BRIEFING PAPER

# Dietary calcium and health

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**Summary**

Calcium is an essential nutrient as all living cells require calcium to remain viable; calcium is also required for a number of specific roles in the body. The majority (~99%) of calcium present in the body is found in bone, with a smaller amount found in teeth. The remainder (<1%) is found in soft tissues and body fluids. The average adult skeleton contains 1200 g of calcium, present in the form of hydroxyapatite, an inorganic crystalline structure made up of calcium and phosphorus [$Ca_{10}(PO_4)_6(OH)_2$], which provides rigidity. Calcium is essential for bone growth as it is required for the mineralisation (impregnation of the bone matrix with minerals)

of bone; the rate of calcium deposition in bone is proportional to rate of growth. An adequate intake of calcium is one of a number of factors which are important for acquiring bone mass and attaining peak bone mass (PBM). Diets containing insufficient amounts of calcium may lead to a low bone mineral density, which may have implications for bone health, notably risk of osteoporosis, in later life.

As well as having a skeletal function, calcium plays a regulatory role in a number of specialised functions in the body. Calcium plays a role in muscle (including cardiac muscle) contraction, neurotransmitter secretion, digestion and blood coagulation (clotting). Calcium also plays a structural role outside of the skeleton, for example in organelles and membranes. Disturbances in the structural and regulatory roles of calcium can have implications for health and disease. For this reason, calcium homeostasis is tightly regulated to ensure that plasma concentrations of calcium ions are maintained within a set range (*i.e.* 1.1–1.3 mmol/L). Homeostasis is controlled at three main sites: the kidneys, bone and the gastrointestinal tract. Control is mediated through the calciotropic hormones: parathyroid hormone (PTH), calcitriol and calcitonin. In response to changes in plasma calcium concentrations, absorption of calcium from the gastrointestinal tract can be altered, along with urinary excretion and calcium resorption from bone.

The UK reference nutrient intake (RNI) for calcium for adults aged over 19 years is 700 mg/day; requirements are higher during childhood, adolescence and during lactation. No guidance has been issued on high intakes, although exceeding an intake of 1500 mg calcium/day in the form of supplements is discouraged as this can cause stomach pain and diarrhoea. Calcium intake appears to have increased over the last 30 years or so. On average, British men consume 1007 mg calcium/day, whilst the average British woman consumes 777 mg/day (Henderson *et al.*), but intakes of calcium are a concern amongst certain groups of the population. For example, a high proportion of teenage boys and girls and women aged 19–24 years fail to meet the lower reference nutrient intake (LRNI) for calcium, *i.e.* their intakes are likely to be inadequate.

A wide number of foods contain calcium, but the amount of calcium, provided per 100 g or per serving, and its bioavailability vary considerably. The major source of calcium in British diets is milk and milk products (providing more than 40% of calcium intake amongst adults), followed by cereals and cereal products (providing 30% of intake). The contribution from cereals is high because although they are not a rich source, they are consumed in relatively large amounts and also some cereal products are fortified with calcium. For example, it is a mandatory requirement that white and brown wheat flours contain specified amounts of calcium, which is achieved through fortification. Additional sources of calcium include plant foods, including soya beans, some animal products (*e.g.* eggs) and water. The bioavailability of calcium from a food is influenced by the presence of a number of other compounds within a food. Dietary factors that influence absorption of calcium include fat (reduces absorption), protein and phosphorus (both increase absorption). The bioavailability of calcium from milk and milk products is in the region of 30% compared to 5% from spinach. Spinach, although containing a relatively large amount of calcium, is not considered a bioavailable source, as it contains a high concentration of oxalic acid which inhibits the absorption of calcium. Phytic acid and

uronic acid, also found in plant foods, have a similar effect. However, the bioavailability of calcium from other plant foods is good, *e.g.* broccoli (see *Bioavailability of calcium from foods*). Soya beans are also a notable exception, in that they contain high quantities of both oxalic and phytic acids, yet are a bioavailable source of calcium (bioavailability is in the region of 30–40%). The bioavailability of calcium from soya products will vary depending on the product.

A low intake of calcium during growth has implications for bone mass, as the amount of calcium consumed in the diet influences the amount of calcium that can be retained by the skeleton during periods of growth. An inadequate intake of calcium combined with adequate energy and protein intakes may result in a low calcium content of bone, which may have implications for bone health later in life. The attainment of a high PBM in early adulthood is important as bone mineral (including calcium) content starts to decline thereafter. PBM has been reported to be reached as early as the late teenage years or as late as the mid-thirties; this depends on the site in the skeleton [*e.g.* PBM is reached in the femoral neck (hip) before it is reached in the forearm]. A number of factors influence bone mineral losses, *e.g.* physical activity (immobility accelerates loss), hormonal status and gender. In women, loss of bone mineral is accelerated around the time of the menopause, as a result of a fall in circulating oestrogen concentrations. An excessive loss of bone associated with ageing can lead to osteoporosis, which is characterised by micro-architectural changes in bone tissue, loss of bone mineral and reduced strength of bone which ultimately increases the risk of bone fracture. Osteoporosis is associated with morbidity and increased mortality and is a major concern in the UK and across the developed world. As the population ages, the incidence of osteoporosis will increase and bring with it additional costs to the health system and the economy.

There is some evidence that increased intakes of calcium later in life may help slow the rate of bone loss associated with ageing. The evidence is strongest amongst older postmenopausal women, rather than during the early stages (first 5–10 years) of the menopause. It appears that most benefit is obtained from consuming additional calcium in the long-term. Further research is needed to investigate optimal dietary calcium intakes in relation to minimising bone mineral losses and reducing the risk of osteoporosis.

Calcium may have a role in the aetiology of chronic disease, with evidence suggesting that increased calcium intakes may help in the prevention of colorectal cancers. There is weaker evidence to suggest that calcium may offer some protection against breast cancer and more research needs to be conducted to confirm or refute an effect. Calcium has long been suggested to play a role in the aetiology of cardiovascular disease; early ecological studies suggested that consumption of hard (calcium-containing) water was associated with a reduced risk. Calcium exerts modest blood pressure and lipid-lowering effects, which may be of relevance in reducing risk of cardiovascular disease. In addition, there is preliminary evidence suggesting that calcium may play a role in weight management. Data from epidemiological studies suggest an inverse association between calcium intake and bodyweight. Human trials in this area are still in their infancy; at present findings must be interpreted with caution. A number of mechanisms that may underlie this effect

of calcium on bodyweight are currently being investigated and more human trials are underway.

**Keywords:** bone, calcium, chronic disease, homeostasis, metabolism, osteoporosis

## 1 Introduction

Calcium is the most abundant mineral element in the body: in adults it accounts for about 2% of bodyweight, which is equivalent to about 1200 g of calcium. The majority (~99%) of calcium is found in the skeleton and teeth, mainly as hydroxyapatite, an inorganic crystalline structure made up of calcium and phosphorus [$Ca_{10}(PO_4)_6(OH)_2$], which provides rigidity. The remainder is present in soft tissues and body fluids, and accounts for less than 1% of total body calcium. Calcium is an essential nutrient, not only for the mineralisation of bones and teeth but for regulating intracellular events in most, if not all, body tissues. Calcium plays a role in muscle contraction and nerve function, for example.

The major source of calcium in the diet is milk and milk products, providing over 40% of calcium intake in adults, followed by cereals and cereal products providing 30% (see section 7.1 *Main dietary sources*). Ensuring that adequate calcium is consumed is important for achieving peak bone mass (PBM) and helping to reduce bone mineral losses or reduce the risk of osteoporosis with advancing age. There is particular concern about calcium intakes among adolescents and young women as a notable proportion of these groups are consuming low amounts (see section 7.2 *Current intake in the UK*).

This briefing paper discusses both the skeletal and regulatory role of calcium, and also calcium homeostasis. This is followed by information on dietary reference values, sources of calcium in the diet and information on calcium intake in the UK, including trends in intake. Bioavailability of calcium from foods is also discussed as this is an important determinant of the relative value of food sources of calcium. Finally, calcium and bone health, and the evidence for a role of calcium in cancer, cardiovascular disease and weight management are discussed.

## 2 Skeletal functions of calcium

Calcium plays an important structural role in the body, being the most abundant mineral in the skeleton. The majority (~99%) of calcium in the body is present in bone, with the average adult skeleton containing 1200 g of calcium (Ilich & Kerstetter 2000).

### 2.1 Bone

Bone is essentially a protein matrix within which calcium (and other mineral) salts are deposited. Bone contains cells and specialised collagen fibres encrusted with crystalline material. These fibres are fixed within a 'ground substance' of mucopolysaccharides and other compounds. Collagen cells and 'ground substance' make up the organic matrix or osteoid. The skeleton is a complex 'supporting' structure. It consists of long bones (*e.g.* in the limbs) (see Fig. 1), vertebrae and the skull. The epiphyses (*i.e.* ends) of the long bones are where lengthening takes place during growth.

Calcium, phosphate and magnesium are the most important minerals in bone, of which calcium is the most abundant. Calcium is present along with phosphate in the form of a crystalline complex; hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]. The composition of bone mineral is similar to that of hydroxyapatite, but it is not pure hydroxyapatite since it contains carbonate, citrate, sodium, magnesium and traces of fluoride. The crystals of bone mineral are very small, with a diameter of the order of 20–30 nm and a thickness of 2–3 nm. The ions at the surface of the tiny crystals interact with ions from the body fluids; in fact bone has been likened to a large ion exchange column.

Bone tissue is distributed within bones in two forms: compact (cortical) bone and trabecular (cancellous) bone. Compact bone forms the cortices (outer parts) of bones, in particular the shafts of long bones, whilst trabecular bone is made up of a meshwork of trabeculae (strut like structures) and is found mainly in the vertebrae of the spine, pelvis and inner parts of the long bones. All bones contain both forms of bony tissue, although the relative amounts of trabecular and compact bone are variable. Approximately 80% of bone is compact bone and 20% is trabecular. Compact bone is thick and dense and functions in a structural role whilst trabecular bone has a sponge-like appearance and a metabolic function (Department of Health 1998).

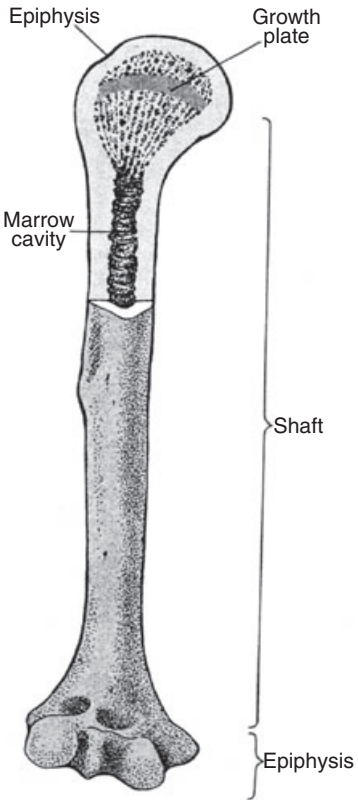


**Figure 1** Long bone. Source: BNF (1989).

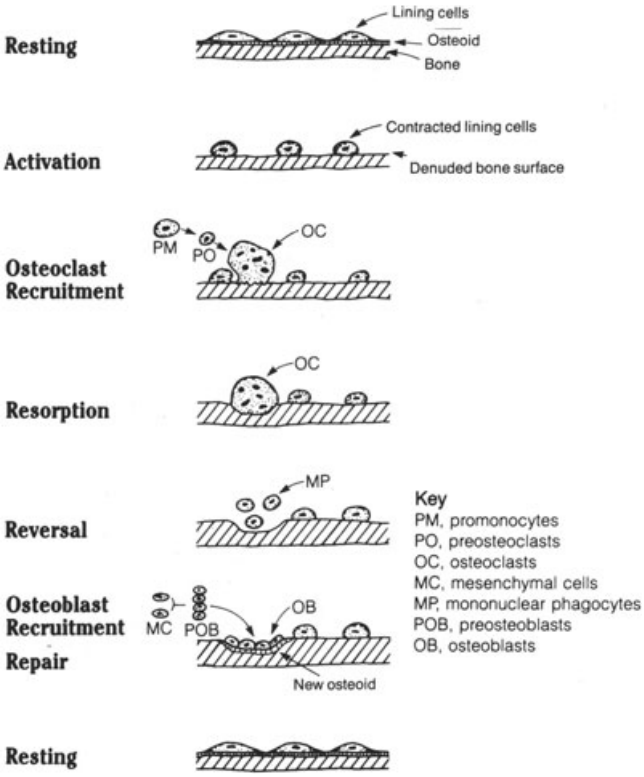


**Figure 2** Bone remodelling. Source: BNF (1989).

Bone contains a number of specialised cells which are involved in the formation and resorption of bone. Osteoblasts, a form of fibroblast, are bone-forming cells. They are responsible for the production of bone collagen fibres and other organic components of the matrix, the process of bone mineralisation and, in part, for the regulation of bone resorption. Osteoblasts, which are present in immature bone and at fracture sites for example, mature into osteocytes as they become encased in mineralised bone; osteocytes cannot form new bone material. Osteoclasts are located on the surface of bone and are responsible for bone resorption. They are macrophages derived from stem cells of the bone marrow.

Bone formation begins before birth and increases in bone mass may continue to around the late teenage years to the mid-thirties, depending on the site in the skeleton. Most bones are formed from cartilage rods in the developing fetus, which are later calcified. Bone formation can be regarded as a two stage process:

(1) Osteoblasts lay down collagen fibres and the other components of the organic matrix;
(2) The matrix is impregnated with minerals (mineralisation).

Primary mineralisation of bone collagen fibres normally takes place about 10 days after they are formed. They then contain about 80% of their final mineral concentration. Secondary mineralisation takes place over the next 6 months, but the final achievement of maximum mineral concentration might take several years. Thus, old bone is more heavily mineralised than young bone. The mineralisation of bone collagen normally depends on the adequate availability of calcium, phosphorus and vitamin D. When the second (mineralisation) stage of bone formation fails, as in vitamin D deficiency, unmineralised bone collagen accumulates in abundance and leads to osteomalacia (characterised by softening of the bone, weakness and pain) in adults and rickets in children.

Bone formation and bone resorption take place throughout life, although at different rates at different times. This process is known as bone remodelling and is shown in Figure 2. While the deposition of matrix and accretion of mineral is proceeding at the outer surface of the bone, bone resorption (removal of both mineral and matrix) is going on at the inner surface of the marrow cavity as a result of osteoclast activity. Depending on the relative rates of deposition of bone on the outer surface and resorption on the inner one, thickening or thinning

of the cortex will take place. The rate of bone resorption up until puberty is always less than the rate of bone deposition on the outer surface. From the age of 30–35 years onwards (or earlier depending on skeletal site), following the attainment of PBM, the reverse is true. This leads to a continuous thinning of the entire substance of the cortex and an enlargement of the marrow cavity and a decline in bone mass. The amount of bone lost is separately and independently related to the magnitude and duration of both the effects of bone formation and resorption. In women, bone turnover (*i.e.* the process of resorption followed by partial deposition of bone) usually accelerates at the menopause.

Bone formation and bone resorption are influenced by a variety of humoral, physical, nutritional and other factors (Seibel 2002). Bone formation is stimulated during growth and by weight-bearing exercise, and is depressed by immobility, undernutrition (energy and protein deficiencies) and glucocorticosteroids. Bone resorption is stimulated by the calciotropic hormone, parathyroid hormone (PTH) and inhibited by another, calcitonin, in order to maintain plasma calcium homeostasis (see section 4 *Calcium homeostasis and metabolism*).

## 2.2 Bone growth

During infancy and childhood, physical growth occurs; stature is progressively and permanently increased at varying rates until the adult state is achieved. The process is accompanied by the development and maturation of all systems in the body, with associated changes in energy consumption and expenditure, mode of nutrition and behaviour. Growth in childhood is not a uniform process; rather growth follows a 'sigmoid' curve between birth and adult life, with characteristic periods of acceleration and deceleration. The maximal growth rate for length is encountered soon after birth, when body mass is least. Subsequently, there is a rapid deceleration in the rate of growth in length to about one-half of the first year value at the end of the second year, and thereafter a progressive decrease in rate to less than one-third of the first year value by age 10 years in females and age 12 years in males (Matkovic *et al.* 2004). The ensuing couple of years are characterised by accelerated growth rate in the so-called pre-pubertal growth spurt. Peak rates of the order of one-half of those encountered in the first year of life are reached at age 12 years in females, and at age 14 years in males. Thereafter, progressive deceleration occurs until adult stature is attained. Gender, ethnicity, socio-economic status, diet and genetics will all influence bone growth.

In long bones, the deposition of new bone takes place primarily on the outer surface, enabling the bone to become wider. The process is rapid during the first two years after birth; it then becomes slower but increases again during the adolescent growth spurt. At this time, the rate of deposition of bone in males exceeds that in females, so that on average, a 20-year-old man has wider as well as longer bones than a woman of the same age. Elongation of the long bones results from osteoblasts present in the shaft end of the epiphyseal growth plate converting cartilage to bone. Other bone cells, known as chondrocytes, lay down cartilage at the same time. As the process continues the shaft lengthens. Elongation of the long bones stops when all of the cartilage in the epiphyseal growth plate has been converted to bone, a process known as epiphyseal closure. Deposition of bone on the outer surface does not cease when the epiphyses close and lengthening of the bone stops. The density, strength and thickness of bones can continue to increase until the mid-thirties (though bone accretion may cease as early as the late teenage years, depending on the skeletal site); at which time PBM is achieved. Thereafter, bone deposition continues but at a much slower rate, and at a slower rate than bone resorption.

## 2.3 Body calcium changes

Between birth and maturity, the total calcium in the body of a well-nourished individual increases from 20–30 g (Koo *et al.* 1999; Abrams 2001) to about 1200 g (Ilich & Kerstetter 2000). Calcium cannot be made in the body; all the calcium required for this increment is derived from the diet. A greater proportion of dietary calcium is absorbed during periods of growth than in adulthood, and urinary excretion is reduced to conserve the amount available for bone mineralisation. A total increment of 1170 g calcium over 18 years amounts to an average of 1.25 g per week or 178 mg a day, although growth rates are not constant throughout childhood. During periods of rapid growth in stature, the calcium deposited in the skeleton is greater than when growth proceeds more slowly.

### *2.3.1 Fetal growth*

Approximately 80% of the calcium present in bone at birth is deposited within the bone matrix during the third trimester of pregnancy. Calcium transfer across the placenta requires adequate maternal calcitriol (active vitamin D, see section 4.1 *Plasma calcium homeostasis*) concentrations, although the amount required for optimal bone mineral accretion is unknown. It is estimated that calcium accretion averages 200 mg/day during the

**Table 1** Bone calcium deposition rates at different stages of the life cycle

| Group | Age (years) | Weight (kg) | Bone calcium deposition (mg/kg/day) | Total bone calcium deposition (mg/day) |
|---|---|---|---|---|
| Premature infants | – | 1.34 | 160 | 214 |
| Infants | 0.8 | 8 | 90 | 720 |
| Pre-pubertal | 8.3 | 28 | 52 | 1456 |
| Pubertal | 10.2 | 35 | 53 | 1960 |
| Post-pubertal | 15.4 | 59 | 21 | 1240 |
| Adults | 30–60 | 60 | 5–10 | 300–600 |

Source: Abrams (2001). Reproduced with kind permission of the author.

third trimester; increasing from 50 mg/day at 20 weeks gestation to 330 mg/day at 35 weeks, so that the total calcium content of the infant is 20–30 g of calcium at birth. During fetal development, calcium deposition is greater than at any other stage of the life cycle (see Table 1). Most of the calcium that accumulates in the bones of the fetus is derived from an increase in intestinal calcium absorption that occurs during pregnancy. As fetal demands for calcium are increased, maternal bone turnover is also increased.

Maternal plasma calcium concentration is one of a number of factors that influence fetal bone mineral accretion, others include genetics (*e.g.* vitamin D receptor genotype differences), smoking and physical activity. Calcium supplementation during pregnancy does not influence fetal bone development and growth if calcium intakes are adequate; however, benefits are seen in women with initially low calcium intakes.

### *2.3.2 Pre-term infants*

A pre-term infant born at 26 weeks gestation has just over 40% of the body calcium that is present in term infants. Pre-term infants, particularly those of a very low birth weight (< 1.5 kg), have a lower bone mineral content than full-term infants of the same postnatal age. The same is seen when adjustments are made for gestational age. Pre-term babies are at increased risk of osteopenia (characterised by reduced calcification of bone, reduced density and/or mass) and fracture; although rates of fracture and osteopenia have fallen since the feeding of nutrient-enriched breast milk or specialist pre-term infant formulae was introduced. In pre-term infants, during the period following what would be considered to be full-term, bone mineralisation is increased, at a gradient similar to that observed during the last trimester of gestation. Catch-up mineralisation occurs up until 25–50 weeks after full-term. Growth patterns during the first year of life may influence bone mineralisation; lumbar spine bone mineral content at the age of seven years has been shown to be inversely associated with bodyweight at one year of age (Kurl *et al.* 1998). Expressing bone mineral content corrected for bodyweight, there appears to be little difference in bone mineral content between full-term and pre-term children. In the longer term it appears that bone mineral content is not influenced, as premature birth is associated with a shorter stature.

### *2.3.3 Infancy*

There is limited data available on calcium kinetics and growth in infants. During the first year of life, term infants accrue calcium at a rate of 90 mg/kg/day, a lower rate than during fetal life but at a higher rate than at other stages of life (see Table 1). It has been reported that infants fed with infant formulae accrue a greater amount of bone mineral compared to breastfed infants during the first six months of life. The differences are not significant at 12 months (Specker *et al.* 1997), suggesting that the observed effects are not sustained in the long-term. Potentially, differences may be explained by the difference in phosphorus content between infant formulae and breast milk. Further research needs to be conducted to confirm these findings.

### *2.3.4 Childhood and adolescence*

The amount of calcium present in the diet influences the amount of calcium the skeleton can retain during periods of growth. Calcium deposition slows down between the third and fourth years of life. During childhood both males and females, in the developed world, grow in stature at an average rate of 5.5 cm/year and bone mineral density (BMD) increases by ~1%/year (Matkovic *et al.* 2004); rates of calcium deposition are proportional to the increase in stature.

Some children, in parts of the developing world, consume as little as 300 mg of calcium/day, yet bones grow and develop normally. This may be explained by a number of factors such as physical activity levels and other environmental factors that interact with the level of calcium intake. A poor dietary supply of calcium, coupled with protein-energy malnutrition, seen in parts of the developing world, is associated with slow growth in height and weight as well as bone growth and maturation. This slow growth and development of the skeleton is not due simply to a shortage of calcium, but is part

and parcel of the general state of malnutrition affecting all parts and constituents of the body. Children who are undernourished and grow slowly, continue to grow until a later age than those who are better nourished, giving the opportunity to catch-up. Today, children in developed countries reach puberty earlier, grow faster and reach their adult height at a younger age than in the past; this has mainly been attributed to better nutrition (Karlberg 2002). Better nutrition has undoubtedly included a higher intake of calcium, although calcium alone would not have had this effect. In parts of China, general nutrition has improved and adult height has increased but calcium consumption has not increased. This results in a low calcium content of bone, which may have implications for osteoporosis risk in the long-term.

During puberty, the total amount of calcium deposited per day is greater than at any other time in life although, expressed per kg of bodyweight it is less than during infancy and childhood (see Table 1). Therefore, total calcium needs are greater during adolescence than at any other time in life. During puberty longitudinal bones grow in length and mass; bone mass, size and density increases by ~4%/year in developed countries. In females, mean growth rates for height reach 12 cm/year by the age of 12 years (increased from 6 cm/year at the age of 10 years). In males, growth rates average 5 cm/year at the age of 12 years, increasing to 10 cm/year by the age of 14 years. Growth rates slow to near zero by the age of 15 years in females and 17 years in males. All in all, between the ages of 8–17 years the mean gain in height in females is 19%, with an increase of total body calcium of 132% (Matkovic *et al*. 2004). As would be expected, more bone mass is accrued during periods of rapid growth compared to slower periods of growth.

Absorption of calcium is greater during adolescence than in childhood and adulthood, due to hormonal changes. A corresponding increase in serum calcitriol (active vitamin D) concentration is observed and such change correlates with growth rate. The increase in calcium absorption and bone growth is short-lived in females and calcium absorption falls within 2–3 years following menarche. In males the increase in calcium absorption remains until around 17–18 years of age.

Calcium supplementation trials have reported a beneficial effect of supplementation on bone mass in children (Johnston *et al*. 1992; Lee *et al*. 1995; Bonjour *et al*. 1997, 2001) and young adolescents (Lloyd *et al*. 1993; Nowson *et al*. 1997) with greatest benefit being observed in those consuming lower intakes initially (< 800 mg/day). It has been suggested that BMD may change by between 1 and 5% following supplementation, differing according to the skeletal site (New 2001).

Fewer studies have investigated the influence of calcium supplementation during late adolescence. Stear *et al*. (2003) reported a positive effect of calcium supplementation (1000 mg/day for 15.5 months) on bone mineral status but not on bone size in females aged 16–18 years, whilst Prentice *et al*. (2005) demonstrated a positive effect of calcium supplementation (1000 mg/day for 13 months) on bone mineral content and skeletal growth in males of the same age. This increase in bone mineral content diminished after adjustment for height; the authors suggest that the increase in bone mineral content may be explained by increased skeletal growth.

Few studies have investigated whether the effects of supplementation persist once supplementation has ceased, but there is evidence that the effects of supplementation may remain for a number of years (Bonjour *et al*. 2001; Dodiuk-Gad *et al*. 2005; Matkovic *et al*. 2005). Further trials are required to determine whether increasing calcium intake during childhood and adolescence increases bone mass in the long-term.

Achieving an adequate calcium intake is important for optimising bone mass and it is of concern that many adolescents fail to meet dietary recommendations for calcium (see section 7.2 *Current intake in the UK*), which may have long-term implications for bone mass and density.

### 2.4 Attainment of peak bone mass

As mentioned previously, bone mineral accretion continues even after growth has ceased. Between the ages of 18 and 30 years, bone mass may increase by a further 10%, corresponding to a 120 g increase in calcium retention, although PBM (the maximum amount of bone mass attained during life) has been reported to be reached as early as the late teenage years or as late as the mid-thirties depending on the site in the skeleton [*e.g.* PBM is reached in the femoral neck (hip) before it is reached in the forearm; Löfman *et al*. 2000; Matkovic *et al*. 2004].

The amount of bone accumulated by the time of bone maturity varies among individuals and is governed by genetic and environmental forces. Approximately 80% of the variability of PBM in adults is accounted for by genetics (see McGuigan & Ralston 2003; Ferrari 2004). Other factors (see Table 2), including gender, account for around 20% of PBM. PBM is an important factor for determining risk of osteoporotic fracture; a 10%

**Table 2** Factors that affect peak bone mass

| | |
|---|---|
| Genetics | Family history (heredity)<br>Genetic polymorphisms<br>Some ethnic groups may have stronger bones than others |
| Gender | Men tend to have a greater bone mass than women |
| Diet | Supply of calcium and vitamin D in particular, also protein and energy, influence bone mass |
| Physical activity | Regular weight-bearing exercise is important for strong bones |
| Bodyweight | Heavier people have stronger bones |
| Hormones | In women irregular periods or their absence can cause bone loss |

Adapted from Phillips (2004).

increase in PBM is associated with a 50% reduction in fracture risk (Bonjour *et al*. 2003).

### 2.5 Skeletal calcium changes in later life

Following the attainment of PBM, age-related bone loss occurs whereby mineral, including calcium, is lost from bone. Figure 3 shows the attainment and consolidation of bone mass along with age-related bone loss. Bone and calcium losses occur at a steady rate until the onset of the menopause in women, when loss is accelerated for a period of approximately 5–10 years. Bone calcium losses are covered in detail in section 9 *Bone calcium loss*.

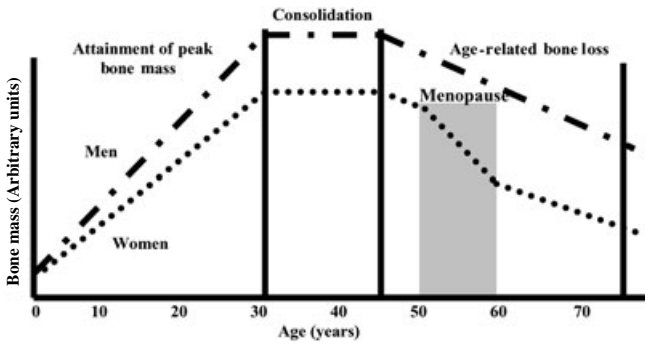


**Figure 3** Changes in bone mass over the life course.
Source: New (2002). Reproduced with kind permission of the author.

### 2.6 Calcium and dental health

Teeth consist of three types of hard tissue: enamel, dentine and cementum. As with bone, dentine and enamel are composed of calcium and phosphate in the form of hydroxyapatite. The mineralisation of teeth begins before birth, with the process of enamel formation being completed during the first year of life. The only part of the tooth that is exposed to the oral environment is the enamel. However, with ageing, dentine may be exposed through the loss of enamel or if the tissue at the gum margin supporting the teeth recedes.

Diet can influence teeth after they have erupted through local effects. For example, calcium helps to maintain the mineral composition of teeth, which are subject to both demineralisation and remineralisation dependent on a number of dietary factors and the pH of the oral environment. Plaque bacteria ferment sugars, producing acids that decrease the pH (*i.e.* more acidic) at the tooth surface, which in turn promotes demineralisation by the dissolution of calcium (and phosphate) from hydroxyapatite in enamel. If dental hygiene is not good (*i.e.* plaque bacteria are not removed by brushing) and availability of fluoride ions is low, a carious cavity may form. Enamel demineralisation takes place below a pH of about 5.5 (the critical pH). It is worth noting that the critical pH is inversely related to both the calcium and phosphate concentration of plaque and saliva (which are influenced by diet) and, therefore, does not have a fixed value (Dawes 2003). Acids are neutralised by saliva, raising the pH of the tooth surface above the critical pH, promoting remineralisation (van Loveren 2000). The balance between remineralisation and demineralisation (and high and low pH) is favoured by reduced frequency of fermentable sugar consumption along with twice daily brushing with fluoridated toothpaste.

The concentration of calcium in plaque influences demineralisation of tooth enamel and, thus, risk of caries (see BNF 1999); the greater the concentration, the lower the rate of demineralisation and risk of dental decay. Also, the greater the concentration of calcium in plaque, the greater the fall in pH that can be tolerated before demineralisation occurs. The presence of calcium in foods can help protect against dental caries as this increases the concentration of calcium in plaque. Certain other foods, for example acidic foods and drinks, can reduce the concentration of calcium in plaque.

## 3 Regulatory role of calcium

### 3.1 Introduction

All living cells require calcium (at various concentrations) to remain viable and to carry out their specialised functions. The body needs calcium not only to maintain

essential skeletal structures but also to control the behaviour of its cells and tissues when these respond to a change in environment, be it diet, a stimulus, or a pathogen. The diverse functions of calcium in the body can be divided into skeletal (discussed in section 2 *Skeletal functions of calcium*) and non-skeletal functions. Non-skeletal functions can be subdivided into structural functions and regulatory functions.

Structurally, calcium is involved in the maintenance of intracellular structures such as organelles and chromatin. Calcium bound to amines, such as catecholamines, plays a structural role in the secretory granules of endocrine cells and nerve terminals. Calcium, bound to phospholipids and proteins is necessary for maintaining integrity and permeability properties of biological membranes, and when bound to DNA, it is required for determining some of the structural features of chromosomes.

The regulatory role of calcium can be classed as either passive or active. Calcium is a biochemical regulator of enzymes but not in the physiological sense. Changes in plasma calcium neither provoke nor significantly alter these events and hence calcium operates in a 'passive' sense. In contrast, a change in calcium concentration inside living cells operates in an 'active' fashion, enabling them to change their behaviour in response to a physiological stimulus such as a hormone or neurotransmitter. The quality, and indeed the survival, of human life requires the right balance between the supply of calcium and its processing within cells. Mobilisable calcium is stored not only extracellularly in bone, but also in specialised compartments within cells. Release from the latter into the cell cytosol is responsible for provoking events and responses.

### 3.2 Intracellular calcium

The concentration of intracellular calcium varies according to the cell type; from as little as 0.02 mmol/L cell water in red blood cells with no organelles, to more than 5–15 mmol/L cell water in cells such as muscle or platelets with large stores of calcium. In contrast to plasma in which 50–60% of calcium is bound, more than 99.9% of cell calcium is bound within organelles such as the endoplasmic reticulum, mitochondria, specialised vesicles and the nucleus.

The concentration of free calcium in the cytosol of a resting cell is about 0.1 µmol/L, compared to 1.10 mmol/L in plasma. Thus, a 10 000-fold electrochemical gradient of calcium exists across the cell membrane. A small increase in the permeability of the cell membrane, or a small release of calcium from an internal store, causes a very large-fold rise in cytosolic calcium concentration, and will either 'switch' the cell on or injure it. The electrochemical gradient of calcium is maintained by a pump, which counterbalances the small passive leakage of calcium into the cell. An overload in the concentration of intracellular calcium may result in cell injury or death.

A vital biological role for calcium is its ability to trigger events within the cell. Cellular events, responsible for changes in cell behaviour, are initiated by a primary stimulus. This may be physical, such as touch or an action potential, or chemical, such as a hormone or neurotransmitter. The stimulus acts at the cell membrane to transmit a signal, through intracellular messengers, to structures and enzymes within the cell (see Fig. 4). Calcium is one of the most important and wide ranging of these intracellular signals. A rise in cytosolic calcium is responsible for all forms of muscle contraction and vesicular secretion, as well as certain examples of cell aggregation (*e.g.* blood clotting), cell transformation, cell division and activation of intermediary metabolism. In order to support these key activities, plasma calcium concentrations must be tightly controlled within a narrow range (see section 4.1 *Plasma calcium homeostasis*).

The main mobilisable intracellular calcium store in all cells is the endoplasmic reticulum. In skeletal muscle, calcium is released from this store directly by an electrical signal. In heart muscle, release is brought about by the small amount of calcium which moves into the cell with the action potential. In all other cells, calcium is released by the action of inositol trisphosphate ($IP_3$) forming a 'calcium cloud' within the cell. Recovery of the cell after removal of the stimulus involves replenishment of the calcium store, and pumping some calcium out of the cell via calcium–magnesium ATPases or

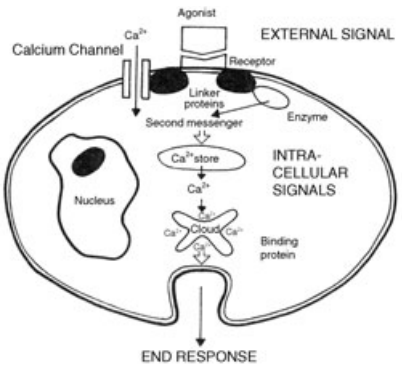


**Figure 4** Intracellular mechanism of action of calcium. Source: BNF (1989).

sodium–calcium exchanges. The ability of calcium to trigger the cell depends on the 'calcium cloud' reaching the appropriate calcium binding protein. These calcium binding proteins include calmodulin, found in nearly all cells, troponin C in muscle, and a family of cytoskeletal proteins. Binding of calcium either triggers the event directly or leads to phosphorylation of other proteins, which cause the event.

### 3.3 Role in blood clotting

Calcium is essential for blood coagulation (clotting), a process that involves two pathways: the intrinsic pathway and the extrinsic pathway. Calcium plays a role in both pathways. The process of clot formation involves a cascade of proteolytic reactions, whereby inactive enzymes or clotting factors are activated. Each activated enzyme or clotting factor then, in turn, activates another inactive factor, with the response amplifying each time, ultimately resulting in the production of thrombin from prothrombin and the production of a fibrin clot (see Fig. 5).

In the intrinsic pathway, following damage to the blood vessel wall, collagen is exposed to inactive factor XII, bringing about the activation of the clotting factor, which in turn activates the intrinsic cascade. Calcium is required for the activation of factor X within the intrinsic pathway (see Fig. 5). In the extrinsic pathway, the exposure of tissue factor (present in the membrane of blood vessels) and its subsequent binding to inactive factor VII induces the activation of this clotting factor, and thus the extrinsic coagulation cascade. Within the extrinsic pathway, the interaction between tissue factor and inactive factor VII is calcium-dependent. Calcium is also required for the activation of factor IX, factor X and factor VIII. In both pathways, at each step of the coagulation cascade, there is amplification in the number of active molecules produced, so that when the two pathways converge, thousands of thrombin molecules are formed in order to catalyse the formation of a stable fibrin clot and prevent the clot being dissolved prematurely. Calcium is also required for the conversion of prothrombin to thrombin, forming a complex with factor V, which acts as a cofactor in the conversion.

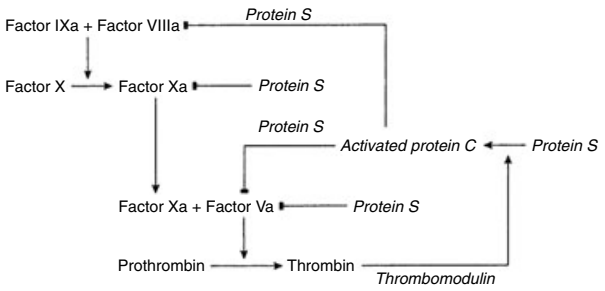


**Figure 5** The coagulation cascade. From Miller & Bruckdorfer (2005) The Haemostatic System: Coagulation, Platelets and fibrirolysis. In: *Cardiovascular Disease: Diet, Nutrition and Emerging Risk Factors* (ed Stanner S). Blackwell Publishing: Oxford. Reproduced with kind permission of Blackwells Publishing.

### 3.4 Role in digestion

Calcium is required for the optimal activity of several extracellular digestive enzymes, including proteases, phospholipases and nucleases. Along the length of the gastrointestinal tract a calcium ion sensing receptor is expressed, and it is thought that the expression of this receptor plays a role in gastric acid secretion.

### 3.5 Role in neurological and muscular function

Calcium plays an important role in provoking neurotransmitter release from nerve cells and in muscle contraction. Both nerve and muscle cells are electrically excitable and their cell membranes contain calcium selective ion channels; these open when the membranes are depolarised (*e.g.* upon arrival of action potentials via nerves), causing an influx of calcium and an increase in cytosolic calcium concentration. In nerves, this results in the release of neurotransmitters (*e.g.* acetylcholine).

Muscle fibres are composed of thick (mainly myosin) and thin (actin) filaments. Calcium plays an integral role in skeletal, heart and smooth muscle contraction, controlling the interaction of thick and thin filaments in muscle fibres. Muscular contraction follows the formation of myosin cross-bridges between myosin and actin filaments. Present on the actin-containing thin filaments of muscle fibres is a myofilament regulatory protein complex, composed of the regulatory proteins troponin and tropomyosin. This protein complex inhibits cross-bridge formation when the muscle fibre is at rest, as tropomyosin blocks access to actin cross-bridge binding sites. In skeletal muscle, action potentials cause the rapid release of calcium ions from the sarcoplasmic reticulum. These calcium ions can then bind to calcium-binding sites on the troponin-binding molecule, inducing conformational change, which results in the shifting of tropomyosin away from the actin cross-bridge binding site. Thus, actin cross-bridge binding sites are exposed to myosin cross-bridges, allowing cross-bridges

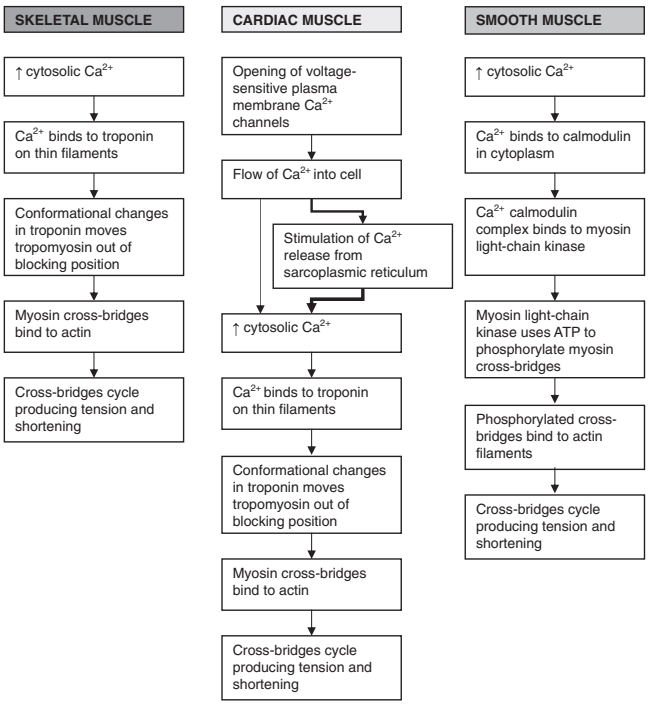


**Figure 6** Role of calcium in skeletal and smooth muscle contraction. Adapted from Widmaier *et al.* (2004).

to form. Such binding exerts force on the thin filament and muscular contraction results. Following contraction, cytosolic calcium concentrations fall and relaxation results as calcium is pumped back into the sarcoplasmic reticulum via calcium-ATPases. Cross-bridges detach and the interaction between actin and myosin is inhibited once again.

A similar series of events causes heart muscle contraction. The role of calcium in the contraction of smooth muscle (*e.g.* the muscle lining the lungs and digestive tract) differs from that of skeletal and heart muscle contraction as the thin filaments of smooth muscle do not contain troponin. Rather, in smooth muscle, an increase in intracellular calcium ion concentration brings about the binding of calcium to calmodulin (which is structurally similar to troponin) in the cytosol. The resultant calcium–calmodulin complex brings about the phosphorylation of myosin, allowing myosin cross-bridges to form with actin and, thus, the muscle to contract. In smooth muscle only phosphorylated myosin can form cross-bridges with actin. Relaxation is induced by dephosphorylation. Figure 6 summarises the different role of calcium in skeletal and smooth muscle contraction.

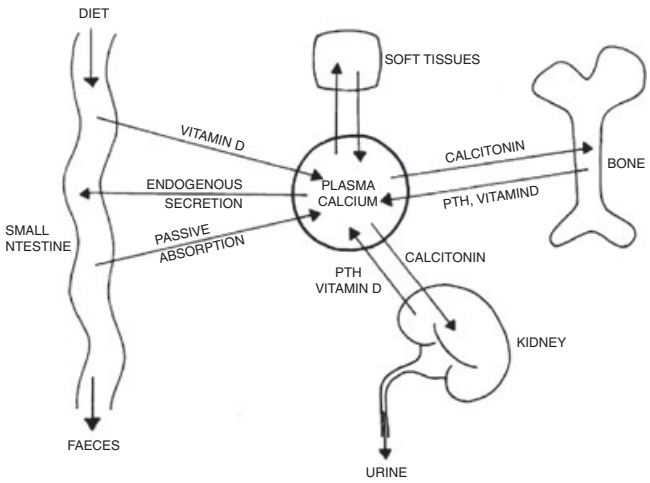


**Figure 7** Factors influencing calcium homeostasis © BNF (1989).

## 4 Calcium homeostasis and metabolism

### 4.1 Plasma calcium homeostasis

Plasma concentrations of ionised calcium are tightly regulated between 1.1 and 1.3 mmol/L. If the plasma calcium concentration falls below this, neuromuscular excitability is increased and, if calcium concentrations fall too low, hypocalcaemic tetany may occur. This causes paraesthesia (itchy, tingly skin), laryngeal spasms, respiratory arrest and cardiac arrhythmia and can be fatal. Excess accumulation of calcium in plasma results in hypercalcaemia (see section 10.4 *Hypercalcaemia*).

Calcium homeostasis occurs at three main sites: the kidneys, bone and gastrointestinal tract (see Fig. 7). Calcium homeostasis at these three sites is controlled, directly or indirectly by PTH, which is secreted by the parathyroid gland. PTH is one of three major calciotropic hormones involved in calcium homeostasis, the others being calcitonin and calcitriol (1α, 25-dihyroxy vitamin $D_3$) (see below). The production and secretion of PTH is governed by plasma calcium concentration; a decrease in calcium concentration leads to the secretion of PTH, which acts to restore plasma calcium concentrations, whilst an increase in plasma calcium concentration inhibits PTH release.

There are four major ways in which PTH regulates plasma calcium concentration. Within the kidney, PTH acts to increase calcium reabsorption and, therefore, decrease urinary excretion. PTH also acts to decrease phosphate reabsorption, leading to an increase in phosphate excretion and a reduction in plasma phosphate

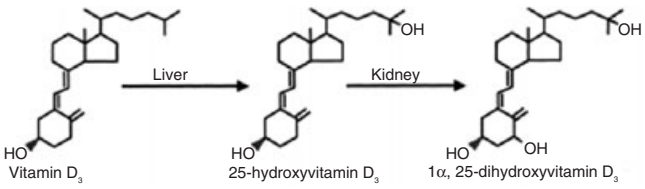


**Figure 8** Metabolism of Vitamin D (from DeLuca 2004). Reproduced with permission by the *American Journal of Clinical Nutrition*. © Am J Clin Nutr. American Society for Clinical Nutrition.

concentration. This is important as PTH causes the release of both calcium and phosphate from the bones in order to maintain plasma calcium concentrations. An increase in plasma phosphate concentration, however, would prevent any further calcium resorption from bone. Phosphate also promotes the deposition of both calcium and phosphate on bone. In addition, PTH acts in the kidney to increase formation of calcitriol (the active form of vitamin D), increasing plasma calcitriol concentration, which acts in the intestine to increase absorption of calcium. Ultimately, these four actions of PTH restore plasma calcium concentrations; once restored secretion of PTH is inhibited. In addition, the hormone calcitonin is secreted into the circulation by the thyroid gland. Although it does not strictly play a role in calcium homeostasis, calcitonin acts on bone to inhibit resorption and protect the skeleton under times of stress, for example during pregnancy and growth.

The metabolism of vitamin D is closely involved in plasma calcium homeostasis, through its influence on calcium absorption in the intestine. In order to understand fully the role of vitamin D and its metabolites in calcium homeostasis, it is important to briefly describe vitamin D metabolism (see Fig. 8). The term vitamin D describes a group of similar compounds. Vitamin $D_3$ (cholecalciferol) is formed through the action of sunlight (UV radiation) on 7-dehydrocholesterol present in the skin. Vitamin D is present in the diet as vitamin $D_2$ (ergocalciferol) and is structurally similar to vitamin $D_3$. Within the circulation, both vitamin $D_2$ and vitamin $D_3$ are bound to vitamin D-binding protein; some of the bound vitamin D is deposited in adipocyte stores whilst the remainder passes to the liver. In the liver, vitamin D undergoes hydroxylation to form calcidiol (25-hydroxy vitamin $D_3$). From the liver, calcidiol passes to the kidney where further hydroxylation occurs. PTH activates the enzyme (cytochrome $P_{450}$-25-hydroxyvitamin D-1-hydroxylase) which catalyses metabolism to form calcitriol (1α, 25-dihydroxy vitamin $D_3$). It is this form that is considered to be the active form of vitamin D. The main function of calcitriol is to regulate calcium homeostasis.

### 4.2 Absorption

Usually between 20 and 30% of calcium consumed in the diet is absorbed in the gastrointestinal tract (individual variability ranges between 10 and 50%), although fractional absorption increases during growth, pregnancy and lactation. Calcium that is not absorbed is excreted in faeces. The amount absorbed will depend on how calcium is present in food (*i.e.* what it is bound to), the amount present, its solubility and the presence of dietary factors which inhibit or promote absorption, as well as age (see section 8.1 *Dietary factors affecting calcium absorption*).

Calcium is absorbed predominantly in the small intestine where conditions are acidic, and to a lesser extent in the colon (where conditions are more alkaline), where absorption occurs following the release of calcium from plant foods during bacterial fermentation (Basu & Donaldson 2003).

Calcium must be present in a suitable form before it can be taken up by the intestinal mucosal cells. Most calcium present in foods is in the form of complexes with other dietary constituents. The extent to which calcium is first solubilised in the stomach and then the intestinal lumen influences its bioavailability. At low intakes, calcium is mainly absorbed by active transport, but as intakes increase this mechanism becomes saturated and additional calcium is absorbed by carrier-mediated (non-saturable) diffusion. The net result is an increase in the absolute amount of absorbed calcium with increasing intakes but a decrease in fractional absorption (*i.e.* the proportion of the amount consumed). Fractional absorption of calcium from foods is inversely related to the amount of calcium consumed over a range of 15–500 mg calcium (Heaney *et al.* 1990).

Calcium uptake through active transport is controlled by the circulating concentration of ionised calcium in the blood. Should this fall below 1.1 mmol/L, the amount of calcium absorbed is increased; conversely, should concentrations rise above 1.3 mmol/L, absorption is reduced. Calcium uptake through active transport occurs predominantly in the small intestine and is regulated by calcitriol. As well as being stimulated by a low concentration of ionised calcium in the circulation, absorption is up-regulated during pregnancy, lactation

and growth. Calcium absorption appears to decline with age in both men and women, and is thought to be the result of a reduction in intestinal responsiveness to serum calcitriol rather than a reduction in serum concentrations of calcitriol (Scopacasa *et al.* 2004).

Calcium enters intestinal cells at the brush border membrane and is transported through epithelial calcium channels. Expression of calcium channels appears to be up-regulated with low-calcium diets, as shown in animal studies (Van Cromphaut *et al.* 2001). Once inside the cell, calcium crosses through the cytoplasm bound to a vitamin D-dependent calcium-binding protein. Calcium then passes into the circulation through the action of a calcium-pumping ATPase.

Passive diffusion also occurs in the small intestine. This mechanism of absorption is non-saturable and is independent of physiological and nutritional status; rather absorption is increased following increased calcium intake.

### 4.3 Markers of calcium absorption and status

No functional marker for calcium status exists. Measuring plasma calcium concentrations does not give an indication of body calcium stores, and for this reason there is controversy with regards to dietary calcium recommendations (see section 5 *Dietary reference values*). Calcium absorption can be measured in a number of ways; traditionally this has been done through measuring faecal excretion over a known period of time and subtracting the amount lost from the amount consumed (known as the metabolic balance method). It is worth noting that calcium is present in gastric secretions (*i.e.* previously absorbed calcium is secreted back into the stomach), and the amount of calcium absorbed from the intestinal calcium pool includes calcium from this source as well as dietary calcium. Radioactive or stable isotopes are also used to measure absorption. Urine is collected and the amount of labelled calcium determined.

As plasma calcium concentrations are highly regulated and a wide number of factors influence urinary calcium excretion, there are no biochemical markers that can be used to determine the calcium status of an individual. Therefore, determination of total calcium intake (from dietary sources and supplements) is the sole method available for assessing the calcium status of an individual. Whole body calcium content can be determined by neutron activation, whereby a beam of fast neutrons fired at the body leads to the capture of energy and the formation of short-lived radioactive calcium isotopes (as $^{49}Ca$) which can then be measured using a whole body radioactivity counter.

### 4.4 Excretion

Most calcium is excreted in urine and faeces, although small losses do occur through hair, skin and sweat. Calcium, previously absorbed from the diet re-enters the gastrointestinal tract via secretions from the pancreas, bile and saliva. Not all of this is reabsorbed; some is excreted in the faeces.

Under normal conditions, dietary calcium that reaches the bloodstream passes through the kidneys. Each kidney is made up of more than a million nephrons; in each nephron blood is filtered through the glomerulus (see Fig. 9), where proteins and other high-molecular weight compounds are trapped and retained. Unbound calcium in the blood passes through the glomerulus into the proximal tubule along with water, electrolytes and low-molecular weight substances, whilst calcium bound to protein is trapped and remains in the blood (up to 50% of calcium in blood is bound to protein). Most of the calcium that passes into the tubule is reabsorbed back into the bloodstream rather than being lost into the urine. The amount reabsorbed will vary according to age (reduced in old age), gender and hormonal status, calcium and sodium consumption, protein intake and the amount of phosphorus in the diet. Under normal conditions, at least 97% of the calcium which passes into the tubule is reabsorbed with approximately 85% being reabsorbed in the proximal tubule and the thick ascending limb of Henle's loop through passive diffusion along with sodium. A further 15% is absorbed in the distal convoluted tubules, through an active transport mechanism. Any calcium that is not reabsorbed then passes into what is now urine and into the bladder.

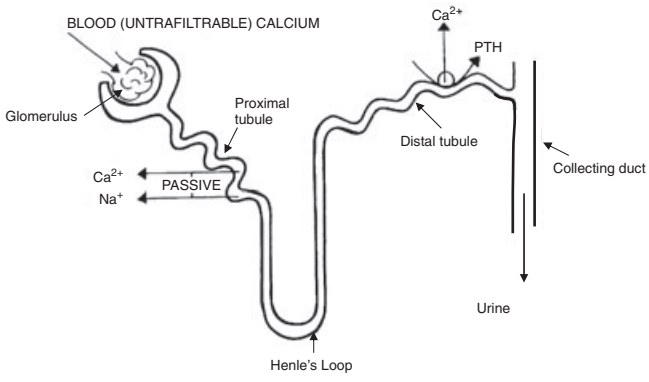


**Figure 9** Urinary excretion of calcium in the kidney nephron. Adapted from BNF (1989).

#### *4.4.1 Factors that influence urinary calcium excretion*

Sodium intake is positively associated with urinary calcium excretion and calcium excretion can vary considerably even when intakes of sodium are within the normal range of intake. It has been suggested that an increase of 100 mmol (2300 mg) of sodium in the diet (equivalent to 5.75 g salt) leads to a 1 mmol (40 mg) increase in calcium excretion in the urine (Nordin *et al*. 1998). Urinary calcium excretion correlates with sodium excretion independently of calcium absorption, suggesting that sodium influences calcium reabsorption in the kidney. It is thought that calcium and sodium ions share a common, or linked, reabsorption pathway within the kidney. The additional excretion of calcium associated with increased intakes of sodium may, in part, be compensated for (in healthy individuals) by an increase in calcium absorption mediated by PTH (Harrington & Cashman 2003).

Potassium from supplements (3.5 g over a period of 4 weeks) has been shown to reduce urinary calcium excretion in postmenopausal women, even when sodium intake is high (Sellmeyer *et al*. 2002). Further research needs to be conducted to determine whether dietary sources of potassium behave in the same way. It has been suggested that potassium may promote calcium reabsorption in the kidney, through its ability to increase plasma pH and reduce endogenous acid production (Harrington & Cashman 2003).

Protein intake is strongly and positively associated with urinary calcium excretion, suggesting that dietary protein plays a role in the regulation of urinary calcium excretion. The source of the excreted calcium is unclear and further research is needed to establish whether increased bone resorption, increased intestinal absorption and/or reduced renal reabsorption are involved. It has also been suggested that the presence of phosphorus in the diet may help minimise urinary calcium losses associated with a high protein intake. Phosphorus intake is negatively associated with urinary calcium excretion, and it is thought that an inadequate concentration of phosphorus in plasma leads to increased urinary calcium excretion.

The acidity of the diet may also play a role in urinary calcium excretion as the skeleton is involved in maintaining acid-base homeostasis in the body, *i.e.* in keeping the pH of extracellular fluid between 7.35 and 7.45 and concentrations of hydrogen ions between 0.0035 and 0.0045 mmol/L. Consumption of a typical Western diet results in net acid (hydrogen ion) production of 1 mEq/day, due to the predominant consumption of acid precursors compared to alkaline (base) precursors. The skeleton acts as a proton buffer to cancel this out; 2 mEq of calcium/day can cancel out 1 mEq of acid/day (New 2002). Over a period of 20 years, assuming that the body contains 1 kg of calcium, this theoretically could equate to 15% of inorganic bone mass (see New 2002). That said, other mechanisms also act to preserve pH including carbon dioxide exhalation and urinary acid excretion; these will reduce the potential burden on the skeleton.

It has been speculated that increased net endogenous acid production might increase risk of osteoporosis (New 2002), though much more research is needed. A fall in extracellular pH, to more acidic conditions, is associated with increased urinary calcium excretion and negative calcium balance, whilst an increase in pH (to more alkaline conditions) of extracellular fluid is associated with increased osteoclast activity and increased bone resorption. Indeed, an increased net acid content of the diet, as measured by estimating net endogenous acid production, is associated with increased urinary calcium excretion and reduced spine and hip BMD (New *et al*. 2004), which could potentially increase risk of bone fracture. With advancing age, the body becomes more 'acidic' because it is less able to compensate for increased net acid production as renal function, and thus hydrogen ion excretion, for example, declines. Nutrients that promote acid load include sulphur, phosphorus and chloride, whilst nutrients contributing to alkaline load include potassium, magnesium, sodium and calcium (see New 2002).

## 5 Dietary reference values

### 5.1 Dietary reference values

The Department of Health Committee on Medical Aspects of Food Policy (COMA) set dietary reference values (DRV) for calcium in 1991 (Department of Health 1991). Dietary reference values vary according to age and gender and also include an increment for lactation (breastfeeding), with adolescent mothers potentially requiring a higher increment. These are detailed in Table 3. Whilst the estimated average requirement (EAR) for calcium is based on published data on calcium retention, the reference nutrient intake (RNI) is calculated as the EAR plus two 'notional' standard deviations. The RNI is defined as the amount of a nutrient that is sufficient, or more than sufficient to meet the nutritional requirements of practically all (97.5%) healthy people in a population. Therefore, the RNI exceeds the needs of most individuals. The lower reference nutrient intake (LRNI) is the EAR minus two

**Table 3** Dietary reference values for calcium (mg/day)

| Age | Lower reference nutrient intake | Estimated average requirement | Reference nutrient intake |
|---|---|---|---|
| 0–12 months | 240 | 400 | 525 |
| 1–3 years | 200 | 275 | 350 |
| 4–6 years | 275 | 350 | 450 |
| 7–10 years | 325 | 425 | 550 |
| 11–14 years, male | 480 | 750 | 1000 |
| 11–14 years, female | 450 | 625 | 800 |
| 15–18 years, male | 480 | 750 | 1000 |
| 15–18 years, female | 450 | 625 | 800 |
| 19–50 years | 400 | 525 | 700 |
| 50+ years | 400 | 525 | 700 |
| Pregnancy | – | – | – |
| Lactation | – | – | +550 |

From Department of Health (1991).



'notional' standard deviations and refers to the level of intake that meets the needs of just 2.5% of the population. Therefore, intakes less than the LRNI can be considered inadequate for most people. The scientific basis on which the calcium DRV is based has since been reassessed, in light of new data. It was concluded that revision was not warranted but it was suggested that the recommended increment for calcium during lactation may not be required and that this should be re-evaluated as new evidence emerges (Department of Health 1998).

The European Union recommended daily amount (RDA) for calcium, used for food labelling purposes, is 800 mg/day. This value is said to be sufficient to meet or more than meet the needs of groups of European adults and reflects the variation in dietary recommendations across the member states.

Currently there is no international consensus on recommendations for calcium intake; there are very wide differences around the world. This is not the case for most other nutrients. Some of the variation may be explained by the fact that different methods and approaches have been used (Weaver 1999). Some recommendations are based on meeting requirements whilst others have focused on optimising bone mass and minimising age-related bone loss. In the United States and Canada, dietary reference intakes (DRI) do not differ according to gender but are higher for all age groups than the UK RNI. For example, the US/Canadian DRI (based on the concept of maximal retention of calcium in bone) for children aged 4–8 years is 800 mg/day, for adults aged 19–50 years it is 1000 mg/day and for adults over 51 years the DRI is 1200 mg/day (Institute of Medicine 1997). In Australia, dietary recommendations for calcium are higher than in the UK for some but not all age groups. For boys aged 12–15 years the recommended dietary intake is 1200 mg/day, whilst for girls it is 1000 mg/day. For adults aged between 19 and 54 years the recommended dietary intake is 800 mg/day and it is 1000 mg for adults aged over 54 years (National Health and Medical Research Council 1998). The FAO/WHO (Food and Agriculture Organisation/World Health Organization) recommends that men aged between 19 and 65 years and women aged over 19 years, up until the menopause, consume 1000 mg calcium/day and that postmenopausal women and men aged over 65 years consume 1300 mg calcium/day (FAO/WHO 2002).

### 5.2 Guidance on high intakes

The Department of Health, when devising the DRV for calcium, did not issue guidance on high intakes of dietary calcium, as these are rarely the cause of excessive accumulation of calcium in plasma or tissues. More recently the Food Standards Agency has issued guidance in the context of calcium supplements, recommending against taking more than 1500 mg/day of calcium in the form of supplements (Expert Group on Vitamins and Minerals 2003), because of the risk of adverse symptoms such as stomach pain and diarrhoea.

There is also some evidence that high intakes of calcium might potentially cause nutrient deficiencies via interference with the absorption of other minerals such as zinc, copper and magnesium. However, with the possible exception of iron, there appears to be little or no interference with these minerals under normal dietary conditions. With iron, short-term, single meal studies suggest that absorption of both haem and non-haem iron is inhibited (~50–60%) by calcium in a dose-dependent manner at intakes of calcium between 150 and 300 mg (*i.e.* well below the RNI). In the longer term, however, the body seems able to adapt by up-regulating iron absorption, as demonstrated by the fact that non-haem iron absorption is not impaired over a period of 4 days to 5 weeks when consuming a high-calcium diet (1200 mg/day) compared to a low-calcium diet (< 320 mg/day) (Minihane & Fairweather-Tait 1998; Grinder-Pedersen *et al.* 2004). More research needs to be conducted to determine the mechanisms involved.

## 6 Sources of calcium in the diet

A wide range of foods contain calcium; with the amount of calcium provided on a per 100 g or serving basis and its bioavailability varying considerably (see section 8 *Bioavailability of calcium from foods*). (Please note that all figures for the calcium content of foods in this section are derived from UK values).

### 6.1 Milk and dairy products

The calcium content of milk is fairly constant and is virtually unaffected by the cow's diet, lactation stage or the climate. About two-thirds of the calcium present in milk is bound to the protein casein and (to a small extent) other milk proteins, phosphorus and citrate, while the remainder is un-bound. Skimmed milks, dried skimmed milk powder and yoghurts retain essentially all the original calcium present in the milk prior to processing. About 80% of milk calcium remains in Cheddar and other hard cheeses, but butter contains only about 18% (see Table 4). The calcium in milk and milk products has a high bioavailability (see section 8 *Bioavailability of calcium from foods*). The contribution of these foods to calcium intake in the UK and elsewhere is discussed in section 7 *Calcium intake in the UK*.

### 6.2 Cereal products

Cereals *per se* are not considered a rich source of calcium; however, as a result of fortification many cereal products in the UK make a valuable contribution to calcium intake (see Table 5). Until the 18th century, chalk and powdered bone (sources of calcium) were often added to flour. The reason for this was not to improve nutrition but rather because the public desired white bread and it also helped make the flour go further. Such adulteration was forbidden by law in 1758. In 1943 the addition of calcium carbonate to flour was made compulsory following recommendations from the Medical Research Council's Accessory Food Factor Committee. The reasons for this were twofold: it was feared that milk and cheese might be in short supply (and, therefore, calcium intakes limited) during the war and also because of restricted shipping space it was necessary to import flour of 85% extraction, which contains a high concentration of phytate and inhibits calcium

**Table 5** Calcium in selected cereal products (FSA 2002)

| | Calcium (mg/100 g) | | Calcium (mg/100 g) |
|---|---|---|---|
| Wheat flour, brown | 130 | Brown bread | 186 |
| Wheat flour, white, plain | 140 | White bread | 177 |
| Wheat flour, white, self-raising | 350 | Wholemeal bread | 106 |
| Wheat flour, wholemeal | 38 | Pitta bread, white | 138 |
| Rice, brown, boiled | 4 | Rye bread | 80 |
| Pasta, fresh, cooked | 37 | Cornflakes | 5 |
| Digestive biscuits, plain | 92 | Weetabix | 35 |
| Gingernut biscuits | 130 | Frosties | 453 |
| Doughnuts, jam | 72 | Sultana bran | 50 |
| Sponge cake | 69 | Porridge, made with water | 7 |



**Table 4** Calcium content of selected dairy products (FSA 2002)

| | Calcium (mg/100 g) | | Calcium (mg/100 g) |
|---|---|---|---|
| Skimmed milk (average) | 160 | Brie | 256 |
| Semi-skimmed milk (average) | 156 | Cheddar | 739 |
| Whole milk (average) | 118 | Cheddar type, half fat | 840 |
| Channel Island milk (whole, pasteurised) | 130 | Cheese spread, plain | 498 |
| Condensed milk, sweetened | 330 | Cottage cheese, plain, reduced fat | 13 |
| Dried skimmed milk | 1280 | Feta | 360 |
| Goat's milk (pasteurised) | 100 | Edam | 795 |
| Human milk (mature) | 34 | Goats cheese, soft | 133 |
| Sheep's milk (raw) | 170 | Stilton | 326 |
| Butter | 18 | Parmesan | 1025 |
| UHT dairy cream (canned spray) | 54 | Yoghurt, whole milk, plain | 200 |
| Cream, single | 89 | Yoghurt, low fat, plain | 162 |
| Cream, double | 49 | Drinking yoghurt | 100 |
| Crème fraiche | 58 | Ice cream, dairy, vanilla | 100 |
| Crème fraiche, half fat | 95 | Ice cream, non-dairy, vanilla | 72 |

**Table 6** Calcium in selected plant foods (FSA 2002)

| | Calcium (mg/100 g) | | Calcium (mg/100 g) |
|---|---|---|---|
| Baked beans, canned in tomato sauce | 53 | Potatoes, new in skins, boiled | 13 |
| Chick peas, dried, boiled | 46 | Potatoes, old, baked, flesh and skin | 11 |
| Lentils, green/brown, dried, boiled | 22 | Potatoes, old, boiled | 5 |
| Peas, frozen, boiled | 42 | Apples, average | 4 |
| Broccoli, boiled | 40 | Apricots, ready to eat | 73 |
| Cabbage, average, boiled | 33 | Figs, dried | 250 |
| Carrots, old, raw | 25 | Olives, in brine | 61 |
| Curly kale, boiled | 150 | Pineapple | 18 |
| Spinach, boiled | 160 | Banana | 6 |
| Tomatoes, canned | 12 | Oranges | 47 |
| Watercress, raw | 170 | Rhubarb, raw | 93 |
| Lettuce, average | 28 | Sultanas | 64 |
| Soya beans, dried | 240 | Tofu, steamed* | 510 |
| Soya beans, dried, boiled | 83 | Soya non-dairy alternative to milk, calcium fortified | 89 |
| Soya non-dairy alternative to milk, unfortified | 13 | Soya dessert (Provamel) | 108 |
| Soya non-dairy alternative to yoghurt, fruit | 14 | Cashew nuts | 32 |
| Almonds | 240 | Peanuts (plain) | 60 |
| Hazelnuts | 140 | Sesame seeds | 670 |
| Walnuts | 40 | Pumpkin seeds | 39 |
| Sunflower seeds | 110 | | |

*If nigari is used as a coagulant in tofu the calcium content is 150 mg/100 g.



absorption. In order to overcome such inhibitory effects, almost 200 g of calcium carbonate was added to a 127 kg sack of flour (7 oz per 280 lb sack). The amount added was doubled in 1946, so that 100 g of flour contained 125 mg of calcium, compared with the natural content in white flour of 15 mg/100 g. White flour became available again in 1953, but calcium fortification continues today. Under the (UK) Bread & Flour Regulations 1995, all flours derived from wheat, except wholemeal flour, must have a calcium content of between 94 and 156 mg/100 g flour, whilst self-raising flour must have a calcium content of not less than 200 mg/100 g.

### 6.3 Plant foods

Vegetable consumption is lower in the United Kingdom than in many countries of the world. In the UK, approximately 50 mg calcium per person per day comes from vegetable sources (excluding potatoes), whereas in other countries, all plant sources together often provide more than 200 mg calcium and in some countries as much as 400 mg per person per day. The calcium content of vegetables is little affected by methods of cultivation, although calcium bioavailability varies considerably between plants (see section 8 *Bioavailability of calcium from foods*). Calcium is not lost during cooking, but concentrations will be diluted in vegetables which take up water when boiled, unless the water is hard (and so able to contribute calcium).

Fortified soya products are often marketed as alternatives to dairy products, and they form an important part of the diets of many vegetarians and vegans. The calcium content of unfortified soya products is relatively low compared to milk (see Table 6), but fortified products typically contain similar levels. It has been estimated that the bioavailability of calcium from soya beans is approximately 30–40%; similar to that of milk and some dark green leafy vegetables, but higher than many commonly consumed beans. Furthermore, it has been suggested that the bioavailability of calcium from cow's milk is 25% greater than that of added calcium (as tri-calcium phosphate) from soya drinks (Heaney *et al*. 2000). As a result, extra calcium has been added to some soya alternatives to milk on sale in the UK to partially compensate.

### 6.4 Additional sources of calcium

Eggs, some fish and animal products are all additional sources of dietary calcium. A whole raw egg provides 57 mg calcium/100 g of which most is present in the yolk (130 mg/100 g yolk). Shellfish and small fish, such as whitebait, canned salmon and sardines, where the

bones are also eaten, can be significant sources of calcium. Note that canned tuna is not a source of calcium (see Table 7).

Another source of calcium is water; tap water may contain from 1 to 160 mg calcium per litre, depending on its hardness (see below) and the calcium content of bottled mineral water is also variable (see below). It is estimated that tap water contributes up to 4% of total daily calcium intake in some parts of Europe (Nerbrand *et al*. 2003). In the UK, the average adult male consumes 239 mL of water/day (bottled plus tap), whilst the average adult female consumes 314 mL (Henderson *et al*. 2002). These estimates do not take into consideration water consumed with teas, coffees, dried soups and cordials; adult males consume an average of 1021 mL of tea (including herbal tea) and coffee/day, and adult females consume an average of 904 mL of tea and coffee/day, indicating that these drinks make a valuable contribution to water intake. Water consumption appears to have remained relatively stable over the last 20 years; in 1980 the average amount of tap water drunk, as such and in tea, coffee and soft drinks, was nearly 1 L per day, ranging from 0.2 to 3.0 L (Water Research Centre 1980).

The amount of calcium present in tap water will depend on the hardness of the water; the degree of hardness is determined by the amount of calcium and magnesium salts dissolved in the water. The WHO considers water containing 80–100 mg calcium carbonate/L as desirable: water containing more than 150 mg/L is considered unduly hard, and water with a calcium carbonate concentration of less than 100 mg/L is classed as soft water (WHO 2003a). Approximately 60% of homes in the UK receive hard water; hard water is found in central, eastern and southern England, whereas soft water is present in north-west England, Scotland and west Wales. Thus, in hard water areas such as south-east England, water could provide more than 100 mg calcium/day and, potentially, as much as 500 mg. In very soft water areas, such as Strathclyde, it would provide virtually none.

**Table 7** Calcium content of selected animal and fish products (FSA 2002)

| | Calcium (mg/100 g) |
|---|---|
| Egg, chicken, raw | 57 |
| Egg, yolk, raw | 130 |
| Sardines, canned in brine, drained | 540 |
| Salmon, pink, canned in brine, drained | 91 |
| Pilchards canned in tomato sauce | 250 |
| Tuna, canned in brine, drained | 8 |
| Whitebait, in flour, drained | 860 |
| Crab, canned in brine, drained | 120 |
| Prawns, boiled | 110 |
| Mussels, boiled | 52 |
| Pork sausage, chilled, grilled | 110 |
| Tripe, dressed, raw | 52 |
| Burger (economy), grilled | 110 |



The use of jug water filters to improve the taste and reduce some of the hardness of tap water is popular in the UK. However, the process of filtering removes some of the calcium from tap water. It is difficult to quantify the amount of calcium lost from water with filtering as the degree of hardness will influence the amount of calcium salts in tap water.

The calcium content of mineral waters varies considerably; typically from 7 mg/L to 190 mg/L, but up to 486 mg/L. In recent years, a number of mineral waters have been fortified with additional calcium; some mineral waters on sale in Germany and Switzerland contain between 555 and 585 mg/L. It is estimated that in France, highly mineralised water (calcium content in the region of 486 mg/L) may contribute up to 25% of calcium intake if consumed regularly in sufficient quantities (Galan *et al*. 2002).

A number of food additives also contain calcium. As well as calcium carbonate used in flour, calcium phosphates, calcium chloride, calcium citrate and several other calcium salts are used in small amounts in a variety of foods. Antacid remedies contain calcium carbonate and may provide up to 400 mg of calcium per day (Expert Group on Vitamins and Minerals 2003).

Calcium supplements may contain one of a number of forms of calcium, including calcium carbonate, calcium gluconate, calcium lactate and calcium chelates. The proportion of elemental calcium present ranges from 9% (calcium gluconate) to 40% (calcium carbonate). Calcium in the form of calcium chelates is more bioavailable than that in the form of calcium carbonate as it has a lower solubility. However, the absorption of calcium from calcium salts and from milk is similar (Guéguen & Pointillart 2000). Typically, supplements contain calcium concentrations of between 133 mg/tablet (consumed once a day) to 800 mg/tablet (consumed three times a day; the equivalent of 2400 mg/day). The Food Standards Agency recommends individuals do not consume more than 1500 mg of calcium/day from supplements, as taking high doses of calcium can cause stomach pain and diarrhoea (Expert Group on Vitamins & Minerals 2003). It has been suggested that calcium

from dietary supplements is best absorbed when consumed at a dose of not greater than 500 mg at any one time (Dawson-Hughes 1998) and that the timing of meals influences absorption.

## 7 Calcium intake in the UK

### 7.1 Main dietary sources

The basic food supplies in most northern European countries, Australia and New Zealand, where milk is popular, provide in the region of 1000 mg calcium per person per day; average calcium intake in adults is 888 mg/day in the UK. The major dietary sources for adults are milk and milk products (accounting for 43% of all calcium intake from food sources in adults), followed by cereals and cereal products (accounting for 30%) and vegetables which make a small contribution to intake (providing 5% of calcium) (Henderson *et al*. 2003) (see Table 8) (see below for information on children). The reason why cereals and cereal products make such a valuable contribution to calcium intakes in the UK is that many cereal products are fortified (enforced and also voluntarily) with this nutrient.

In the some parts of the developing world, for example in rural Gambia, calcium intakes are approximately 300 mg/day in women and children (Prentice *et al*. 1998; Dibba *et al*. 2000). The difference between these figures and those for the industrialised societies quoted above reflects the lower consumption of milk and dairy products in the developing world.

**Table 8** Percentage contribution of food types to average daily intake of calcium, in British adults

| | % of intake (adults 19–64 years) |
|---|---|
| Cereals and cereal products | 30 |
| *Of which:* | |
| Pizza | 2 |
| White bread | 13 |
| Wholemeal bread | 2 |
| Soft grain bread and other bread | 4 |
| Breakfast cereals | 4 |
| Milk and milk products | 43 |
| *Of which:* | |
| Whole milk | 6 |
| Semi-skimmed milk | 17 |
| Skimmed milk | 4 |
| Cheese | 11 |
| Yoghurt | 3 |
| Eggs and egg dishes | 2 |
| Meat and meat products | 6 |
| Fish and fish dishes | 2 |
| Vegetables (excluding potatoes) | 5 |
| Potatoes and savoury snacks | 1 |
| Fruits and nuts | 1 |
| Sugars, preserves and confectionery | 2 |
| Drinks (includes soft drinks, tea, coffee and water) | 5 |
| Miscellaneous (includes powdered beverages (except tea and coffee), soups, sauces, and condiments | 2 |
| Average daily intake (mg) | 888 |

From Henderson *et al*. (2003).



### 7.2 Current intake in the UK

Data from the most recent National Diet and Nutrition Survey (NDNS) of British adults aged 19–64 years (data collected between July 2000 and June 2001) show that the mean intake of calcium from food sources is 1007 mg of calcium/day for men and 777 mg/day for women (Henderson *et al*. 2003). Mean intake of calcium from food sources is 144% of the RNI for men and 111% of the RNI for women (*i.e*. average intakes are more than adequate). Dietary supplements make a very small contribution to total calcium intake, with the exception of women aged 50–64 years; supplements containing calcium increased calcium intake by approximately 10% in this group (total calcium intake, 903 mg/day). Average intakes of calcium are higher than in the previous NDNS conducted in 1986/87; men were consuming 937 mg/day and women 726 mg/day (Gregory *et al*. 1990).

The average intakes obscure the fact that intakes are low in some subgroups of the population; intakes are lowest in men and women aged 19–24 years (see Table 9) with 8% of women of this age failing to meet the LRNI (400 mg/day) for calcium, which implies an inadequate intake.

Data from the NDNS of young people aged 4–18 years suggest that intakes of calcium from food sources vary widely. Intakes of calcium amongst boys average 784 mg/day (113% of the RNI), whilst amongst girls the average intake is 652 mg/day (105% of the RNI). Intakes of calcium increase significantly with age for boys but not for girls. Amongst older children, a high proportion of boys and especially girls, fail to reach the LRNI for calcium (see Table 10). The major source of calcium in the diets of children is milk and milk products, accounting for 48% of calcium intake in boys and 47% in girls, followed by cereals and cereal products which provide 27% of calcium intake. The contribution

**Table 9** Mean daily intake of calcium and percentage contribution to the reference nutrient intake (RNI), from food sources, according to age and gender: adults 19–64 years.

| | Calcium (mg/day) | % RNI | % consuming less than LRNI |
|---|---|---|---|
| Men | | | |
| 19–24 years | 860 | 123 | 5 |
| 25–34 years | 1017 | 145 | 2 |
| 35–49 years | 1040 | 149 | 2 |
| 50–64 years | 1027 | 147 | 2 |
| All men | 1007 | 144 | 2 |
| Women | | | |
| 19–24 years | 694 | 99 | 8 |
| 25–34 years | 731 | 104 | 6 |
| 35–49 years | 796 | 114 | 6 |
| 50–64 years | 823 | 118 | 3 |
| All women | 777 | 111 | 5 |

LRNI, lower reference nutrient intake.
Adapted from Henderson *et al.* (2003).


**Table 10** Mean daily intake of calcium and percentage contribution to the reference nutrient intake (RNI), from food sources, according to age and gender: children

| | Calcium (mg/day) | % RNI | % consuming less than LRNI |
|---|---|---|---|
| Boys | | | |
| 4–6 years | 706 | 157 | 3 |
| 7–10 years | 741 | 135 | 2 |
| 11–14 years | 799 | 80 | 12 |
| 15–18 years | 878 | 88 | 9 |
| All boys | 784 | 113 | n/a |
| Girls | | | |
| 4–6 years | 657 | 146 | 2 |
| 7–10 years | 656 | 119 | 5 |
| 11–14 years | 641 | 80 | 24 |
| 15–18 years | 653 | 82 | 19 |
| All girls | 641 | 105 | n/a |

LRNI, lower reference nutrient intake.
Adapted from Gregory *et al.* (2000).


of milk and milk products to calcium intake declines with increasing age (Gregory *et al.* 2000).

Intakes of calcium amongst vegetarians appear similar to those of omnivores, and may actually be higher amongst lacto-ovo-vegetarians. This is not the case amongst vegans, as a result of the exclusion of milk and dairy products from their diets, despite the fact that vegetable intake is greater than average. Vegans may also prefer wholemeal bread (which is typically unfortified) to fortified white or brown bread. It has been estimated, in the UK, that vegan men consume 610 mg calcium/day and vegan women 582 mg/day (Davey *et al.* 2003) and that vegans acquire over 40% of dietary calcium from vegetable sources, 33% from cereal products, and 15% from fruit and nuts; however, bioavailability may be poorer from these foods (see section 8 *Bioavailability of calcium from foods*).

### 7.3 Trends in intake

Trends in calcium intakes can best be seen from the National Food Survey (1940–2000), which has been superseded by the Expenditure and Food Survey (2001 onwards). These surveys record domestic food consumption and expenditure, and the nutrient content of food brought into private households in Great Britain, with adjustments for waste. Trends in food and nutrient intake from food surveys need to be interpreted with caution: the fact that the nutrient composition of foods will have changed with time needs to be taken into consideration. Also, values are averaged across the household and refer to the nutritional value of the diet as brought into the home and, until 2001, did not take into consideration foods eaten elsewhere in any detail.

Despite the fact that energy intake has apparently declined over the last 25 years, the calcium density of the diet has increased (440 mg/1000 kcal in 1975; 490 mg/1000 kcal in 2000) (DEFRA 2001). Intakes of a number of important sources of calcium have changed over the last few decades. The consumption of milk, for example, has declined over the last 30 years. In particular, whole milk intake has fallen, and this has not been fully compensated for by increased consumption of semi-skimmed milk (see Fig. 10). The consumption of

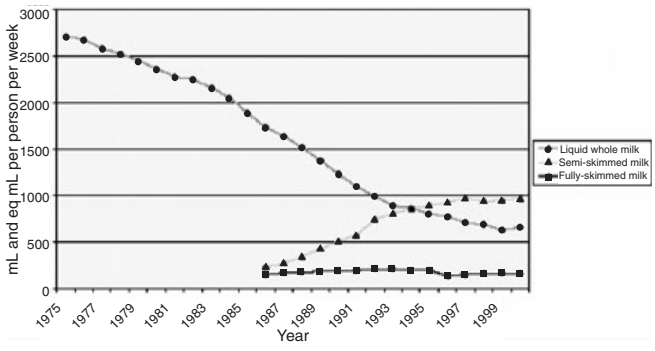


**Figure 10** Household consumption of milk, 1975–2000 (from DEFRA 2001).

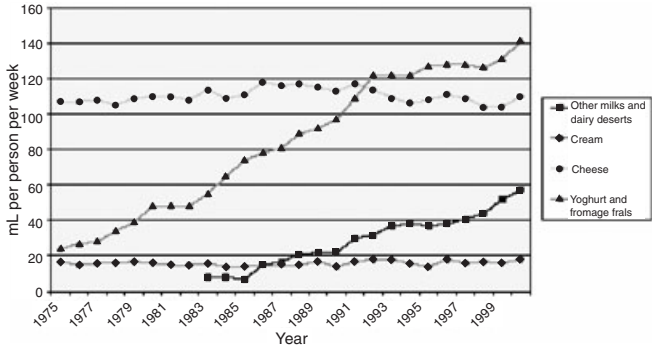


**Figure 11** Household consumption of other milk and milk products, 1975–2000 (from DEFRA 2001).

yoghurts and other dairy desserts have increased six-fold over the last 25 years, but consumption of powdered milk has fallen by 75%. Consumption of other milks (*e.g.* goat's milk, sheep's milk and soya alternatives to milk) has risen by a factor of 6 (see Fig. 11) but still represents a small proportion of intake (DEFRA 2001). The consumption of bread in the home has declined over time, but this may be the result of more individuals purchasing ready-made sandwiches during work hours.

## 8 Bioavailability of calcium from foods

The bioavailability of calcium from foods can be defined as the amount of calcium from different foods and diets that can be utilised by the body for normal metabolic functions. The definition, therefore, encompasses both absorption and retention of calcium, as well as a measure of utilisation of the absorbed calcium.

There are a number of physiological and dietary variables that influence calcium bioavailability. Physiological variables include calcium and vitamin D status, age, pregnancy, lactation and disease. Dietary variables include foods/nutrients that inhibit or promote absorption. It is worth noting, however, that it is often difficult to dissociate dietary factors from some of the physiological variables.

### 8.1 Dietary factors affecting calcium absorption

The physical form of dietary calcium influences its absorption and bioavailability. The relative solubility of calcium complexes in the stomach and intestine is important; gastric acid causes ionisation of calcium and increases calcium absorption, particularly from sparingly soluble compounds. The chemical form of calcium also influences bioavailability; for example, calcium lactate has a higher bioavailability than calcium carbonate. This is of interest as some wheat flours are fortified with calcium carbonate, whilst a number of other food products are fortified with a variety of calcium salts, *e.g.* orange juice may be fortified with calcium malate whilst calcium triphosphate is added to soya alternatives to dairy products.

A number of nutrients and other compounds present in foods have the ability to form complexes with calcium in the intestine, which can influence its absorption. For example, oxalic, phytic and uronic acids present in a number of plant foods, reduce calcium bioavailability and absorption (see section 8.2.2 *calcium from plants*). Other dietary factors are discussed below.

#### *8.1.1 Vitamin D*

Vitamin D, as calcitriol (the active form of vitamin D) influences calcium absorption across the intestine (see section 4 *Calcium homeostasis and metabolism*). An inadequate vitamin D status or intake is associated with reduced absorption of calcium from the diet. Serum calcitriol concentration is positively related to calcium absorption, even within the normal physiological range; and may account for approximately 25% of the variability in calcium absorption (Walters 2003).

Intestinal calcium absorption decreases with age. It is thought that this relates to a reduced sensitivity of the vitamin D receptor to circulating calcitriol (Pattanaungkul *et al.* 2000; Scopacasa *et al.* 2004). The absorption of calcium from a dietary supplement, in the form of calcium carbonate, is increased by the presence of vitamin D. Oral treatment with 25-hydroxyvitamin $D_3$ (the precursor of calcitriol) increases calcium absorption in elderly individuals (Francis *et al.* 1983).

#### *8.1.2 Fat*

Fat is known to influence calcium absorption, but its effect is significant only in cases of fat malabsorption, *e.g.* steatorrhoea. A high excretion of fat in the faeces is associated with increased loss of calcium, which is brought about by the formation of insoluble calcium soap complexes in the intestine through the binding of fatty acids (particularly saturated fatty acids) with calcium.

#### *8.1.3 Protein*

There has been much debate on the effect of protein on calcium absorption as well as status. Recent research indicates that calcium absorption may be positively

associated with protein intake, as measured using dual-stable calcium isotopes (Kerstetter *et al*. 1998, 2000). Diets low in protein may increase concentrations of PTH and calcitriol in the short-term (Giannini *et al*. 1999; Kerstetter *et al*. 2003), suggesting that low-protein diets may induce changes in calcium handling in the intestine and/or skeleton. Such changes may be detrimental to skeletal health in the long-term; further research is warranted.

### *8.1.4 Other dietary factors*

Other dietary components that have been reported to affect calcium absorption include caffeine and alcohol. Caffeine appears to have a slightly negative effect on calcium absorption without influencing urinary calcium excretion to any great extent (Heaney 2002). It has been shown in short-term studies that urinary calcium excretion is increased following caffeine consumption, followed by a later reduction in calcium excretion, although this does not completely compensate for calcium loss; estimated losses are 5 mg calcium per cup of coffee. This should not be of concern in individuals consuming adequate amounts of calcium.

It is well established that excessive alcohol consumption is a risk factor for osteoporosis and reduced bone mass, as demonstrated in alcoholics (Klein 1997; Turner 2000). It has been proposed that low vitamin D intakes and impaired hydroxylation of vitamin D in cirrhotic livers results in calcium malabsorption amongst chronic alcohol consumers (Sampson 1997). On the other hand, moderate alcohol consumption appears to increase/preserve BMD at a number of skeletal sites (Bainbridge *et al*. 2004; Williams *et al*. 2005). The exact mechanism by which alcohol influences bone metabolism is not clear; it appears not to be associated with changes in bone formation or resorption and therefore may be the result of changes in calcium absorption or urinary excretion. Further research is required in this area.

## 8.2 Bioavailability from different dietary sources

### *8.2.1 Milk and milk products*

Calcium in milk is considered to have a higher bioavailability than that of cereals and most vegetables, and is similar to calcium carbonate which is readily absorbed. The typical fractional absorption of calcium from milk is in the region of 30% compared to 5% from spinach (Heaney *et al*. 1988) (see Table 11).

The high bioavailability of calcium from milk may in part be due to the absence of factors that inhibit calcium absorption and a number of constituents of milk (*e.g.* lactose and protein) have been proposed to contribute positively to this high bioavailability. For example, it has been suggested that lactose may prevent or delay calcium ion precipitation, thereby increasing calcium bioavailability. However, this may not be the case as

**Table 11** Comparison of sources of absorbable calcium with milk

| Food | Serving size (g) | Calcium content per serving (mg) | Fractional absorption (%) | Estimated absorbable calcium (mg) | Number of servings needed to equal 240 g milk (total amount*) |
|---|---|---|---|---|---|
| Milk | 240 | 300 | 32.1 | 96.3 | 1.0 |
| Cheddar cheese | 42 | 303 | 32.1 | 97.2 | 1.0 (42 g) |
| Yoghurt | 240 | 300 | 32.1 | 96.3 | 1.0 (240 g) |
| Chinese mustard greens | 85 | 212 | 40.2 | 85.3 | 1.1 (93.5 g) |
| Tofu fortified with calcium | 126 | 258 | 31.0 | 80.0 | 1.2 (151 g) |
| Spinach | 85 | 115 | 5.1 | 5.9 | 16.3 (1386 g) |
| Kale | 85 | 61 | 49.3 | 30.1 | 3.2 (272 g) |
| Chinese spinach | 85 | 347 | 8.36 | 29 | 3.3 (281 g) |
| Broccoli | 71 | 35 | 61.3 | 21.5 | 4.5 (320 g) |
| Pinto beans | 86 | 44.7 | 26.7 | 11.9 | 8.1 (697 g) |
| Rhubarb | 120 | 174 | 8.54 | 10.1 | 9.5 (1140 g) |
| Bok choy | 85 | 79 | 53.8 | 42.5 | 9.7 (825 g) |
| Sweet potatoes | 164 | 44 | 22.2 | 9.8 | 9.8 (1607 g) |

*Total amount in g needed to provide the same amount of calcium as a 240 g serving of milk.

Source: Weaver *et al.* (1999), based on US calcium concentrations. Reproduced with kind permission of the author.

calcium absorption from cow's milk and specially formulated lactose-free milk appears similar. Another proposed milk constituent is the sugar lactulose, which has been shown to increase calcium absorption in a dose-dependent manner in both animals and humans. Further research needs to be conducted to determine whether lactulose increases absorption in the long-term and also to determine the mechanism involved. A role for the milk protein, casein, has also been proposed. Casein phosphopeptides form during food processing or digestion and prevent the formation of insoluble calcium salts, potentially increasing the proportion of soluble calcium within the intestinal lumen and thus calcium absorption. Data from animal studies support this hypothesis; however, there have been few human studies and the data that exist are currently equivocal. Again, further research needs to be conducted in this area.

Non-digestible oligosaccharides, such as inulin and oligofructose, are sometimes added to milk products (*e.g.* yoghurts), which are marketed as functional foods. There is evidence to suggest that the addition of these can promote calcium absorption in the short-term; however, their long-term effect has yet to be determined (Cashman 2002).

Although it is difficult to measure calcium absorption in infants, there is little doubt that calcium is better absorbed from human breast milk than from cow's or formula milk. In order to compensate for this difference in fractional absorption, many commercial formulae contain additional calcium; however, whether this additional calcium is absorbed and retained is not known. This difference in absorption may be related to the amount and nature of the fatty acids present in the milk fat, coupled with a favourable calcium to phosphorus ratio in breast milk.

The sole source of calcium for infants prior to the introduction of weaning foods (typically around the age of 6 months) is milk (breast or formula milk). The average calcium content of mature human milk is 35 mg/100 g (FSA 2002); maternal diet will have little effect on the calcium content of breast milk. It is recommended by statutory instrument that formula milk (cow's milk modified to mimic the nutrient composition of mature breast milk) intended for term infants contains 50 mg calcium/100 g (Thomas 2002).

### *8.2.2 Calcium from plants*

The presence of oxalic, phytic and uronic acids in some plant foods decreases the bioavailability of calcium, as these compounds inhibit calcium absorption. Foods containing high concentrations of oxalic acid include spinach, sorrel, rhubarb, walnuts, celery, okra and beans, whilst foods containing high concentrations of phytic acid include unleavened bread, nuts and grains. As a result, calcium in plant foods is not generally readily absorbed, although there are exceptions (see Table 11).

Many green leafy vegetables (*e.g.* spinach) are rich in calcium, but contain oxalate, which reduces the bioavailability to about 5%. Not only does soluble oxalate render the calcium present in the food itself unavailable, it can also influence the absorption of calcium from other foods consumed at the same meal, such as milk. Calcium is more bioavailable from plant foods such as broccoli, sweet potatoes, kale, bok choy, and other Chinese greens (but not Chinese spinach), which contain lower concentrations of oxalic acid (Fishbein 2004).

Phytic acid combines with calcium to form an insoluble calcium–phytate complex that cannot be absorbed, and reduces calcium absorption in a dose-dependent fashion. Phytic acid present in food can be destroyed to some extent by digestion, food processing and cooking.

Soya beans and soya products are a notable exception amongst plant foods. Soya beans contain high quantities of both oxalates and phytates, yet provide a bioavailable source of calcium (30–40% is absorbed) (Heaney *et al*. 1991). This is not the case for other beans that contain high concentrations of phytate; calcium bioavailability is generally in the region of 20% (Weaver *et al*. 1993). The bioavailability of calcium from soya products depends on the product; for example, the type of coagulant used to precipitate soya protein in the production of tofu influences calcium content (see Table 6) and bioavailability (Fishbein 2004). Many soya alternatives to milk are fortified with calcium (predominantly as tri-calcium phosphate); the bioavailability of (added) calcium from these fortified soya products is estimated to be 75% of the bioavailability of calcium from cow's milk (Heaney *et al*. 2000).

It had been suggested that dietary fibre inhibits absorption of calcium from plant foods, although this has been refuted. The term dietary fibre is not always used consistently and the dietary fibre composition of plants is not uniform, making it hard to interpret its influence on calcium absorption. It is therefore important to look at individual fractions of dietary fibre. Resistant starch has been shown to increase calcium absorption in rats and humans, probably as a result of a reduction in pH in the caecum, which increases the solubility of calcium making it more bioavailable (see Nugent 2005). Also resistant starch increases the production of short chain fatty acids, which increase cal-

cium absorption in the proximal colon. Data from animal studies also suggest that calcium absorption is increased with consumption of soluble fibres such as guar gum and polydextrose (Hara *et al.* 2000). Further research needs to be conducted to determine the influence of different fractions of dietary fibre on calcium absorption, especially in humans.

Data from *in vitro* models of calcium absorption suggest that phytates have the greatest inhibitory effect on calcium absorption when compared to other components of plant foods including oxalates, and wheat and barley fibre extracts (Kennefick & Cashman 2000b). It is believed that this is why calcium bioavailability from cereal products is low, rather than the high-fibre content *per se*.

#### *8.2.3 Other food sources*

Based on a meta-analysis of six studies, the bioavailability of calcium from mineral waters is equivalent to that of calcium from milk and dairy products, or slightly better (Böhmer *et al.* 2000). Fractional calcium absorption rates from mineral water vary between 23.8% and 47.5% (absorption of calcium from milk and dairy produce is in the region of 30%). However, mineral waters cannot be compared directly to milk and dairy products as a source of calcium as the concentrations of calcium vary considerably, and are generally far lower.

## 9 Bone calcium loss

### 9.1 Bone calcium loss

Even in healthy young adults, net loss of calcium from bone will eventually arise if the output from the body regularly exceeds the net absorption from the intestine. This happens as a matter of course from around the mid-thirties (earlier at some skeletal sites). The main routes of loss of calcium from the body are via the faeces and urine and, in a pregnant or lactating woman, the developing fetus and breast milk, respectively.

Calcium is lost from bones when there is complete physical inactivity; bone mass is rapidly reduced. This occurs in individuals who have parts of their bodies in casts after injury. Similar calcium losses occur in those who are immobilised because of denervation, as in paraplegia and poliomyelitis, and in astronauts in a gravity-free environment. The monthly net loss of bone in enforced inactivity has been shown to amount to 4% for trabecular bone and 1% for compact bone (Mazess & Whedon 1983). The main reason for this loss of calcium from bones during periods of inactivity is loss of protein from the bone matrix, which, in turn, is related to the loss of protein from other parts of the body, particularly muscle.

Calcium loss from bone may also occur as a result of extreme exercise. Although a moderate level of exercise increases bone mass, very intensive exercise may decrease it, despite the fact that local muscular activity increases local bone mass. In some female athletes, intensive exercise may result in oestrogen deficiency and amenorrhoea (absence of menstruation), which has been shown to be associated with osteopenia (reduced bone mass, reduced calcification and/or reduced bone density). Oestrogen inhibits bone resorption, although it is believed that this is not the primary reason for the osteopenia observed in some female athletes and ballet dancers. A low serum leptin (a hormone which regulates appetite, which is synthesised in adipose tissue) concentration has been shown to be associated with amenorrhoea in ballet dancers, and leptin has been shown to play a role in skeletal development in mice (Steppan *et al.* 2000). Poor nutritional status and low energy intakes have also been implicated. There is little evidence to link current dietary calcium with bone density in athletes, but there is some evidence to show that habitually low calcium intakes could lead to low bone density. The return of menstruation has been demonstrated to lead to some increase in bone mass. However, the effects of amenorrhoea in the long-term are not known; the deficit in bone mass associated with amenorrhoea may be irreversible.

#### *9.1.1 Pregnancy and lactation*

Calcium demands on the mother are high during the latter stages of pregnancy and during lactation. The skeleton of full-term infants contains 20–30 g of calcium, most of which is accrued during the last trimester of gestation. In order to meet the calcium requirements of the developing fetus, physiological adaptations occur in the mother. Fractional calcium absorption is increased from 20–30% to up to 60% during the last trimester; this increase is associated with an increased plasma concentration of calcitriol, suggesting vitamin D plays a role. In addition, the hormones oestrogen, lactogen and prolactin may stimulate increased calcium absorption. Calcium reabsorption in the kidney tubules is increased, aiding calcium retention (although total urinary calcium excretion also increases as a result of increased calcium absorption). Increased bone mineral resorption from the mother's skeleton liberates calcium, making it available for the developing fetus. The measurement of markers of bone resorption and formation during pregnancy

suggests that maternal bone turnover is increased during pregnancy and longitudinal studies suggest that maternal BMD falls significantly (Ulrich *et al*. 2003; Pearson *et al*. 2004). It appears that about 5% of calcium is mobilised from both trabecular and cortical sites, notably at the lumbar spine, femoral trochanter and femoral neck (hip) (More *et al*. 2001; Pearson *et al*. 2004).

During lactation, approximately 250 mg of calcium is secreted in breast milk each day. Maternal urinary calcium excretion is reduced and bone resorption increased to meet the increased demands for calcium during lactation. There is a recommended increment in the RNI for calcium (+550 mg/day) during lactation, although this may not be necessary (see section 5 *Dietary reference values*). Unlike during pregnancy, calcium absorption is not increased *post-partum* until periods return (Kalkwarf *et al*. 1996), resulting in a reduction in BMD. Following the resumption of menstruation, whether the mother is breastfeeding or not, calcium absorption increases and BMD begins to increase (to within 5% of pre-conceptional values within one year of birth). This increase in calcium absorption is believed to be the result of increased oestrogen concentrations (concentrations are reduced during lactation), stimulating calcitriol production, which acts to increase BMD, compensating for the calcium drain of pregnancy. This increase in maternal intestinal absorption along with a reduction in urinary excretion will compensate, or at least mostly compensate, for the reduction in maternal BMD that occurs during pregnancy and lactation (Kolthoff *et al*. 1998; Hopkinson *et al*. 2000).

Age-related loss of bone is another reason for calcium loss from the skeleton. From the age of 30–35 years (earlier at some skeletal sites), both mineral (including calcium) and protein matrix are removed from the inner surface of the marrow cavity of bone at a more rapid rate than bone is added in the outer sub-periosteal surface; the cortex of long bones becomes progressively thinner and thus more liable to fracture. The vertebrae also lose bone substance; the vertebral bodies collapse becoming wedge-shaped, end plates become concave and the intervertebral discs expand.

The amount of bone tissue per unit volume of bone a person has at a particular age is a function of the PBM achieved in early adulthood (see section 2.4 *Attainment of PBM*) and the timing and subsequent rate of loss of bone. There is no evidence that people with the least amount of bone at the start of adult life are those destined to lose the most bone with advancing age. Nonetheless, young adults with a PBM in the lower part of the normal range could form the majority of those likely to present with fractures in old age. This is because the amount of bone present at the onset of bone maturity is a critical determinant of the amount present at a later age.

From a variety of observations and measurements, it has been concluded that PBM is reached in the mid-thirties (but may be reached as early as the late teenage years depending on the skeletal site). This is followed, in both genders, by a slow phase of bone loss which persists into old age. Bone loss is particularly accelerated for a period of 5–10 years or so after the menopause. The timing of the onset of the bone-wasting process appears to vary with the type of bone tissue. Loss of compact bone seems to start between age 40 and 50 years. Trabecular bone appears to be lost from an earlier age.

It seems likely that the primary cause of calcium loss from the skeleton is loss of the matrix protein in which the mineral is embedded, which is part of the general age-related loss of protein from the body as a whole. Since bone mineral and matrix are lost together, calcium is inevitably removed from the bone along with protein. This is the same course of events that occurs in enforced inactivity, and inactivity in old age must certainly hasten calcium loss. A low calcium intake coupled with secondary hyperparathyroidism or vitamin D deficiency may also increase bone resorption.

### 9.2 Factors affecting age-related bone loss

A large number of factors influence age-related bone loss (summarised in Table 12). Gender is one such

**Table 12** Factors which influence the rate of age-related loss of bone

| |
|---|
| Factors increasing risk of bone loss |
| Immobility |
| Deficiencies of sex hormones (particularly female) |
| Thinness (being underweight) |
| Cigarette smoking |
| Alcohol consumption |
| Corticosteroids |
| Thyrotoxicosis |
| Chronic liver disease |
| Intestinal malabsorption |
| Anorexia nervosa |
| Factors decreasing risk of bone loss |
| Physical activity (especially weight-bearing activity) |
| Hormone replacement therapy (postmenopausal women) |
| Diuretic use (thiazides) |
| Obesity and being overweight |

Adapted from BNF (1989).

factor; women lose more bone than men, especially around the time of the menopause, when loss of both trabecular and compact bone is accelerated due to a reduction in oestrogen production. Losses can be prevented or modified by oestrogen replacement therapy if given at the appropriate time. Following the menopause, the rate of loss of bone declines in a curvilinear fashion to become equivalent to the pre-existing rate of loss after about 10 years. In men, the loss of bone mineral is associated with an age-related decline in gonadal function.

Genetic factors influence BMD. It has been reported that a family history of osteoporotic fracture is associated with an increased risk of fracture in offspring (Seeman *et al*. 1989; Keen *et al*. 1999). A few candidate genes have been associated with reduced bone mass and increased risk of osteoporosis, these include polymorphisms of genes encoding for the vitamin D receptor, the α-oestrogen receptor and the cytokine, (a regulatory protein released by immune cells, which acts as mediators of the immune response) interleukin-6 (Ralston 2003). Other factors associated with decreased bone density include a low bodyweight, alcohol consumption, cigarette smoking, amenorrhoea (absence of menstruation), lack of previous use of oral contraceptives, nulliparity and physical inactivity.

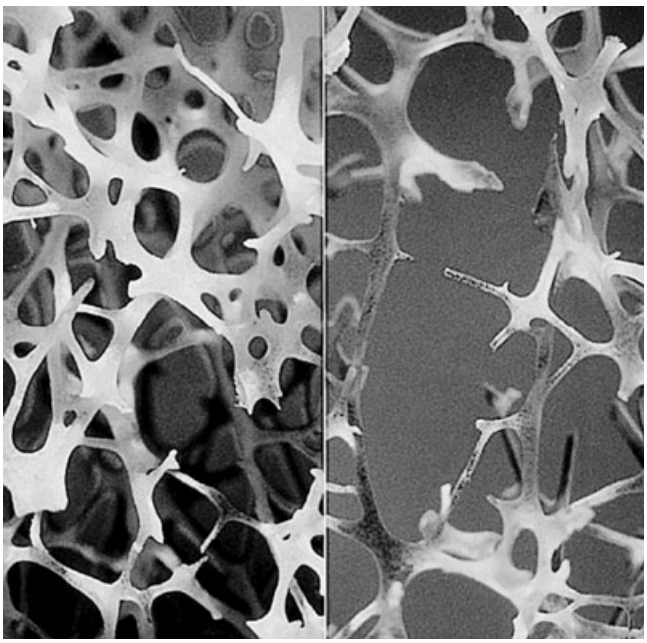

**Figure 12** Normal (left) and osteoporotic bone (right). (source: http://www.osteofound.org/press_centre/images/visuals_bone_xl.jpg).

## 9.3 Osteoporosis

### *9.3.1 Definition*

The WHO defines osteoporosis as 'a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk' (WHO 1994) (see Fig. 12). Osteoporosis is defined as a BMD value of more than 2.5 standard deviations below the population average for young adults, whilst osteopenia (characterised by reduced calcification of bone, reduced density and/or mass) is defined by a BMD value of between 1 and 2.5 standard deviations below the population average. Fractures of the vertebrae, forearm and femoral neck are the most common fractures associated with osteoporosis. Newton-John & Morgan (1968) described osteoporosis as the extreme of the normal atrophy of bone associated with ageing.

### *9.3.2 Public health implications*

Osteoporosis affects millions of people around the world; the WHO cites osteoporosis as the second leading healthcare problem (after cardiovascular disease) in the world (WHO 2003b). Individuals with osteoporosis are four-times more likely to suffer a fracture than individuals with normal bone density. Osteoporosis is associated with morbidity and increased risk of death, especially if fractures occur in the femoral neck. It has been estimated that each year osteoporosis costs the UK economy £1.7 billion (Scott Russell *et al*. 2003) and that each hip fracture costs the NHS £20 000 (Torgerson *et al*. 2000). An estimated 3 million individuals in the UK are believed to suffer from osteoporosis; that is 1 in 3 women and 1 in 12 men aged over 50 years. Each year there are at least 70 000 hip fractures, 50 000 wrist fractures and 120 000 spinal fractures associated with osteoporosis in the UK (National Osteoporosis Society 2001).

The incidence of fracture increases with age; nearly 50% of hip fractures occur in individuals over the age of 80 years. The incidence of osteoporosis in the UK is likely to rise as the proportion of the population aged over 60 years increases; it has been forecast that by the year 2030, over one-third of the UK population will be aged over 60 years. This will, of course, increase the economic burden associated with the disease. The incidence also varies with ethnicity, being much less common amongst African-Caribbean populations.

BMD in older adults predicts future risk of fracture. The risk of fracture is significantly lower in men than women at any given age, with fracture risk in men lag-

ging 5 years behind women (De Laet *et al.* 1997). It is hard, however, to extrapolate data for BMD in younger subjects to their future risk of osteoporosis (Prentice *et al.* 2003).

BMD can be measured at various sites in the body using a number of methods, all of which can be used to diagnose osteoporosis. Two-dimensional dual-energy X-ray absorptiometry (DEXA) is used most commonly and can be used to measure bone mineral content in the spine, hip, forearm, finger and heel, as well as for assessing the bone mass of the whole body. Other techniques include 3-dimensional computed tomography (CT) scans or scanning electron microscopes and quantitative ultrasound.

### *9.3.3 Primary and secondary osteoporosis*

It is conventional to classify osteoporosis as either primary or secondary osteoporosis. Primary osteoporosis includes involutional (postmenopausal and age-related) forms and so-called idiopathic osteoporosis of premenopausal women and young or middle-aged men. Secondary osteoporosis arises in response to an identifiable catalyst, *i.*e. it is secondary to an underlying condition or therapeutic treatment (*e.g.* resulting from long-term corticosteroid therapy, rheumatoid disease, chronic liver disease or intestinal malabsorption).

In primary osteoporosis, when the amount of bone falls below a critical level (the fracture threshold), bones become vulnerable to fracture and break in the face of forces they would normally withstand. Affected people can then be regarded as having the clinical syndrome of osteoporosis. Clearly, some people reach this stage at an earlier age than others, and do so either because of accelerated losses of bone or because they had formed too little bone at the onset of maturity, or both. Primary osteoporosis can be classified as type I (early onset or postmenopausal osteoporosis) or type II (senile osteoporosis). Individuals with type I osteoporosis have less trabecular bone than is normal for their age, and appear to lose bone at an accelerated rate. Individuals with type II osteoporosis are generally older and experience reductions in the amounts of trabecular and compact bone in keeping with their age. Patients with type II osteoporosis typically present with fracture of the femoral neck. The low densities of compact and trabecular bone are clearly related to their age but also to the amount of bone present at the onset of skeletal maturity. The clinical features of type I and type II involutional osteoporosis are illustrated in Table 13. Vertebral fractures occur in both type I and type II osteoporosis: typically crush fractures are associated with type I osteoporosis and wedge deformities of the vertebrae with type II osteoporosis. Vertebral fractures can occur spontaneously or as the result of minimal trauma, such as a cough. Wedge fractures are commonly asymptomatic and predominantly occur in the mid-thoracic region of the spine. They give rise to a smooth curvature of the spine (kyphosis) often referred to as 'dowagers hump'. Crush fractures commonly cause pain of variable intensity lasting several weeks.

**Table 13** Clinical features of the two types of primary osteoporosis

| | Type I | Type II |
|---|---|---|
| Age (years) | 51–75 | > 70 |
| Sex ratio (female : male) | 6 : 1 | 2 : 1 |
| Bone loss | Mainly trabecular | Trabecular & compact |
| Rate of bone loss | Accelerated | Normal |
| Fracture sites | Vertebrae (crush)<br>Distal forearm | Vertebrae (wedge)<br>Femoral neck<br>Proximal humerus<br>Pelvis |
| Intestinal calcium absorption | Decreased | Decreased |
| Main cause | Factors related to menopause | Factors relating to ageing |

Source: Riggs & Melton (1986).

Both type I and type II osteoporosis occur through an imbalance between total skeletal bone formation and bone resorption which is sustained over many years. This negative bone balance is accompanied by a negative calcium balance, which means that over this period of time, the amount of dietary calcium absorbed and retained is insufficient to offset obligatory losses of calcium in the urine and faeces.

The intestinal malabsorption of calcium in both forms of osteoporosis has been attributed to reduced biosynthesis of calcitriol (the active form of vitamin D) and decreased sensitivity of the intestinal cells to it. In type I osteoporosis this is the secondary consequence of increased bone resorption; in type II osteoporosis it results from age-related decline in renal function (as conversion of calcidiol to calcitriol occurs in the kidney). The problem is exacerbated by the low vitamin D status of many older individuals resulting from poor diet and lack of exposure to sunlight. The net effect of these changes in vitamin D metabolism is that the efficiency of calcium absorption is reduced. This compounds the effects of a limited dietary supply of calcium, and thereby contributes to the negative calcium balance. Adaptations to reduced calcium intake can be overcome by increasing the fractional absorption of calcium, but

the capacity of the body to do this declines with advancing age.

## 9.4 Dietary calcium, bone mass and age-related loss of bone

The influence of calcium intake on the risk of osteoporosis and fracture has been the focus of much research and the subject of intense debate. Severe calcium deprivation has been shown in animals to induce osteoporosis. When calcium intakes are so low that plasma calcium ion concentrations cannot be maintained, calcium is mobilised from the skeleton.

The relation between lifelong dietary provision of calcium and bone status has been difficult to demonstrate convincingly. High intakes of milk and dairy produce during adolescence have been shown to be associated with higher bone mass in postmenopausal women and, theoretically, reduced risk of fracture. It is, however, difficult to separate the effects of calcium from other nutrients present in milk and their effects on bone mass. In spite of this, two studies have shown that a high intake of calcium during childhood and adolescence is associated with increased BMD in later life (Välimäki *et al.* 1994; Welten *et al.* 1995). Most studies suggest no significant association exists between current calcium intake and bone mass or loss. Prospective studies, overall, have not been able to establish an association between a high calcium intake and reduced risk of osteoporotic fracture.

Calcium supplementation with higher doses of calcium than normally consumed in the diet offers some protection against age-related loss of bone in men and women; the effect is strongest in those women with very low habitual calcium intakes (*i.e.* < 400 mg/day). Prospective trials of calcium supplementation on age-related bone loss report that prolonged use of a calcium supplement is associated with reduced rates of bone loss, particularly cortical bone loss in postmenopausal women [it has been suggested that ~1000 mg/day may reduce bone loss by as much as 50% (Dawson-Hughes *et al.* 1990; Reid *et al.* 1993; Aloia *et al.* 1994)]. However, the timing of additional calcium supplementation following the menopause appears to be important. This was first demonstrated by Dawson-Hughes *et al.* (1990), who reported a benefit of calcium supplementation (500 mg/day over a period of 2 years) in late-postmenopausal (*i.e.* > 5 years postmenopause) women but not early-postmenopausal women. Such an observation helps explain why not all studies conducted in postmenopausal women report a beneficial effect of calcium supplementation. At present, there is convincing evidence for a benefit of calcium supplementation in late-postmenopausal but not early-postmenopausal women, for whom there is conflicting evidence with regards to the effect.

### *9.4.1 Bone loss and calcium supplementation in early-postmenopausal women*

Bone loss is most rapid during the first 5–10 years following the menopause as a result of reduced circulating oestrogen concentrations. This results in increased bone resorption, releasing calcium ions into the plasma. Serum PTH and calcitriol concentrations fall, together acting to reduce calcium absorption from the gastrointestinal tract. Therefore, it would be expected that calcium supplementation at this time would have a limited impact on changes in BMD; although some studies do suggest that calcium supplementation at this time can reduce rates of bone loss (Elders *et al.* 1991; Aloia *et al.* 1994). It appears that calcium supplementation may slow cortical bone loss at this life stage rather than trabecular bone loss, and this may also help explain the lack of association seen in some studies (Cashman 2002).

### *9.4.2 Bone loss and calcium supplementation in late-postmenopausal women*

In older postmenopausal women, a low intake of calcium is one reason for the increased rate of bone resorption, and it is in this age group that the evidence for increasing calcium intake is more compelling. In postmenopausal women over the age of 65 years, increasing calcium intake to 1000 mg/day through diet or a supplement was shown to inhibit bone loss over a period of 2 years (Storm *et al.* 1998). This finding supports those of other randomised controlled trials, which have shown that calcium supplementation reduces age-related bone loss and incidence of fracture (Dawson-Hughes *et al.* 1990; Recker *et al.* 1996; Devine *et al.* 1997). A recent Cochrane Review found that calcium supplementation in postmenopausal women reduces the risk of vertebral fractures, but it was unclear as to whether calcium influences the risk of non-vertebral fractures (Shea *et al.* 2004). Increasing calcium intake has been shown to reduce bone remodelling and the increase in PTH associated with ageing. However, whether such reductions in the rate of bone loss are sustained in the long-term remains to be seen.

A meta-analysis of calcium supplementation trials

suggests that skeletal preservation is greatest during the first year of supplementation and is less during the second year, suggesting that the beneficial effects of supplementation are not maintained in the long-term (Mackerras & Lumley 1997). In older men and postmenopausal women (≥ 68 years) supplemented with both calcium (500 mg/day) and vitamin D (700 IU/day) for a period of three years, BMD in the spine and femoral neck was shown to differ little from those receiving placebo two years after supplementation had ceased. A modest benefit was observed in total BMD in men, but not in women (Dawson-Hughes *et al*. 2000). It is likely, therefore, that high intakes of calcium would be required in the long-term to maintain any of the reported skeletal benefits of calcium supplementation. Large, long-term randomised controlled trials with calcium supplements are required to determine the influence of calcium supplementation on bone loss and subsequent fracture risk.

#### *9.4.3 Fracture risk*

Whilst there is evidence that a low bone mass is a strong predictor of fracture risk, and that increasing calcium intakes may help slow age-related bone losses, the effects of increased calcium intake on fracture risk are uncertain. A meta-analysis of prospective observational studies failed to show a protective effect of high dietary intakes of calcium on fracture risk in women, with the exception of a study conducted in Chinese women who initially had a very low intake of calcium (Xu *et al*. 2004). This contradicts a previous meta-analysis which reported a beneficial effect of calcium supplementation on fracture risk (Cumming & Nevitt 1997). However, the authors of the former study argue that their exclusion criteria were rigorous and that this may explain the different findings. Few randomised controlled trials have investigated the effect of calcium supplementation on bone fracture, and the results have tended to be inconsistent. A meta-analysis of five randomised controlled trails reported a non-significant trend towards reduced risk of vertebral fracture following calcium supplementation, whilst two studies showed no effect on lumbar spine fracture risk, but the number of fractures were few (Shea *et al*. 2002). A recent secondary prevention trial suggested no benefit of calcium supplementation on risk of fracture at various sites in elderly (> 70 years) men and at a dose of 1000 mg/day over a period of 2 years (Grant *et al*. 2005). Clearly, further research is required in this area to determine whether calcium influences fracture risk or not.

## 10 Calcium in health and disease

### 10.1 Calcium and cancer

Cancer is one of the leading causes of death in the developed world; 26% of deaths in the UK are attributable to this cause. Colorectal cancer is the third most common cancer in the UK. There is moderately consistent evidence to suggest that calcium has a protective effect on colorectal cancer at high intakes. Such an association may, however, be a reflection of the consumption of calcium-rich foods rather than calcium itself. Although the epidemiological data to support a positive association are inconsistent, more recent evidence from prospective cohort trials supports such a protective effect. It has been suggested that a high calcium intake (> 1000 mg/day) may reduce the risk of colorectal cancer by between 15 and 40% (Sellers *et al*. 1998; Wu *et al*. 2002; McCullough *et al*. 2003). A more recent prospective study conducted amongst more than 45 000 American women without a prior history of colorectal cancer suggested that an intake of greater than 800 mg calcium/day (from diet and/or supplements), compared to an intake of less than 400 mg calcium/day, was associated with a 25% reduction in risk of colorectal cancer (Flood *et al*. 2005). It is worth noting that the US DRI for calcium is higher than the UK RNI (see section 5 *Dietary reference values*).

Support for an inverse association between calcium intake and risk of colorectal cancer comes from animal studies, which suggest that calcium exerts anti-tumour effects in the large bowel. A meta-analysis of 24 ecological studies did not find a significant association between calcium intake and risk of colorectal cancers and adenoma (Bergsma-Kadijk *et al*. 1996), although the results of a pooled analysis of 10 cohort studies indicated an inverse association between calcium intake and cancer risk (Cho *et al*. 2004). Human calcium supplementation studies are limited. One such study suggested that calcium supplementation (1250 mg over 2–3 months) in individuals at high risk of colon cancer reduces the rates of colon epithelial cell proliferation to that of low risk subjects (Lipkin & Newmark 1985). Randomised controlled trials have also shown that calcium supplementation reduces the recurrence of colorectal adenomas (often precursor lesions of cancer); although no randomised controlled trials have been published to date investigating the effect of calcium supplementation on colorectal cancer incidence. A Cochrane review of randomised controlled trials with calcium supplements also reported a moderate, yet statistically significant, reduc-

tion in risk of adenomatous polyps, which can be used as a surrogate marker of colorectal cancer risk (Weingarten *et al*. 2004). It is worth noting, however, that only two studies met the specified inclusion criteria for the review.

Calcium supplementation may exert more pronounced protective effects on more advanced colorectal lesions compared to other types of polyps; it is these more advanced lesions that are associated with colorectal cancer (Wallace *et al*. 2004). It is not known what level of calcium intake affords protection from colorectal polyps or cancer; Wu *et al*. (2002) reported that an intake of 700 mg of calcium was associated with reduced risk of cancer, whilst Wallace *et al*. (2004) suggested that intakes of calcium in the region of 1200 mg offered the greatest degree of protection from recurrent adenomas. It has also been suggested that calcium exerts different degrees of protection dependent on the site of the lesion/cancer in the gastrointestinal tract, with some evidence suggesting that a greater degree of protection is afforded if the lesion/cancer is distally located (Wu *et al*. 2002). The effects of calcium may also be dependent on the amount of fat consumed in the diet; it has been speculated that a high intake of calcium in combination with low intakes of fat may afford greater protection against colon cancer (De Stefani *et al*. 1997).

It is thought that calcium acts via the calcium-sensing receptor, which is present on the basolateral membrane of all intestinal cells, human cancer cell lines and malignant cells in the large intestine. The receptor functions to detect changes in dietary calcium concentrations, and is able to increase intracellular calcium concentrations to exert a number of biological effects including the inhibition of growth and the promotion of differentiation and apoptosis of abnormal gastrointestinal cells (Lamprecht & Lipkin 2003).

Calcium also exerts anti-proliferative effects through its ability to bind free bile acids and free fatty acids. Free fatty acids and free bile acids in their ionised form can irritate the epithelial cells of the colon causing cell proliferation, which could lead to an increased opportunity for abnormal DNA incorporation. Neoplasia and tumour formation might eventually follow if the cells are exposed to irritating carcinogens. Any calcium that is not absorbed and passes into the colon is capable of forming insoluble calcium 'soaps' with phosphate, free fatty acids and free bile acids, thus reducing the concentrations and, therefore, toxicity of free fatty acids and free bile acids. Therefore, the less bioavailable a source of calcium is, the more likely that calcium will exert these effects. A calculation based on dietary intakes of calcium, phosphate and fat revealed that a calcium intake of 900 mg/day would be insufficient to bind all free fatty acids, free bile acids and phosphates (Newmark *et al*. 1984).

Case-control studies suggest an inverse association between calcium consumption and risk of breast cancer. Data from a prospective study, conducted amongst 4697 initially cancer-free women over a period of 15 years, suggested that calcium intake is inversely associated with breast cancer risk, although consumption of milk conferred stronger protection (Knekt *et al*. 1996). It is hard, however, to distinguish the individual effects of different nutrients present in milk and dairy produce and their role in the aetiology of breast cancer. Another prospective cohort study investigated the association between consumption of dairy products and calcium (plus vitamin D) in over 88 000 women enrolled in the Nurses' Health Study. Consumption of calcium was significantly associated with reduced risk of breast cancer in premenopausal, but not in postmenopausal women; the relative risk of breast cancer in women consuming the most calcium (> 1250 mg/day) compared to women consuming the least (< 500 mg/day) was 0.80. Relative risk can be defined as the likelihood of an adverse health outcome in people exposed to a particular risk factor, compared with people who are not exposed. So in this instance, for example, women who consume more total calcium (from diet and supplements) are on average, 20% less like to develop breast cancer than women who consume less. Considering dietary calcium in isolation, the relative risk is 0.67 (Shin *et al*. 2002). The major source of calcium in this study was milk and dairy products, again making it difficult to determine whether the association was a result of calcium or some other bioactive compound present in milk. A higher intake of calcium and also dairy produce has been reported to be associated with increased survival rates of women in this same cohort diagnosed with breast cancer (Holmes *et al*. 1999).

### 10.2 Calcium and cardiovascular disease

It has long been suggested that there is an association between cardiovascular mortality and hardness of water, with people in areas served by hard water being less prone to disease (Crawford *et al*. 1971; Pocock *et al*. 1980; Ferrándiz *et al*. 2004). This has been attributed to the calcium content of water and also magnesium.

Calcium intake has been shown to be inversely associated with risk of cardiovascular disease in epidemiological studies whilst randomised controlled trials have shown that calcium supplementation may improve

serum lipid concentrations. High intakes of calcium (≥ 1000 mg/day) may have beneficial effects on lipoprotein profiles, *i.e.* reduce total cholesterol and LDL (low density lipoprotein) cholesterol concentrations and increase HDL (high density lipoprotein) cholesterol concentration (Bell *et al.* 1992; Denke *et al.* 1993; Reid *et al.* 2002). Reid *et al.* (2002) noted a 7% increase in HDL cholesterol and a 16% increase in the HDL- to LDL cholesterol ratio following consumption of 1000 mg/calcium over a period of a year in postmenopausal women, and stated that this may be associated with a 20–30% reduction in cardiovascular events. Numerous animal studies support a hypolipidaemic effect of calcium. Calcium can bind to saturated fatty acids and bile acids in the gastrointestinal tract, causing fat malabsorption and their excretion in faeces.

Calcium is required for normal muscle (including heart muscle) contraction and relaxation, and, therefore, vascular tone and blood pressure regulation. Elevated blood pressure is a well-established risk factor for cardiovascular disease; it has been suggested that for each 20 mmHg increase in systolic blood pressure (SBP) (between the ages of 40–69 years), the risk of death from heart disease, stroke and other vascular diseases increases twofold (Lewington *et al.* 2002). Modest reductions in blood pressure can reduce rates of morbidity and mortality from stroke and coronary heart disease significantly.

A low serum-ionised calcium concentration and a low dietary intake of calcium have been shown to be associated with elevated blood pressure and increased risk of hypertension in a number of epidemiological studies, suggesting an inverse relationship between calcium intake and blood pressure. Meta-analyses of randomised controlled trials involving calcium supplementation (from diet and supplements) suggest that calcium exerts a modest hypotensive effect at high intakes in both normotensive and hypertensive individuals, and that both SBP and diastolic blood pressure (DBP) are significantly reduced (Allender *et al.* 1996; Bucher *et al.* 1996; Griffith *et al.* 1999). Griffith *et al.* (1999) reported that a pooled analysis of 42 trials gave a 1.4 mmHg reduction in SBP and a 0.8 mmHg reduction in DBP at doses of calcium greater than 1000 mg/day. It appears that calcium exerts greater hypotensive effects at initially higher blood pressures. Despite this, the current evidence does not support a role of calcium supplementation in therapeutic blood pressure reduction. The Canadian Hypertension Education Program does, however, suggest that normotensive individuals at risk of developing hypertension ensure that they consume adequate amounts of calcium (Touyz *et al.* 2004).

Dietary intervention studies in which individuals are, amongst other things, encouraged to increase calcium consumption through increased intake of reduced or low-fat dairy products have been shown to improve blood pressure. An example of this is the DASH (Dietary Approaches to Stop Hypertension) diet, which also encourages consumption of fruit, vegetables, fish, poultry, whole grains and nuts, and reductions in salt, total and saturated fat, sugar and red meat intake. The DASH diet, followed for a period of 8 weeks, has been shown to significantly lower blood pressure in individuals with mild hypertension, with and without concurrent sodium restriction (Appel *et al.* 1997; Sacks *et al.* 2001). The intervention diet provided an average of 1265 mg calcium/day compared to 443 mg/day in the control group. In hypertensive individuals, the DASH diet without concurrent sodium restriction reduced SBP by 5.5 mmHg; with concurrent sodium restriction SBP was reduced by 11.5 mmHg. Although significant reductions in both SBP and DBP were observed relative to the control group, it is hard to determine to what extent calcium contributes to the observed reduction in blood pressure as numerous dietary constituents may be involved. The reasons why the DASH diet produced such a large reduction in blood pressure have not been fully elucidated. Individually, calcium, magnesium and potassium exert modest hypotensive effects and it is thought that these nutrients act synergistically, amplifying their hypotensive effects (Sacks *et al.* 1995). It has been suggested that nutrients from food sources exert greater hypotensive effects than nutrients from supplements, due to differences in bioavailability (Sacks *et al.* 1995). Additionally, magnesium and potassium are also present in fruits and vegetables.

There have been a number of potential mechanisms proposed whereby calcium acts to control/lower blood pressure (see Kotchen & Morley-Kotchen 1994). However, further research needs to be conducted to elucidate the mechanism involved.

There is some preliminary evidence to suggest that calcium may play a role in the fetal programming of blood pressure; with maternal calcium status influencing the blood pressure of offspring later in life. Pre-natal maternal intake of calcium has been shown to be associated with blood pressure in infants, and pre-natal calcium supplementation trials have shown that calcium intake is inversely associated with blood pressure in young children (Belizán *et al.* 1997; Hatton *et al.* 2003). In addition, maternal calcium intake has been shown to be inversely associated with blood pressure in young children (Gillman *et al.* 1992). Further research needs to be conducted to confirm whether calcium intake does

contribute to fetal programming of blood pressure and to elucidate the mechanism; it has been suggested that calcium-regulating hormones, such as calcitriol and PTH are involved (Hatton *et al*. 2003).

### 10.3 Calcium and weight management

Epidemiological data, including longitudinal studies, in children point to an inverse association between calcium intake and bodyweight, percentage body fat and total body fat (Carruth & Skinner 2001; Skinner *et al*. 2003). In adults, it has been observed that calcium intake is inversely associated with lower bodyweight and a lesser gain of body fat over a period of time, and that differences in calcium intakes have been suggested to explain between 3 and 10% of the observed variation in adult bodyweight (Davies *et al*. 2000; Heaney 2003).

Evidence for a possible anti-obesity effect of calcium comes from a small number of studies conducted in overweight adults (Davies *et al*. 2000; Zemel *et al*. 2000a) and animal models (Zemel *et al*. 2000b; Shi *et al*. 2001). For example, an association between calcium intake and fat loss was noted in obese African-American adults participating in calcium supplementation trials, which increased calcium intake from 400 mg to 1000 mg for a period of a year (Zemel *et al*. 2000a). Data from a calcium supplementation trial primarily looking at spine fracture in women over the age of 60 years, suggest that a calcium intake of 1.2 g is associated with a modest weight loss of 0.33 kg/year over a period of 4 years without intentional energy restriction relative to placebo treatment (see Davies *et al*. 2000).

Only a few studies to date have investigated the effect of calcium intake on bodyweight in randomised controlled trials. Numbers have tended to be small and, therefore, results need to be interpreted with caution. In a pilot study, Zemel *et al*. (2003), randomised 16 obese subjects to consume a control diet (400–500 mg calcium/day) and 18 obese subjects to consume a high-calcium diet (provided as yoghurt) (1100 mg calcium/day) for a period of 12 weeks, whilst reducing energy intake by 2.09 MJ/day (500 kcal/day). The higher intake of calcium was associated with a greater reduction in body fat (–4.4%) compared to the control group (–2.75%, $P < 0.005$) and a significant reduction in waist circumference was observed. Subsequently, a calcium-rich diet has been reported to accelerate fat loss in obese subjects undergoing caloric restriction over a period of 6 months (Zemel *et al*. 2004). Thirty-two subjects were randomised to one of three diets with an energy deficit of 2.09 MJ/day (500 kcals/day). A control group consumed 0–1 servings of dairy products/day and received a calcium supplement providing 400–500 mg calcium/day (1200–1300 mg/day in total). A second group received a daily calcium supplement providing 800 mg calcium/day and consumed no more than one portion of dairy produce/day (total calcium intake 1200–1300 mg/day), whilst a third group consumed 3–4 servings of dairy foods/day (total calcium intake 1200–1300 mg/day). Weight loss was observed in all three groups: 6.6 kg (6.4% of initial bodyweight) in the control group; 8.6 kg (8.6% of initial bodyweight) in the high-calcium supplement group and 11.1 kg (10.9% of initial bodyweight) in the high-dairy foods group. Fat loss followed a similar trend. A change in body fat distribution was also noted, with most fat mass being lost from the trunk, suggesting that visceral fat was lost. More recently, a larger year-long study conducted in 155 healthy women of a normal bodyweight, whereby milk was used as a source of calcium, failed to report a statistically significant difference in bodyweight loss or fat mass loss between control (providing an average of 742 mg calcium/day), medium-dairy (providing an average of 1026 mg calcium/day), and high-dairy groups (providing an average of 1131 mg calcium/day) consuming isocaloric diets (Gunther *et al*. 2005).

As yet no mechanism has been identified, but it has been suggested that dietary calcium plays a role in regulating intracellular calcium concentrations in adipocytes, changes in which influence triacylglyceride stores and thus lipogenesis (fat synthesis) and lipolysis (fat breakdown). It has also been suggested that metabolic rate is increased (Zemel *et al*. 2000b; Shi *et al*. 2001; Zemel *et al*. 2004) or that calcium may influence the absorption of fat from the gastrointestinal tract, through the ability of calcium to bind fatty acids and bile acids (see section 8.1.1 *Vitamin D*) (Zemel *et al*. 2004). In a randomised cross-over trial of 10 individuals, a high intake of calcium (1800 mg/day) compared to a low intake (500 mg/day) was associated with increased faecal excretion of fat and energy over a period of a week (an increase of 8.2 g fat and 361 kJ, respectively). No change in energy expenditure or fat oxidation (a marker of metabolic rate) was observed (Jacobsen *et al*. 2005).

Further research is required in this area to determine whether or not calcium plays a role in weight management, and if so what the mechanisms may be. It is too early to promote weight-loss benefits of additional calcium.

### 10.4 Hypercalcaemia

Body calcium is under such close homeostatic control that an excessive accumulation in blood or tissues from over-consumption is virtually unknown. There are a number of conditions, however, that result from failure of the calcium control mechanisms either generally or locally. General failure of one or more control mechanisms results in hypercalcaemia (high blood calcium concentrations). Local disturbances, usually related to impaired arterial supply and consequent tissue necrosis, result in the deposition of calcium salts. Hypercalcaemia is characterised by anorexia, nausea and, sometimes, vomiting, muscle weakness, generalised itchiness and excessive thirst and urination. If onset is acute, confusion or stupor may result. Kidney failure usually occurs unless treatment is given. Hypercalcaemia occurs as a result of either increased mobilisation of calcium from bone or increased tubular reabsorption or decreased glomerular filtration in the kidneys. More than one mechanism is usually involved. The resultant increase in concentration of circulating calcium results in the deposition of calcium salts in many tissues including the heart and kidneys.

### 10.5 Calcium stone formation

Calcium salt deposition most commonly occurs in the kidneys. Between 1 and 5% of the population in the developed world are likely to form kidney stones at some time in their lives; the most common type of stones contain calcium (as calcium oxalate or calcium phosphate or both) and account for 60–80% of all stones. Kidney stones are most common in men, with occurrence being 50% greater than in women. Current theories contend that calcium stone formation is initiated by nanobacterial disease (Çiftçioglu *et al*. 1999). Nanobacteria are small cytotoxic intracellular bacteria that have a calcium phosphate shell, and it is thought that the presence of these nanobacteria in the kidney initiates stone formation and that diet and other factors stimulate stone growth. Nanobacteria have been reported to be present in 97% of kidney stones and are capable of producing stones in culture.

Risk factors for calcium stone formation can be divided into urinary and pre-urinary risk factors. Urinary risk factors include a low urine volume (the most important risk factor), excess urinary excretion of oxalate, increased urinary pH, increased uric acid excretion, and hypercalciuria. Hypercalciuria (more than 200 mg of calcium in urine/24 h) is implicated in 40–60% of kidney stone cases and may be the result of abnormally high absorption of calcium from the gastrointestinal tract, resulting in an increase in plasma calcium ion concentration, impaired reabsorption of calcium in the kidney or the presence of primary hyperparathyroidism (characterised by excessive bone resorption). Pre-urinary risk factors for stone formation include a number of environmental, epidemiological and metabolic factors, such as age, gender, season, climate and diet, along with a family history of stones, primary hyperparathyroidism and gout.

The growth of stones occurs through crystallisation when urine becomes supersaturated with calcium oxalate and/or calcium phosphate. Many stones are asymptomatic but can result in pain in the groin region, blood in the urine, and painful and slow urination.

A number of dietary factors can influence the risk of calcium stone formation; some promote stone formation, others protect. A high-calcium diet is not in itself the cause of stone formation; if anything, dietary calcium (but not calcium from supplements) reduces risk (Curhan *et al*. 2004). A high dietary intake of oxalate (present in some vegetables, *e.g.* spinach and rhubarb) increases urinary oxalate excretion and is a risk factor for stone formation in susceptible people. Individuals consuming both low amounts of calcium and high levels of oxalates are at increased risk of stones as a low calcium intake is associated with increased urinary oxalate excretion. One of the biggest myths surrounding stone formation is that calcium intake should be limited: restriction is unnecessary and may increase risk of stone formation (Martini 2002; Pizzato & Barros 2003). A high protein intake, particularly of purine-rich animal protein, is associated with increased risk of stones, as urinary excretion of calcium and oxalate is increased and urinary pH reduced.

Once an individual has had a kidney stone they have a 50% chance of experiencing a second. Dietary advice to help prevent recurrent stone formation is as follows (Parmar 2004):

- Increase fluid intake so that at least two litres of urine are passed each day;
- Reduce consumption of oxalate-rich foods (*e.g.* spinach, chocolate and rhubarb);
- Increase consumption of fruits and vegetables (that are not oxalate-rich);
- Reduce consumption of sodium;
- Consume a normal amount of dietary calcium;
- Limit consumption of animal protein.

## 11 Conclusions

Calcium plays an essential and varied role in the body and is vital for health. The majority (~99%) of calcium present in the body is found in bone, where it plays a structural function, forming an essential constituent of hydroxyapatite, a crystalline structure which provides rigidity. It is important to optimise calcium intakes to ensure PBM is maximised and to minimise age-related bone losses, as this may influence risk of developing osteoporosis later in life. Osteoporosis, typically a disease of older age, is likely to become an increasing public health problem over the next few decades as the average age of the population is increasing, and is a problem which needs to be addressed. The remainder of calcium (<1%) present in the body is found in soft tissue and body fluids, where calcium plays a life supporting functional role, as it is involved in blood clotting, muscle contraction and neurotransmitter secretion, for example.

Data from national UK surveys (*i.e.* NDNS) show that average intakes of calcium in some groups of the population are low compared to recommended intakes. For example, on average teenage boys and girls are consuming approximately 80% of the RNI for calcium, with between 10–20% of teenagers consuming less than the LRNI, an intake which is considered to be inadequate for most. Furthermore, 8% of women aged 19–24 years have an intake of calcium below the LRNI. The fact that a relatively large number of adolescents are consuming less than the LRNI is a concern particularly as there is a danger that such habits may track into adulthood. Ensuring an adequate intake of calcium during childhood and adolescence (an important window of opportunity for bone formation) is imperative for maximising PBM.

The exact impact on bone health of a long-term low calcium intake remains to be established; but it is believed that this may lead to a sub-optimal PBM being attained which has implications for risk of osteoporosis in later life. Therefore, optimising dietary calcium intakes may help increase bone mass in those children and adolescents whose intakes are low. Increasing calcium intake in later life may also help to slow bone calcium losses later in life.

Following the attainment of PBM (between the late teenage years and the mid-thirties, depending on the skeletal site), there is a gradual net loss of calcium from bones associated with a progressive loss of bone tissue which carries on into old age. Losses are accelerated in women for a period of approximately 5–10 years following the menopause, making women at particular risk of osteoporosis in later life. There is some evidence that increasing calcium intake to a level above the RNI in older men and post-menopausal women may offer some protection against age-related bone loss. The impact of additional calcium administration in post-menopausal women appears to depend on the timing and habitual calcium intake; little benefit is seen in the first five years post-menopause and the effect is strongest in those women with a very low habitual calcium intake (<400 mg/d). More research is required to determine fully whether additional calcium can benefit bone health in older men and women, and whether it can reduce the risk of osteoporosis in the long-term. In efforts to tackle osteoporosis, the relevance of other dietary factors, *e.g.* vitamin D and regular weight bearing physical activity must not be overlooked.

There is a limited amount of evidence that calcium may play a role in the prevention of chronic disease such as cardiovascular disease and colorectal cancers. More research is required to confirm such associations before specific public health advice can be issued. Many studies investigating associations between calcium intake and cancer risk use milk as a marker of calcium intake or source of additional calcium, making it hard to determine whether it is calcium or another component of milk that is influencing risk. Largely based on preliminary evidence, it has been suggested that calcium may play a role in weight management. However, to date, few human studies have been conducted in this area and such results must be interpreted with caution. Again, more research is required in this area to determine whether the effects observed to date are replicable.

Data from the UK national surveys (*i.e.* NDNS) show that milk and milk products make the biggest contribution to calcium intake in the UK (>40% in adults), followed by cereals and cereal products (providing 30% of intake in adults). It is often reported in the media that milk and milk products are a poor source of calcium, and that other foods, such as vegetables are a more valuable source. Such information is largely incorrect, and milk and milk products remain an important source of calcium. Whilst the fractional absorption of calcium present in some vegetables, such as kale and broccoli, may be higher, the absolute amount absorbed per 100 g is much less due to the lower calcium content to begin with. Bioavailability from other vegetables, such as spinach, is very poor (~5%). As mentioned above, average intakes of calcium are low compared to recommended intakes in some groups of the population, *e.g.* teenage boys and girls and young women. It is important that intakes of calcium in these groups of the population are optimised to ensure a high peak bone mass is achieved,

and public health campaigns may be required to achieve this.

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