0	0.3
Low-density bone‡: mg	1050	2450	3500
% total bone Ca	0.1	1.2	0.3
Total deficit: mg	5250	8750	14 000
% total bone Ca	0.6	4.2	1.3

\* The volume of bone temporarily missing because of the time delay between bone resorption and formation.

†The volume of bone temporarily replaced by unmineralized protein matrix during bone formation.

‡The difference in mineralization between newly-formed bone (< 6 months old) and mature bone.

Changes in the reversible Ca deficit act to minimize fluctuations in the Ca concentration of extracellular fluid caused by dietary influences (Kanis, 1991). An increase in Ca intake depresses bone turnover due to decreased activation frequency of osteoclasts, producing a lower rate of resorption, a reduction in the remodelling space and an increase in bone mineral content. Conversely, a decrease in Ca intake promotes osteoclast activation, increases bone turnover and decreases bone mineral. Changes in diet composition that affect Ca excretion or absorption would be expected to produce similar effects. This process may also underlie the physiological mobilization of Ca from the skeleton at times of high requirement, for example in early lactation (Prentice, 1994; Laskey *et al.* 1996). In some circumstances, dietary effects on the reversible Ca deficit can produce sufficiently large changes in bone mineral mass to be measurable by DXA and other precise measures of bone status (Kanis 1991, 1994a).

It is difficult to equate effects on the reversible Ca deficit with evidence of nutritional need or fracture risk. Ca supplements taken by post-menopausal women can produce a small increase in cortical BMD during the first months of treatment but bone loss generally returns to pre-supplementation rates within 1–2 years (Parfitt, 1980; Kanis, 1991). It is probable that increasing the dose further after a period of time would illicit another transient rise in bone mineral density. This suggests that, in this situation, the extra Ca acts pharmacologically on bone turnover rate, rather than corrects a nutritional deficiency in the classical sense (Kanis, 1991, 1994b). While temporary relief from bone loss may be beneficial for some post-menopausal women, the implications of a decrease in turnover for the bone health of other population groups, such as children and young adults, are not known.

#### METHODOLOGICAL PROBLEMS

The examination of the importance of diet to bone health is fraught with methodological and interpretative problems. As can be appreciated from the previous sections, studies that investigate the impact of diet composition or nutrient intakes on Ca balance are difficult to interpret unless they are conducted over a substantial period of time, which is rarely the case. In addition, there is considerable variation between individuals in their response to dietary change which makes extrapolation from small, detailed studies to the wider population unsafe. A decrease in the reversible Ca deficit as a result of some dietary modification may be detected as an increase in bone mineral status, but this may not necessarily translate into a benefit for bone health.

A further problem, that has been identified recently, is the widespread use of BMD, measured by DXA, as a measure of bone mineral status in epidemiological studies (Prentice *et al.* 1994). The problem arises because BMD, derived by dividing BMC by scanned bone area (BA), is not a true volumetric measurement and is highly correlated with BA at most skeletal sites. Failure to include BA in regression models can lead to spurious relationships emerging between BMD and size-dependent variables, such as nutrient intakes (Prentice *et al.* 1994). An efficient method of minimizing the potential for size-confounding is to include BA, body weight and height as independent variables in all regression models involving BMD (Prentice *et al.* 1994). BMI, a commonly-used measure in bone studies, is not effective in adjusting for size in this context (Cole & Prentice, 1992; Prentice *et al.* 1994).

Although there have been a large number of observational studies that have investigated the association between diet and either Ca balance or bone mineral status, few are sufficiently detailed to provide a clear insight into nutrient requirements for optimal

bone health and reduced fracture risk. For example, there have been two meta-analyses published in recent years exploring the relationship between bone mineral (generally BMD) and diet; both concluded that Ca intake is a significant determinant of bone status (Cumming, 1990; Welten *et al.* 1995). However, the magnitude of this effect is small, at about 1% of the population variance, and size-confounding must be suspected since none of the examined studies adjusted for bone size, and few normalized for body weight or height. The possibility of size-confounding, the difficulties associated with assessing energy and nutrient intakes accurately, and the likelihood that the absence of significant associations between bone status and specific nutrients tends to remain unreported, mean that much of the observational evidence relating bone mineral to specific dietary components is unreliable.

At present, the most useful information is provided by long-term intervention studies that examine the direct effects of dietary modification on bone mineral status or fracture incidence. Biochemical measurements of Ca and bone metabolism, especially functional indicators such as the bone turnover markers osteocalcin and deoxypyridinoline, provide supplementary data to explore possible mechanisms. There have been comparatively few such studies. Two nutrients are discussed in some detail to illustrate the current state of understanding in this area and the complexity of the issue: Ca and vitamin K.

#### CALCIUM

Supplementation studies indicate that an increase in Ca intake for women during the early menopause is not effective in retarding bone loss from trabecular regions of the skeleton, including those most vulnerable to fracture in Type I osteoporosis (Riis *et al.* 1987; Dawson-Hughes *et al.* 1990; Elders *et al.* 1994). Reductions in cortical bone loss are observed during this period (Polley *et al.* 1987; Riis *et al.* 1987; Smith *et al.* 1989; Elders *et al.* 1994), but these are not as great as those achieved with hormone-replacement therapy (Riis *et al.* 1987) and tend not to be sustained (Kanis, 1991; Elders *et al.* 1994).

For older women, Ca supplementation reduces bone loss at the hip (Dawson-Hughes *et al.* 1990; Nelson *et al.* 1991; Reid *et al.* 1993; Chevalley *et al.* 1994; Prince *et al.* 1995), especially for subjects with low habitual Ca intake (Dawson-Hughes *et al.* 1990). Impressive reductions in hip-fracture incidence have been achieved in elderly women using a combination of  $\text{Ca}_3(\text{PO}_4)_2$  and vitamin D supplements (Chapuy *et al.* 1992, 1994). Correction of poor vitamin D status and reduction in parathyroid hormone levels appear to be central to the mechanism of this effect. Increases in Ca intake have little effect on spinal-bone mineral in older women (Nelson *et al.* 1991; Chevalley *et al.* 1994; Prince *et al.* 1995).

There have been only a few published supplementation studies in children and adolescents that have examined bone mineral status (Johnston *et al.* 1992; Lloyd *et al.* 1993; Andon *et al.* 1994; Lee *et al.* 1994, 1995; Nowson *et al.* 1995). The emerging picture is that, particularly in pre-pubertal children, an increased Ca intake is associated with higher bone mineral status of approximately 1–5% depending on the skeletal site (Table 2). Curiously, the effects observed in these studies were of similar magnitude, despite marked differences in the initial Ca intake of the volunteers and in the increase in Ca intake achieved by supplementation (Prentice, 1995). In addition, the interventions had the greatest impact in the early months of the supplementation period (Johnston *et al.* 1992; Nowson *et al.* 1995), and the effect disappeared after the supplement was withdrawn (Slemenda *et al.* 1993; Lee *et al.* 1995). These observations suggest that the increase in bone mineral was associated with a reduced reversible Ca deficit. This is compatible with

Table 2. Published calcium supplementation studies in children and adolescents

Reference	Country	Sex	n*	Age† (years)	Ca (mg/d)		Duration of Ca supplementation (months)	Bone effect	Osteocalcin	Follow-up‡
					Diet	Supplement				
<b>Pre-puberty</b>										
Johnson <i>et al.</i> (1992), Slemenda <i>et al.</i> (1993), Andon <i>et al.</i> (1994)	USA	M+F	22§	7	900	1000	36	+	Reduced	0
Nowson <i>et al.</i> (1995)	Australia	F	5§	11	1000	1000	12	+	?	?
Lee <i>et al.</i> (1994)	China	M+F	79	7	280	300	18	+	?	0
Lee <i>et al.</i> (1995)	Hong Kong	M+F	42	7	570	300	18	+	?	0
<b>Peri and post-puberty</b>										
Johnson <i>et al.</i> (1992), Andon <i>et al.</i> (1994)	USA	M+F	23§	11	900	1000	36	0	0	0
Nowson <i>et al.</i> (1995)	Australia	F	25§	14	1000	1000	12	0	?	?
Lloyd <i>et al.</i> (1993)	USA	F	48	12	950	500	18	+	?	?
Andon <i>et al.</i> (1994)	USA	F	120	11	884	500 and 1000	6	+	?	?

+, Significant increases at one or more bone sites (1–5%); 0, no significant difference; ?, not reported.

\* No. in supplemented group.

† Age at entry (years).

‡ Difference between groups several months after withdrawing the supplement.

§ Twin studies.

the size of the observed effects, and is supported by the account, in the one study that reported biochemical measurements, of lower circulating osteocalcin concentrations in supplemented children (Johnston *et al.* 1992; Slemenda *et al.* 1993). It would appear, therefore, that the higher level of Ca intake attained in these studies would have to be sustained indefinitely in order to achieve lasting effects on bone mineral status. However, whether reducing the rate of remodelling during childhood is beneficial for the acquisition of optimal peak bone mass and long-term bone health is not known.

On the basis of data such as these, there have been calls for large increases in recommended Ca intakes, particularly for older women and adolescents (National Institutes of Health, 1994). Whether the observed effects on bone mineral status associated with increases in Ca intake represent the correction of a nutritional deficiency is a matter of considerable controversy and debate (Kanis, 1994a). It may be that a step increase in Ca intake at certain vulnerable times may benefit the bone health of some individuals by the regulation of bone turnover, but the incorporation of this concept into the derivation of dietary reference values and nutritional guidelines will require a redefinition of the accepted criteria for dietary adequacy (Beaton, 1988; Department of Health, 1991). It is, however, worth reflecting that, on a global basis, osteoporotic fracture incidence is highest in populations with high Ca intakes, such as in Northern Europe (Royal College of Physicians, 1989), suggesting that low Ca intake *per se* is not a major predisposing factor for osteoporosis.

#### VITAMIN K

Vitamin K is a cofactor of  $\gamma$ -glutamylcarboxylase, an enzyme involved in the post-translational carboxylation of protein-bound glutamic acid residues (Vermeer *et al.* 1992). The resulting  $\gamma$ -carboxyglutamate residues (Gla) bind Ca ions avidly, and this is the basis of the biological activity of Gla-proteins. Hepatic Gla-proteins are important in blood coagulation; bone Gla-proteins, principally osteocalcin, are involved in the regulation of bone calcification (Vermeer *et al.* 1992).

Older people, patients with osteoporosis and newborn infants have a comparatively high proportion of circulating undercarboxylated osteocalcin which can be decreased by vitamin K supplements (1 mg/d; Jie *et al.* 1992; Szulc *et al.* 1994; Douglas *et al.* 1995; Vermeer *et al.* 1995). In addition, decreased serum levels of vitamin K have been reported in hip-fracture patients (Hart *et al.* 1984; Hodges *et al.* 1993) and there is limited evidence from Japan that vitamin K supplements at high doses (45 mg/d) may increase bone mineral status (Vermeer *et al.* 1995). To what extent vitamin K insufficiency is involved in the pathogenesis of osteoporosis is not known, but this question deserves further attention (Consensus Development Conference, 1993).

#### POOR NUTRITIONAL STATUS

It is important not to lose sight of the fact that poor nutritional status, in the broad sense, is a recognized risk factor for osteoporosis. Elderly patients with hip fracture are often malnourished on admission to hospital, and their prognosis is improved by the provision of dietary supplementation (Delmi *et al.* 1990). Low body weight and excessive dieting in younger women is associated with low bone mineral status and increased fracture risk, especially when normal gonadal function is disturbed (Frusztajer *et al.* 1990; Mazess *et al.* 1990; Prior *et al.* 1990). Poor vitamin D status in elderly people is associated with



increased fracture risk, and dietary vitamin D provision becomes important in this age-group because of decreased skin production of this vitamin (Department of Health, 1991).

#### CONCLUDING REMARKS

The issue of whether nutrition is important in the aetiology of osteoporosis is complex and unresolved. The unsatisfactory nature of much of the available data hampers the formulation of rational strategies based on diet and lifestyle for the prevention of osteoporosis and the reduction of fracture risk. A greater awareness of the methodological pitfalls inherent in many of the current techniques used to investigate this question, plus an increased emphasis on examining the underlying biological mechanisms, may help to simplify some of the apparent contradictions in the future.

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