Bone health: the role of micronutrients

Susan A New

Centre for Nutrition and Food Safety, University of Surrey, Guildford, UK

Development and maintenance of skeletal health is essential since the resultant effect of poor bone health is an increased risk of osteoporotic fracture. Osteoporosis is currently a major public health problem and with predicted demographic changes, its future health and economic impact is likely to be phenomenal. Adult bone health is predominantly governed by two factors: (i) maximum attainment of peak bone mass; and (ii) rate of bone loss which occurs with ageing. Both aspects are determined by a combination of endogenous and exogenous factors and, although genetic influences are believed to account for up to three-quarters of the variation in bone mass, there is still room for the modifiable factors (including nutrition) to play an important role. There is now good evidence to show that calcium is important not only to peak bone mass development but also in reducing bone loss in women who are greater than 5 years postmenopause. Vitamin D and calcium (and possibly vitamin K) are vital to fracture prevention in the elderly. Our knowledge of the influence of other micronutrients on bone health remains limited and further research is required to establish the essential ingredients for optimum bone health.

Predisposition to poor bone health will result in an increased risk of fracture and hence the clinical diagnosis of osteoporosis. This term was first described in France around 1820 as 'porous bone' and is now considered a disorder in which there is a diminution of bone mass without detectable changes in the ratio of mineralized to non-mineralised matrix. Since 1991, osteoporosis has been defined as: 'a disorder characterised by increased skeletal fragility due to decreased bone mass and to microarchitectural deterioration of bony tissue'. This newer definition shifts the focus of attention from reduced bone mass to that of bone fragility and, hence, reflects the growing recognition that bone weakness is related to poor structural quality as well as decreased bone mass. An illustration of 'normal' and 'osteoporotic' bone is shown in Figure 1.

The clinical significance of osteoporosis is related to the fractures which occur, affecting in particular the proximal femur (hip fractures), the spine (vertebral crush fractures) and the distal radius (Colles fracture). It is estimated that about 1.66 million hip fractures occurred world-wide in
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Fig. 1 Comparison of enlargement of normal healthy bone as in a woman of 35 years with bone in a woman over 60 years with severe osteoporosis. Reproduced with permission from the National Osteoporosis Society, UK.

1990 and lifetime risks are 17.5% in women and 6.0% in men with approximately 70,000 hip fractures occurring in British women each year. Osteoporosis is clearly a major public health problem with annual costs to the UK National Health Service estimated at nearly £750 million for women alone and around £942 million if the costs of treating male fractures are included. Furthermore, the future health and economic impacts of osteoporosis will be phenomenal when it is considered that by the year 2030, elderly people are predicted to account for one in four of the adult UK population with a projection of the rise in the number of fractures from 1.66 million in 1990 to 6.26 million by the year 2050.

Two mechanisms principally determine adult bone health: (i) the maximum attainment of peak bone mass (PBM) which is achieved during growth; and (ii) the rate of bone loss with advancing age. Both mechanisms are believed to be determined by a combination of endogenous and exogenous factors, namely: genetic, endocrine, mechanical and nutrition, with extensive interactions between them. Studies of bone mass in monozygotic and dizygotic twins and in mother–daughter pairs, together with the findings of an association between polymorphisms of the vitamin D receptor gene, oestrogen receptor gene and collagen I α1 gene and bone mass provide strong evidence that the genetic factors account for up to three-quarters of the variation in bone mass. However, there is still room for the modifiable factors (including nutrition) to play a vital role in bone health.

This chapter will focus on the importance of micronutrients to bone health by examining our current knowledge on the relationship between nutrition and bone mass within the three key stages of skeletal health, namely: (i) in the development of maximum peak bone mass; (ii) in the reduction of perimenopausal and postmenopausal bone loss; and (iii) in the
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Risk of fracture. Attention will focus on calcium, since most studies have concentrated on this nutrient but consideration will also be given to the role of other micronutrients including: vitamin D, magnesium, phosphorus, the trace elements (zinc, copper and manganese), vitamin C, vitamin K and potassium. The chapter will conclude with a summary of the clinical relevance of these nutrients and indications of areas for further research.

Role of micronutrients to peak bone mass attainment

Calcium

The important minerals within bone are calcium, phosphate and magnesium with approximately 1 kg of calcium being contained within the adult skeleton as a complex crystalline material with phosphate in the form of hydroxyapatite. It is important to understand that the skeleton is not just a repository for calcium but has a mechanical as well as biochemical function. Furthermore, in trying to understand the importance of nutrition to bone health, it should be emphasised that the skeleton is not inert but is being continually removed and replaced by the actions of the cells within it and that these cells are controlled by a number of mechanical and hormonal factors.

The importance of calcium to peak bone mass attainment was first highlighted by the work of Boyd Orr in the 1920s, who showed that children provided with milk grew taller than those without a milk supplement. A formal assessment of their bone health was, of course, not available. Although the importance of dietary calcium to PBM attainment has been highlighted by a number of cross-sectional studies, it was not until 1992 that the first 3 year, double blind, placebo-controlled trial on the effect of calcium supplementation on bone mineral density in children was undertaken. A total of 45 pairs of identical twins (22 prepubertal and 23 postpubertal), with one twin serving as a control for the other were studied. The calcium supplement enhanced the rate of increase in bone mineral density in the prepubertal group.

Other calcium supplementation studies have since followed, each showing that an increased calcium intake is associated with higher bone mineral status of approximately 1–5% (particularly in prepubertal children) depending on the skeletal site and with the greatest impact in the early months of the supplementation period. The importance of calcium to PBM development has been further highlighted by supplementation trials using calcium enriched foods and dairy products. The first British study was published in 1997 and using milk as the supplementation source; PBM was enhanced in the milk group. Although there is some concern that the effects may, in part, be influenced by increased...
cereal consumption in the milk group, the interesting observation of raised insulin-like growth factor I (IGF1) levels in this group may point to a stimulation of periosteal bone apposition. The resultant effect would be a slightly larger skeletal envelope in the milk group. Other possible explanations point to an IGF-1 response to changes in intake of other nutrients in the milk supplemented group, namely protein and energy. Studies are now required to see if the effect on bone mass is greatest in milk or in a calcium supplementation alone. Furthermore, while several of the calcium supplementation studies have shown that the benefits are lost once supplements are stopped, the milk and calcium enriched food studies have both shown that the effect persists one year after stopping treatment.

Other micronutrients

Virtually all published studies on nutrition and PBM attainment have focused on calcium which explains why our knowledge of the relationship between nutrition and bone health is still largely undefined. A diet which is low in calcium is also likely to be low in a large number of other micronutrients, all of which have plausible mechanisms for a role in maintaining skeletal health, but until recently have received very little scientific attention.

Recent evidence suggests that dietary phosphorus has an important and positive role to play in the development of PBM. As phosphate, this nutrient makes up roughly half the weight of bone mineral and, therefore, must be present in adequate amounts in the diet to mineralise and maintain the skeleton. As it is available in relatively adequate amounts in the diet, attention has tended to focus on excessive amounts being harmful to bone health and the characteristics of a low calcium to phosphorus ratio. There is some evidence that increased phosphorus intake depresses ionised calcium leading to an increase in parathyroid hormone and, hence, a rise in the rate of bone resorption. However, most studies have failed to show a deleterious long-term effect on bone health.

Results from the largest reported cross-sectional study to date on nutrition and bone mass investigating 1000 healthy UK premenopausal women suggest that high, long-term intakes of nutrients found in abundance in fruit and vegetables (namely magnesium, potassium, fibre and vitamin C) may be important to bone health. In this study, women in the lowest quartile of energy-adjusted intakes of these nutrients were found to have significantly lower bone mass, independent of important confounding factors including weight, height, smoking and socio-economic class. A significant difference in bone mass was also found in those women who reported consuming a low intake of...
Fig. 2  Increase in LS BMD (mean ± SEM) with quartiles of energy adjusted magnesium intake. F-test for linearity (P < 0.004) ANOVA (P < 0.01) ANCOVA (P < 0.02). Adjusted for age, weight, height, physical activity, smoking and social status. Data from New et al.\textsuperscript{35}.

Fig. 3  Increase in LS BMD (mean ± SEM) with quartiles of energy adjusted potassium intake. F-test for linearity (P < 0.005) ANOVA (P < 0.007) ANCOVA (P < 0.06). Adjusted for age, weight, height, physical activity, smoking and social status. Data from New et al.\textsuperscript{35}.

Fruit during their childhood and early adulthood. Further support is provided by a second study in the same population group (but different women) which found bone resorption to be higher in those women consuming low intakes of the same nutrients\textsuperscript{36}. As noted by Wachman and Bernstein, the skeleton is not only a labile reservoir of calcium responsive to the mechanisms which maintain ionic calcium, but it is also a reservoir of alkaline salts of calcium, which in turn provide a source of labile base\textsuperscript{37}. This base can be mobilised to react to both blood pH and plasma bicarbonate concentrations. The failure to maintain acid–base homeostasis in adults has been proposed as the mechanism behind the progressive decline in bone mass seen with age, and that such bone loss may be attributable to the life-long mobilisation of skeletal
salts to balance the endogenous acid generated from foods which are acid producing, such as meat. This theory may help to explain why some studies have shown a difference in bone mass in vegetarians compared to omnivores. Furthermore, findings by Sebastian et al (1994) that supplementation of potassium bicarbonate was found to improve calcium and phosphorus balance, reduced bone resorption and increase the rate of bone formation in postmenopausal women lends further support to this hypothesis.

There is very little documented evidence for the effect of other micronutrients on PBM development and this is certainly an area which requires further research. Of major concern is the growing evidence that nutrient intakes, (in particular calcium and iron) and physical activity levels are declining in British adolescents, while smoking habits and alcohol intake are on the increase. The long-term implications of these trends are not favourable to adult bone health and, hence, more research to target the ‘at risk’ groups are required.

Role of micronutrients in reducing peri- and postmenopausal bone loss

Calcium

Following attainment of PBM, a gradual loss of bone occurs with ageing. Before the menopause, the amount lost is very small but it then increases to approximately 1–2% per annum over the next 5–10 years. These respective changes in bone mass with the menopause have resulted in enormous interest over the last two decades as to the effectiveness of calcium supplementation in reducing perimenopausal bone loss. Debates have been intense and indeed continue. Table 1 provides a summary of calcium supplementation trials in peri- and early postmenopausal women. The failure of many studies in the postmenopausal stage to identify the special circumstances created by oestrogen withdrawal in the years following hormonal loss may help to explain why there was so much disagreement amongst studies as shown in the table. In 1990, Dawson-Hughes’s study was the first to divide women into years postmenopause. Calcium supplementation (500 mg/day) failed to reduce bone loss in women who were less than 5 years postmenopause, but, in women who have been postmenopausal for 6 years or more and with a daily calcium intake of less than 400 mg/day, bone loss was significantly reduced. This finding has received further support from other supplementation studies which have divided women according to their time since menopause. As shown in Table 2, all of
Table 1 Calcium supplementation studies in peri- and early postmenopausal women

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study duration (years)</th>
<th>n</th>
<th>Age (years)</th>
<th>TSM (years)</th>
<th>Ca-C (mg)</th>
<th>Ca-S (mg)</th>
<th>Ca-effect</th>
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<tr>
<td>Aloia et al (1994)^a</td>
<td>2.9</td>
<td>101</td>
<td>52</td>
<td>3-6</td>
<td>470</td>
<td>1700</td>
<td>+ve</td>
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<tr>
<td>Elders et al (1991)^b</td>
<td>3</td>
<td>248</td>
<td>49</td>
<td>1.2</td>
<td>1150</td>
<td>2500</td>
<td>+ve</td>
</tr>
<tr>
<td>Dawson-Hughes et al (1990)^c</td>
<td>2</td>
<td>67</td>
<td>54</td>
<td>&lt; 5</td>
<td>513</td>
<td>1013</td>
<td>No change</td>
</tr>
<tr>
<td>Ettinger et al (1987)^d</td>
<td>2</td>
<td>73</td>
<td>51</td>
<td>&lt; 3</td>
<td>994</td>
<td>2950</td>
<td>No change</td>
</tr>
<tr>
<td>Riis et al (1987)^e</td>
<td>2</td>
<td>36</td>
<td>49</td>
<td>&lt; 3</td>
<td>—</td>
<td>2000</td>
<td>+ve</td>
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TSM, time since menopause in years; Ca–C, control group calcium intake (mg); Ca–S, supplemented group calcium intake (mg); Ca–effect, effect of Ca supplementation.

Table 2 Calcium supplementation studies in late postmenopausal women

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study duration (years)</th>
<th>n</th>
<th>Age (years)</th>
<th>TSM (years)</th>
<th>Ca-C (mg)</th>
<th>Ca-S (mg)</th>
<th>Ca-effect</th>
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<tr>
<td>Dawson-Hughes et al (1995)^g</td>
<td>2</td>
<td>169</td>
<td>60</td>
<td>&gt; 5</td>
<td>283</td>
<td>783</td>
<td>+ve</td>
</tr>
<tr>
<td>Prince et al (1995)^h</td>
<td>2</td>
<td>168</td>
<td>63</td>
<td>&gt; 10</td>
<td>787</td>
<td>1672</td>
<td>+ve</td>
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<tr>
<td>Reid et al (1995)^i</td>
<td>4</td>
<td>78</td>
<td>58</td>
<td>9</td>
<td>710</td>
<td>1570</td>
<td>+ve</td>
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<tr>
<td>Reid et al (1993)^j</td>
<td>2</td>
<td>122</td>
<td>58</td>
<td>9</td>
<td>730</td>
<td>1590</td>
<td>+ve</td>
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<td>Nelson et al (1991)^k</td>
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<td>36</td>
<td>60</td>
<td>11</td>
<td>761</td>
<td>1462</td>
<td>+ve</td>
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TSM, time since menopause in years; Ca–C, control group calcium intake (mg); Ca–S, supplemented group calcium intake (mg); Ca–effect, effect of Ca supplementation.

these show a positive effect of calcium supplementation in reducing late postmenopausal bone loss^50-55. The study by Reid et al (1995) provides evidence that calcium is still effective in reducing bone loss after 4 years of supplementation^52.

Vitamin D

Vitamin D is the generic term for two molecules, egocalciferol (vitamin D<sub>2</sub>) and cholecalciferol (vitamin D<sub>3</sub>). The former is derived by UV irradiation of the ergosterol that is widely distributed in plants and other fungi, whereas the latter is formed from the action of UV irradiation on the skin. The action of sunlight on the skin converts 7-dehydrocholesterol to previtamin D which is then metabolised to vitamin D by a temperature-dependent isomerization. The vitamin D is then transported via the general circulation to the liver where the enzyme 25-hydroxylase converts it to 25 hydroxy-vitamin D. Further conversion to 1,25 (OH)<sub>2</sub>D<sub>3</sub> occurs...
in the kidney. 25 OHD is the main circulating vitamin D metabolite and is the best indicator of clinical status, whereas 1,25 OH₂D₃ is the active form of the vitamin which is involved in calcium homeostasis. It is now well established that there are two sources of this vitamin: (i) endogenous (skin); and (ii) exogenous (diet). Although, the relative contributions of these two sources are known to vary widely among individuals and between different geographical areas, it is generally believed that the major source of vitamin D is the exposure of skin to the UV B-rays contained in sunlight.

**Influence of climate on vitamin D status**

Much of the UV in sunlight is absorbed by clouds, ozone and other forms of atmospheric pollution. Thus, due to the reduced zenith angle of the sun and increased path length of sunlight through the atmosphere, the effective level of UV energy decreases north-south distance from the seasonally varying latitude at which the sun is directly overhead. In a recent paper investigating 117 published studies of vitamin D status from a total of 27 regions, variation was shown, not only between seasons, but also between geographical area such that levels were lower during the winter and spring/autumn months in Europe than in either North America or Scandinavian countries. In the UK, there is no UV radiation of the appropriate wavelength (280–310 nm) from the end of October to the end of March and for the remaining months of the year, 60% of the effective UV radiation occurs between 11.00 am and 3.00 pm. Studies in the UK have shown there to be a seasonal variation in vitamin D levels being highest in the summer months and lowest in the winter months in a variety of regions including London, Middlesex, West Midlands, Sunderland and Manchester.

**Influence of dietary intake on vitamin D status**

Dietary intake of vitamin D, although of lesser significance to vitamin D status than UV radiation, is still a crucial factor to be considered when assessing vitamin D status, especially during winter time when there is no skin production of the vitamin. In the paper cited earlier investigating differences in vitamin D status between the different geographical areas world-wide, oral intake of vitamin D was found to be significantly lower in Europe compared with both North America and Scandinavia. Furthermore, the study also showed that residents in North America and Scandinavia, both young and old, were more apt to take vitamin D supplements than their counterparts in Europe. For example, in the UK and Ireland only 15% of the elderly take supplements compared with 30% in North America and 50% in Denmark.
There are actually relatively few dietary sources of vitamin D, the major providers being fat spreads, fish, eggs, fortified cereals and pastry products\textsuperscript{58,59}. Up until fairly recently, information on vitamin D intake from meat was not available, but new analytical data for the composition of meat now includes the contribution from the metabolite 25-hydroxycholecalciferol (25(OH)D\textsubscript{3}) rather than just cholecalciferol itself\textsuperscript{60}. Recently published work in this area has highlighted meat to be much more significant contributor to vitamin D intake than was previously considered\textsuperscript{61}.

**Vitamin D and bone health**

Vitamin D status is known to be affected by the ageing process and there is now some good evidence to show that: (i) vitamin D levels fall with age\textsuperscript{62}; (ii) vitamin D levels are inversely related to PTH\textsuperscript{63} (which is also known to have seasonal variation\textsuperscript{64}); (iii) menopausal bone loss is partially regulated by dietary intake of vitamin D\textsuperscript{65}; and (iv) the elderly population\textsuperscript{66} are susceptible to vitamin D deficiency or vitamin D 'insufficiency'. The effect of vitamin D and its metabolites on bone is very complex. It is known to stimulate matrix formation and bone maturation, enhance osteoclastic activity and may influence differentiation of bone cell precursors. Together with PTH and calcium, it regulates calcium and phosphorus metabolism and promotes calcium absorption from the gut and kidney tubules. A deficiency of vitamin D has been shown to reduce calcium absorption, increase PTH excretion thereby stimulating osteoclastic activity and thus increasing bone loss\textsuperscript{67}.

Supplementation of 25(OH)D has been found to improve calcium absorption, lower PTH levels\textsuperscript{64}, and reduce winter time bone loss in postmenopausal women\textsuperscript{68}.

**Other micronutrients**

Zinc, copper and manganese may also have an important role to play in bone health since they are known to be essential metallic cofactors for enzymes involved in the synthesis of various bone matrix constituents. Supplementation of these trace minerals have been shown to be effective in older postmenopausal women\textsuperscript{69}. Furthermore, together with vitamin C they may also function in their antioxidant capacity and thus high intakes may be important if the connective tissue of bone is a target for free-radical damage. Two recent studies suggest that they may have an important role to play in bone health but further research is required\textsuperscript{35,36}. 
Role of micronutrients to the risk of fracture

Calcium

Epidemiological studies investigating the relationship between calcium and risk of fracture published in the last decade have shown conflicting results. Holbrook et al in a 14 year longitudinal US study showed that hip fracture rates were lower in individuals ingesting high calcium diets\(^70\) and these findings have been further supported by data published on populations from Hong Kong\(^71\). However, two UK studies did not find a protective effect of calcium on risk of fracture in women\(^72,73\). This discrepancy may be explained, in part, by the fact that there were differences in the distribution of calcium intake within each of the population groups. In more recent studies, calcium supplementation has been shown to reduce fracture rates in late postmenopausal women\(^74\) and the elderly\(^75\).

Vitamin D

Reduced vitamin D levels have been reported in patients with hip fracture and hence attempts have been made to investigate the effect of vitamin D supplementation on prevention of fracture. In a three-year study of 3270 institutionized elderly, supplementation with cholecalciferol and calcium resulted in a significant reduction in fracture rate. Protection was apparent after 6–12 months of treatment with a reduction of fractures of more than 30% by 18 months\(^76\). The only randomised placebo controlled clinical trial of vitamin D supplementation alone and fracture incidence showed that after 3 years of supplementation with 10 (i.g of vitamin D, there was no difference in fracture rates between the supplemented and unsupplemented groups\(^77\).

Vitamin K

Vitamin K was first discovered as an anti-haemorrhagic factor, and is now known to be required for the production of \(\gamma\)-carboxylated glutamyl residues in several blood coagulation factors and coagulation inhibitors (prothrombin – Factors VII, IX and X – proteins S and C). It may have a role in bone metabolism as bone \(\gamma\)-carboxyglutamic acid (bone Gla protein; the principal non-collagenous protein of bone) and matrix Gla protein (found in most mineralized tissues and cartilaginous tissues) are dependent upon vitamin K for their synthesis\(^78\).

Two forms of vitamin K exist – vitamin K\(_1\) (phyloquinone) and vitamin K\(_2\) (menaquinone), which is a family of compounds whose side
chains consist of a number of isoprene units which vary from 1–14 (MK). There is now some evidence of significantly reduced circulating levels of menaquinone-8 (MK-8) in healthy elderly women and following osteoporotic fractures of the spine and hip. Knapen et al (1989) reported increased urinary calcium and hydroxyproline excretion in patients with osteoporosis, with levels falling in response to physiological doses of vitamin K. Although bone Gla protein has also been shown to be under-carboxylated in osteoporotic women, with recovery in response to physiological doses of vitamin K there are considerable technical problems associated with its measurement, as indicated by the number of conflicting reports in the literature. Furthermore, osteocalcin is dependent on vitamin D for its synthesis and, hence, supplementation with vitamin D alone may have an ability to normalise the carboxylation values.

It is important to note that poor nutritional status has been associated with osteoporotic individuals and, thus, vitamin K levels (which are generally good indicators of nutritional status) may merely be reflecting this, rather than suggesting an independent effect per se. Further work is required. Due to the lack of dietary vitamin K databases, few studies have examined the direct relationship between dietary sources of vitamin K and bone mass. With recently developed tables in both the US and UK, the importance of dietary vitamin K to bone health can now be established.

Conclusions

The changes which occur in bone mass with ageing highlight the importance of maintaining adequate nutrition during peak bone mass development and in reducing postmenopausal bone loss. Our knowledge as to the essential ingredients for optimum bone health throughout life is yet to be fully established due to a focus of attention on calcium with little reference to other micronutrients, many of which have plausible mechanisms of action on bone metabolism. There is, however, a general consensus of opinion that calcium is important to maximising peak bone mass, but more work is required to see if the effect is greatest in calcium alone or in a combination of milk and milk products. Consistent data have also been reported as to the positive effect of increased calcium intake in reducing bone loss in women who are greater than 5 years postmenopause, but clearly more research is required to see if additional micronutrient supplementation would assist women in the earlier stages of menopause, when bone loss is at a greater intensity. For the elderly, more research is required to identify whether malnutrition per se is a key risk factor for fracture and within specific communities, how best this is treated.
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On a final note, within a population based strategy, clearly a healthy lifestyle should be encouraged at all ages, with the inclusion of a varied and adequate dietary intake and appreciable level of physical activity which has an emphasis on its weight bearing capacity. This strategy is one of the main recommendations of the recently published COMA report on nutrition and bone health. Furthermore, whilst the genetic component has a major role to play in the pathogenesis of osteoporosis, it may be useful to target specific nutrition intervention on those individuals who are genetically more susceptible to poor bone health.

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