

Calcium, physical activity and bone health – building bones for a stronger future

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Abstract

Adequate provision of nutrients composing the bone matrix and regulating bone metabolism should be provided from birth in order to achieve maximal bone mass, compatible with individual genetic background, and to prevent osteoporosis later in life. Low calcium intake ($<250 \text{ mg day}^{-1}$) in children is associated with both a reduced bone mineral content and hyperparathyroidism. Optimal calcium intake is, however, still a matter of controversy. The minimisation of fracture risk would be the ideal functional outcome on which to evaluate lifetime calcium intakes, but proxy indicators, such as bone mass measurements or maximal calcium retention, are used instead. Calcium recommendations in Europe and the United States are based on different concepts as to requirements, leading to somewhat different interpretations of dietary adequacy. Minerals and trace elements other than calcium are involved in skeletal growth, some of them as matrix constituents, such as magnesium and fluoride, others as components of enzymatic systems involved in matrix turnover, such as zinc, copper and manganese. Vitamins also play a role in calcium metabolism (e.g. vitamin D) or as co-factors of key enzymes for skeletal metabolism (e.g. vitamins C and K). Physical activity has different effects on bone depending on its intensity, frequency, duration and the age at which it is started. The anabolic effect on bone is greater in adolescence and as a result of weight-bearing exercise. Adequate intakes of calcium appear necessary for exercise to have its bone stimulating action.

Keywords
Mineral requirements
Bone growth
Osteoporosis
Children
Adolescents

Introduction

Osteoporosis, a disease affecting several million people in the world, should be prevented from childhood by achieving maximal bone mass compatible with individual genetic background. It is even possible that prevention should start as early as during pregnancy, since maternal health and nutrition affects in utero bone growth and development¹.

Bone mass increases until the third decade of life, then slowly decreases. In women, 15% of the peak bone mass will be lost in the first 5 years after menopause² and up to 30–50% before the age of 70³, when menopause-related bone loss is concluded. The bone loss rate associated with the process of ageing is approximately 1% per year in men and women⁴. Therefore, having a larger bone capital and spending it more parsimoniously, i.e. reducing bone loss, delays the attainment of a bone density level at which fracture risk is high. Fracture incidence in individuals whose bone density is greater than 1 SD above the mean is 50% lower at 80 years⁴.

Peak bone mass is determined by the genetic background of the individual and by a combination of environmental influences that can explain up to 40% of the variance in bone mass, including usual body weight, weight-bearing physical activity and intake of certain nutrients known to compose the bone matrix or regulate its metabolism⁵. This review intends to summarise the role of calcium, other minerals and vitamins and physical activity in the achievement of the maximal peak bone mass allowed by a given genetic potential.

Calcium

Since approximately 70% of the bone weight is accounted for by calcium phosphate crystals, it is obvious to think of calcium as the first nutrient to be required for optimal bone growth. Very low calcium intake in children induces rickets, osteomalacia and growth retardation. Infants having intakes below 200 mg day^{-1} have radiographic appearance of rickets and 5-year-old Chinese children consuming less than 250 mg day^{-1} of calcium had

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reduced bone mineral content (BMC) and reduced growth compared to Hong Kong children having a calcium intake of 500 mg day⁻¹ (Ref. 6). Marginally low calcium intake in children induces hyperparathyroidism⁷. X-rays of children in Surinam did not show bone rarefaction⁸, but a more sensitive indicator as forearm BMC relative to body size was indeed reduced in Gambian children⁹.

Population Reference Intakes have recently been revised by the American Institute of Medicine¹⁰. Calcium requirements have been established using three indicators: risk of fracture, bone mass measurements and maximal calcium retention. The minimisation of fracture risk would be the ideal functional outcome on which to evaluate lifetime calcium intakes. Paradoxically, cross-cultural comparisons have reported positive correlations between calcium intake and fracture risk¹¹, but the cross-sectional nature of the data and the absence of controls for confounding factors, such as genetic and lifestyle differences, points towards a fluke association. However, longitudinal clinical trials investigating the effects of calcium intake on fracture rates have not been carried out so far because of difficulties in the estimation of calcium intakes and the long follow-ups required.

Bone mass measurements are predictive of fracture risk and have been used as an indicator of outcome in observational studies and supplementation trials^{10,12,13,14}. Observational retrospective and cross-sectional research reach non-uniform conclusions regarding the role played by calcium intake in bone mineral density (BMD) during childhood and adolescence. Differences in the methodology used, the age and mean calcium intake of the populations studied, and the skeletal sites selected to evaluate bone mass significantly contribute to the above discrepancies, making their interpretation more difficult. Overall, it appears that calcium intake is a determinant for bone mass acquisition from early childhood to pre-pubertal stages in healthy children with no hormonal imbalances^{5,15,16,17,18}. During infancy and puberty, calcium absorption is maximised to meet the increased needs through hormonal mechanisms and, as long as calcium intake is above a minimum threshold around the RDA, its influence on bone mass gain is widely overwhelmed by genetic factors^{19,20,21}. The above is especially true for the weight-bearing sites of the skeleton, which are more likely to be affected by nutritional influences^{21,22}. This may explain why studies linking current calcium intakes with BMD at the forearm in adolescents fail to find an association^{23,24}, while investigations considering calcium intake during childhood, or for long periods of time during childhood and adolescence, report significant correlations with BMD at the hip and lumbar spine in children, adolescents and adults^{18,25}.

As for the optimal calcium intake required to ensure the level of skeletal retention of calcium for maximal peak bone mass, supplementation trials carried out in US

Table 1 Dietary factors affecting calcium balance

	Decrease	Increase
Absorption	Fibre Phytate Oxalate Caffeine Fat Phosphorus	Food Lactose Carbohydrates Lysine Fat
Excretion	Phosphorus Alkaline ash	Protein Sodium Chloride Acid ash

children and adolescents consistently indicate that calcium intake should be increased above the current RDA in that country. Supplementation with 500 mg/d of calcium in children and adolescents with either low intakes or intakes close to the RDA significantly increases BMD at weight-bearing sites, at least initially^{26,27}. Whether this effect is maintained later in life after supplement withdrawal, and whether differences with controls are increased or stabilised by maintaining calcium supplements for more than 1 year, has yet to be clarified²⁸. In any case, usual consumption levels (around one half of the RDA) are insufficient for maximal peak-bone mass achievement^{15,26,27,29}.

Maximal calcium retention is the intake level above which there is no additional increase in balance. It is related to maximal skeletal calcium and is the primary indicator to establish calcium requirements. Factors affecting calcium balance, i.e. bioavailability, physical activity and nutrient-nutrient interactions, are essential in setting the requirements.

Calcium absorption is regulated by a number of dietary and individual factors. It is enhanced when the needs are greater, such as in infancy and adolescence. Fractional calcium absorption is highest in infancy (60%), decreases in childhood, then rises with puberty (34%), stabilises in adulthood (25% in young adults), and progressively decreases with ageing^{15,30}. In extraordinary physiological conditions, such as pregnancy, oestrogens significantly promote calcium absorption to preserve the maternal skeleton. Generally speaking, fractional calcium absorption is inversely correlated to calcium intake³¹, meaning that absorption is more efficient when calcium is short in the diet. Protein-energy malnutrition reduces the efficiency of calcium absorption³², while recovery from malnutrition can enhance calcium retention up to 87%³³. Table 1 summarises the factors affecting calcium absorption and excretion. Absorption efficiency of calcium is maximal for dairy products and lower for vegetable sources, probably because fiber and phytates present in plant foods may inhibit calcium absorption^{34,35,36}. However, the ingestion of calcium-rich plant foods may increase calcium retention indirectly by reducing the acid load of the overall diet and therefore, limiting urinary excretion of calcium. The opposite effect is associated

Table 2 Adequate intakes of calcium in infants and children in the United States¹⁰

Age group	Adequate intake (mg day ⁻¹)	Evidence considered
0–6 m	210	Breast milk intake
6–12 m	270	Breast milk + solid food intakes
1–3 y	500	Balance studies
4–8 y	800	Intervention studies
9–13 y	1300	Maximal calcium retention BMC
14–18 y	1300	Epidemiological evidence

with dairy product consumption, especially when high, because of the animal protein component. Together with animal protein and the acid load of the diet, sodium is a determinant dietary factor influencing obligatory urinary losses of calcium^{37,38}.

Table 2 summarises the US Institute of Medicine consensus panel resolution on Adequate Intakes of calcium for different age groups and indicates the evidence considered to set the values. In the first year of life observational studies are taken into account. In older children, balance studies and studies on maximal calcium retention are instead considered.

The recommendation regarding optimal calcium intake is a matter of controversy. Fig. 1 illustrates the differences between European and US recommendations. Even within Europe there are differences between the UK and the Nordic region, for example. This is due both to a slightly different concept of requirements, (Population Reference Intake in the UK, Adequate Intake in the US), and to different data taken into account (for example, the European and the Nordic recommendations are not based on maximal retention). Recommendations for infants under 2 years are higher in Europe than in the US, while recommendations in older children and adolescents are higher in the US.

There is a wide spectrum of calcium intakes in different world populations. Fig. 2 shows data on children's intake in Europe, the US and in several developing countries. In the developed world calcium adequacy is generally good, although inadequacy may be argued according to the

recommendation that is chosen. In the developing world there may be several areas of frank inadequacy.

Coverage of requirements could be achieved by the diet only, by fortified foods, by supplement consumption or by a combination of the different approaches. In the US, only about 25% of boys and 10% of girls aged 9 to 17 are estimated to meet the NIH recommendations because of low intake of dairy products³⁹. In European diets dairy products are the major source of calcium. Coverage of requirements by diet only may be difficult in population groups that have to keep total energy intake low, in groups with high requirements that are not accustomed to consuming foods with high calcium density, or in lactose intolerant subjects⁴⁰. For example, in Italian adolescents the consumption of milk decreases while that of dairy products does not increase until young adulthood, thus leaving a window of low intakes relative to requirements (D'Amicis, personal communication).

Other nutrients

Minerals and trace elements other than calcium are involved in skeletal growth, some of them as matrix constituents, such as magnesium and fluoride, others as components of enzymatic systems involved in matrix turnover, such as zinc, copper and manganese. Insufficient dietary supply of these nutrients results in reduced bone growth or in the formation of defective bone. Vitamins also play a role in calcium metabolism (e.g. vitamin D) or as co-factors of key enzymes for skeletal metabolism (e.g. vitamins C and K). Some of the evidence relating those nutrients to bone growth and development is reviewed in this section.

Magnesium is involved in hydroxyapatite crystal formation and 50% of the total body content of this mineral is stored in the skeleton. Clinical studies suggest a role for magnesium in determining skeletal mass but there is not enough evidence to give a recommendation about the intake required to maximise it¹⁰. One study has shown a correlation between dietary magnesium intake and BMD in postmenopausal women⁴¹. A four-year supplementation trial reports no effect of magnesium supplements on BMC in pre- and post-menopausal women⁴², while two other studies showed an effect of magnesium supplements on BMD in osteoporotic women, either alone⁴³ or in combination with calcium and oestrogen

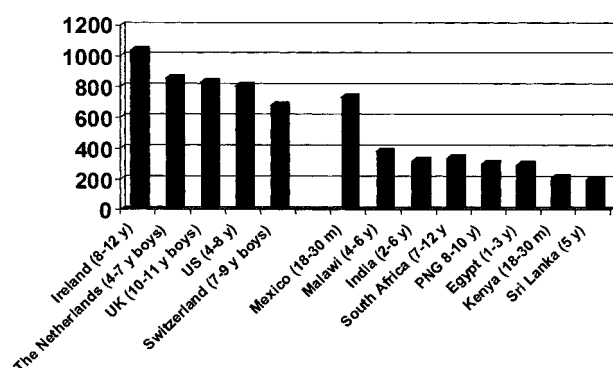


Fig. 1 Calcium requirements established by US and European expert committees.

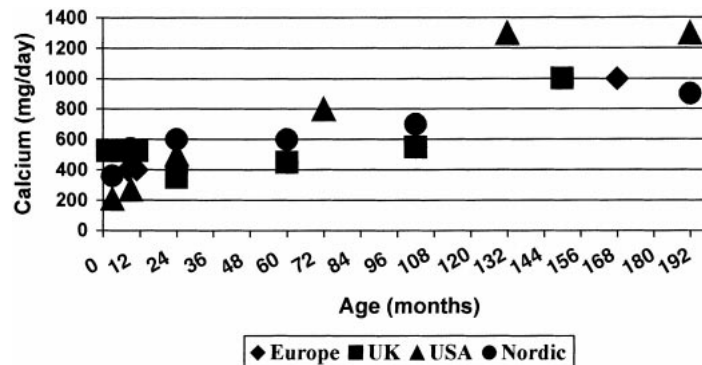


Fig. 2 Calcium intake in various world countries.

therapy⁴⁴. Discrepancies between studies may well be caused by the baseline magnesium status of the enrolled subjects, since magnesium-deficient individuals are more likely to benefit from therapy than non-deficient volunteers.

Fluoride is also involved in the formation of hydroxyapatite crystals. Experimental deficiency leads to a delay in skeletal development in animals. Evidence in humans is controversial as to whether water fluoridation is associated with a higher BMD⁴⁵. Indeed, excess fluoride may lead to brittle bones, more susceptible to fractures⁴⁶. Zinc deficiency is typically characterised by the arrest of growth. The bones of zinc deficient animals are very thin and fragile, with a marked reduction of all the cellular elements, depressed bone formation and increased bone resorption⁴⁷. Combined zinc and calcium supplementation in post-menopausal women has induced a smaller decrease in BMD compared to women treated with calcium only⁴⁸. Copper is important for the mechanical characteristics of the bone matrix, such that the bones of copper deficient animals are less resistant to mechanical stress⁴⁹. Manganese deficiency causes reduced growth and skeletal abnormalities in animals and in humans, with decreased bone turnover⁵⁰. Boron has not been studied in children, but in post-menopausal women supplementation of a conventional low-boron diet led to a decrease in urinary calcium excretion⁵¹.

Vitamin D is required for calcium absorption. A few minutes of sun exposure are sufficient for endogenous synthesis. However, at latitudes above 40° N and below 40° S vitamin D3 endogenous synthesis is absent during the winter months⁵². Based on serum 25(OH)D levels, a recommendation for Adequate Intake has been set at 5 µg day⁻¹ in children of all ages¹⁰. Vitamin C is required for the synthesis of type I collagen (the main organic component of bone), for the subsequent extracellular modifications that allow formation of collagen crosslinks, and for the synthesis of other important matrix constituents, such as glycosaminoglycans. Patients affected by scurvy are also osteoporotic, but there is no information about optimal intakes. The antioxidant role of vitamin C

might also be important to modulate skeletal metabolism⁵³. Vitamin K is required for the synthesis of functional osteocalcin, an important structural protein of the bone matrix. An increased fracture rate has been observed in vitamin K-deficient elderly⁵⁴. Excess vitamin A intake may be detrimental to bone health. In a cross-sectional and nested case-control study on a cohort of Swedish adult women, Melhus *et al.*⁵⁵ found a dose-dependent correlation between vitamin A intake, reduced bone density, and risk of hip fracture. This may be a public health issue, since in Scandinavian countries vitamin A intakes reached levels up to three-fold the recommended allowances and was six-fold higher than in southern Europe⁵⁶.

The peculiar role of micronutrients is demonstrated by the significant positive effects that multi-micronutrient supplementation had on bone growth of Saharawi refugee children, while mere protein supplementation had no effect compared to unsupplemented children (Lopriore and Branca, personal communication). From a public-health point of view, it is unclear whether mineral supplementation may have a positive impact on bone health in well-nourished populations, but it appears that mineral deficiency would substantially impair bone growth and mineralisation.

Most of the studies presented refer to adult skeletal metabolism and not to children's. Furthermore, the requirements of these minerals have not been calculated with reference to bone density and it has not been established whether the current recommendations are adequate to grant optimal skeletal mass during growth.

Physical activity

The functional demand imposed on bone is a major determinant of its structural characteristics. Biomechanical studies indicate that stress applied to a skeletal segment affects the geometry of the bone, the microarchitecture and the composition of the matrix⁵⁷. Body weight, which represents the more constant load applied to an individual's skeleton, is a major determinant of bone

mass. This is illustrated by the fact that normal weight and underweight individuals have lower bone mass and a greater risk for hip fractures than overweight or obese individuals, although diverse mechanisms other than the mechanical stress applied to bone may account for part of the differences^{58,59}. Second to body weight, weight-bearing physical activities, such as walking or gymnastics, represent the most important mechanical stimulus for bone formation⁶⁰. Clinical trials and observational studies have shown that physical activity leads to greater bone density in children and adolescents and, to a lesser extent, in adults^{61,62,63}. Conversely, a reduction in the loading history leads to a reduced bone cross section, as in children with neuromuscular diseases⁶⁴. It is important to note that the effects of weight-bearing activities on bone mass and bone density is maximal at the hip and lumbar spine (weight-bearing sites of the skeleton) and very small, if any, at the forearm (non weight-bearing site). This may be a reason why studies choosing the latter as an outcome tend to underestimate the role of physical activity on bone mass accretion²³.

Physical activity has different effects on bone depending on its intensity, frequency, duration and the age at which it is started. A sustained level of activity leads to greater peak bone mass, as demonstrated by a 15-year longitudinal study in which physical activity was correlated to BMD at the lumbar spine at age 27, especially when initiated well before puberty⁶⁵. However, intense exercise programs that lead to excessive weight loss and hormonal imbalances, such as amenorrhea in elite gymnasts, may be detrimental for bone health despite the high loading achieved during the training program⁶⁶.

It is unclear whether the level of exercise affects the requirements for calcium or other nutrients. Calcium intake appears to modify the effect of gross motor activity on bone mass accretion in infants at moderately high levels of calcium intake, but at moderate to low calcium intakes, infants in a gross motor programme have less bone mass accretion than controls⁶⁷. A meta-analysis of studies conducted in postmenopausal women has shown that the combination of calcium supplements (1000–1500 mg) and physical activity programmes leads to remarkable increases in BMD at the lumbar spine, while supplementation or physical activity individually have either marginal or no effects²². Thus, at least for calcium, adequate intakes appear necessary for the exercise to have its bone stimulating action.

Conclusion

The achievement of the full genetic potential of bone mass can be achieved by combining an adequate intake of nutrients required to manufacture bone tissue with high mechanical loads (weight bearing physical activity). Full coverage of mineral (calcium, magnesium, fluoride,

zinc, copper, manganese) and vitamin (D, C and K) requirements should be granted throughout childhood and adolescence. However, mineral requirements for optimal skeletal growth are still a matter of controversy and warrant further investigation. Meanwhile, as high as possible calcium intakes should be achieved through a balanced diet and can also be facilitated by the consumption of fortified foods. Dietary factors impairing positive calcium balance (mainly animal protein and sodium) should be minimized. For vitamins and other minerals recommendations based on other physiological indicators should be followed. A good level of physical activity should be promoted in children of all ages through organised sport, leisure and everyday habits.

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