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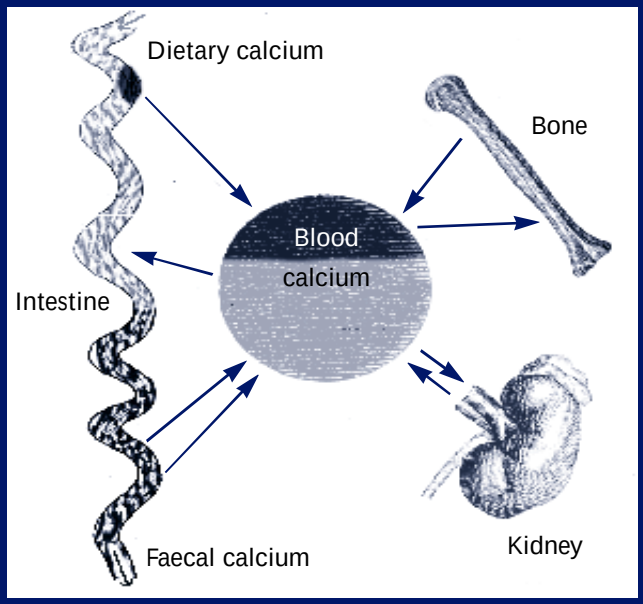

CALCIUM IN NUTRITION

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FOREWORD

Calcium is the most abundant mineral in the body. It plays an important role in the structure and the strength of bones and is also vital in the regulation of functions such as the contraction of muscles.

Dietary calcium is a focus for current attention because low intakes are thought to be a risk factor for failing to meet peak bone density and for osteoporosis. There is also an increasing interest in the possible relationships between low calcium intake and high blood pressure or greater risk of colon cancer.

ILSI Europe's Calcium in Nutrition Task Force initiated the elaboration of the current concise monograph on the state of the art of calcium in nutrition. This document will be a valuable resource for regulatory authorities, health professionals and others throughout Europe who need a better understanding of the role of calcium.

The concise monograph is based on several recent scientific reviews and is intended to update in a more concise form the previous ILSI publication, *Calcium in Human Biology* (1988). The document describes the function and metabolism of calcium particularly in relation to bone development and maintenance and explores the dietary and non-dietary (e.g., genetic and lifestyle) factors that influence bone health. Other aspects of calcium and nutrition are addressed including calcium requirements. The concise monograph also highlights some future research needs.

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INTRODUCTION: CALCIUM, A VERSATILE NUTRIENT

Calcium is the most abundant mineral element in the body. It has two key roles. A very small proportion of body calcium plays a vital part in regulating critical functions including nerve impulses, muscle contractions and the activities of enzymes. More than 99% is located in the bones, where it plays an important role in their structure and strength (see the sections on *Functions of calcium* and *Calcium in bone*). So critical is calcium's role in metabolic regulation that its concentration in the blood needs to be maintained within a narrow range. If insufficient calcium is obtained from the diet for this purpose (see *Calcium as a nutrient*), the bones act as a store of calcium from which the element can be withdrawn to keep the blood level constant (see *Calcium metabolism*). In short, we walk about on a vast store of calcium.

Whereas small reductions in the size of this calcium store have no practical significance, if protracted withdrawals from the "bone bank" occur, the structure of the skeleton will be affected and its strength compromised. Osteoporosis is a disease in which loss of bone material, including calcium, results in weakening of the bone structure, which increases the likelihood of fractures occurring (see *Calcium status and health*). Because this disease now affects an increasing number of people around the world, especially in developed countries, there is increasing interest in the role of calcium in the diet and in the body.

The aim of this Concise Monograph is to present a summary of current knowledge on all aspects of the role of calcium in human nutrition and health. An important part of the monograph is devoted to how different components of the diet, as well as many non-nutritional factors, influence the metabolism of calcium in the body, particularly in the bones. When scientific controversy exists in the field of nutrition, it often arises because the methods available for the study of human metabolism are insufficiently rigorous and lead to erroneous interpretation of data. Care will be taken in the monograph to indicate where problems of methodology exist.

It is not the purpose of the monograph to make recommendations for calcium intakes. Current views on the amounts of calcium needed under different circumstances are discussed (see *Calcium requirements*) and key issues for further research are highlighted (see *Future research needs*). References to scientific statements are not cited, but a comprehensive list of publications for further reading is presented (see *Further reading*).

In scientific writing, it is usual to refer to measurements of the amounts or concentrations of calcium in SI units (*Système international d'unités*) (moles or moles/l). However, as many readers of this monograph are likely to be more familiar with these quantities in g or g/l, the latter units have been used consistently here. The conversion factor can be found in the *Glossary*.

FUNCTIONS OF CALCIUM

The body of an adult man contains about 1.2 kg calcium, accounting for about 2% of body weight. The element is present in two body "compartments" with quite distinct functions (Figure 1). The greater part (99%) is present as a type of calcium phosphate in the skeleton, where it contributes to the mechanical properties of bone ("structural" role); about 7 g is also present in the teeth. Less than 1% is found in the soft tissues (7 g) and body fluids (1 g) where it performs several vital physiological functions ("regulatory" roles).

Structural role of calcium in the skeleton

Bone consists of protein fibres encased in a crystalline mineral. The latter is a complex salt, which is mainly a calcium phosphate but also contains other minerals. The mineral part contributes to the strength of bone because it is particularly good at resisting compression.

However, the purpose of bone mineral is not simply to provide structure and strength. The many tiny crystals that constitute bone mineral have calcium ions at their surfaces. These interact with ions in the body fluids, so that bone mineral behaves like a large ion exchanger without any net change in the amount of calcium in the bones. These properties are important in relation to the role of bone as a reserve of calcium that is able to maintain a constant concentration of blood calcium, which is needed to fulfil many vital physiological functions (see the next section on the *Regulatory roles of calcium* and the later section on *Calcium metabolism*).

A detailed description of the nature of bone and the role of calcium can be found in the section on *Calcium in bone.*

Regulatory roles of calcium

The regulatory functions of calcium can also be subdivided into "passive" and "active" functions.

Passive roles

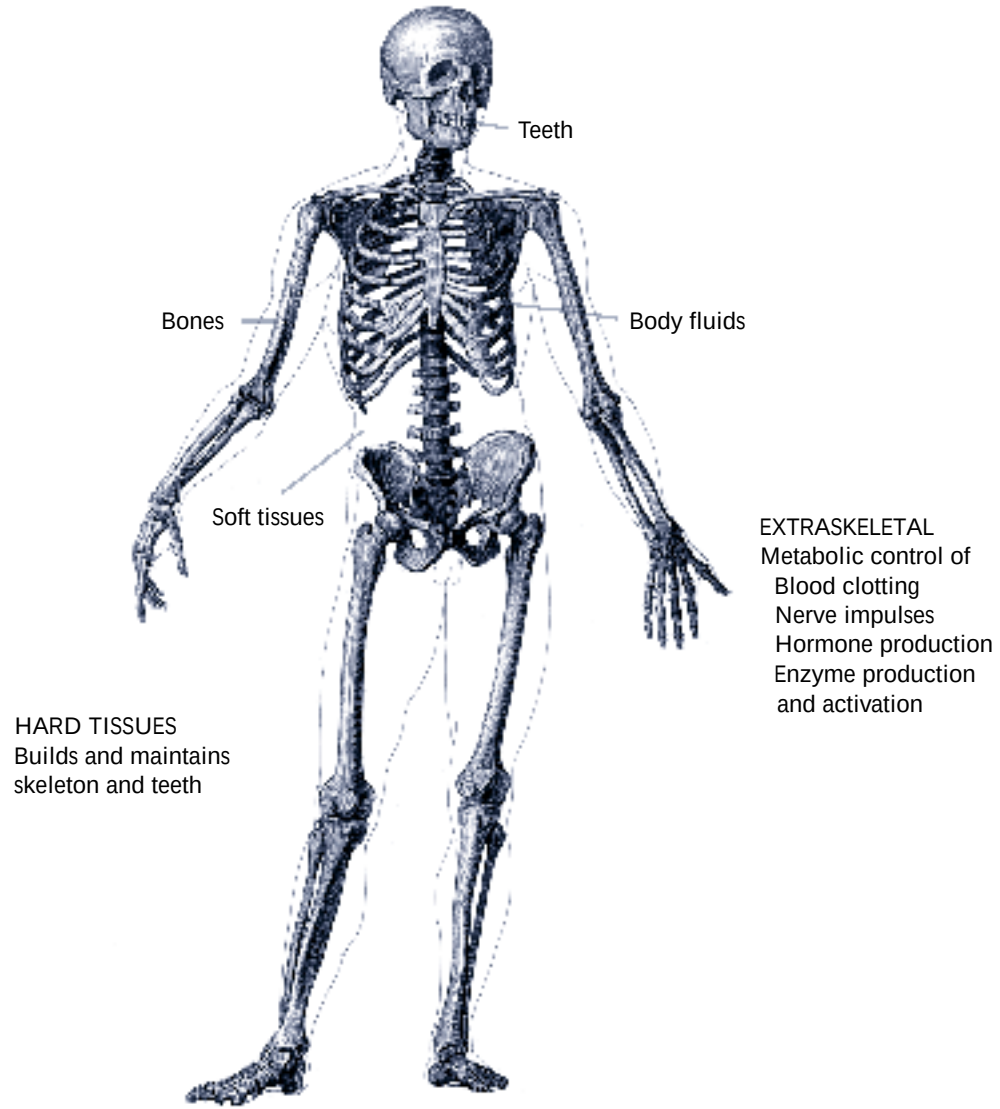
Many enzymes require a chemical association between calcium and an enzyme's protein(s) for full catalytic activity to occur. Several digestive enzymes are included in this category, as well as several enzymes in the blood-clotting cascade and the "complement" system of enzymes involved in immune defence. Such functions are not affected by changes in plasma calcium concentration (there is always sufficient calcium present for full activity), hence the term "passive".

Active roles

Calcium in the blood. Active roles refer to those functions that respond to changes in blood calcium concentration. Calcium circulates in the blood plasma at a concentration that normally lies between 90 and 110 mg/l. Calcium in the blood is involved in communications between cells and assists in regulating their behaviour. It is vitally important that the concentration of calcium in the blood plasma be precisely regulated within certain limits. This is achieved by the coordinated action of a group of hormones, principally parathyroid hormone, calcitriol and calcitonin (see the section on *Calcium metabolism*).

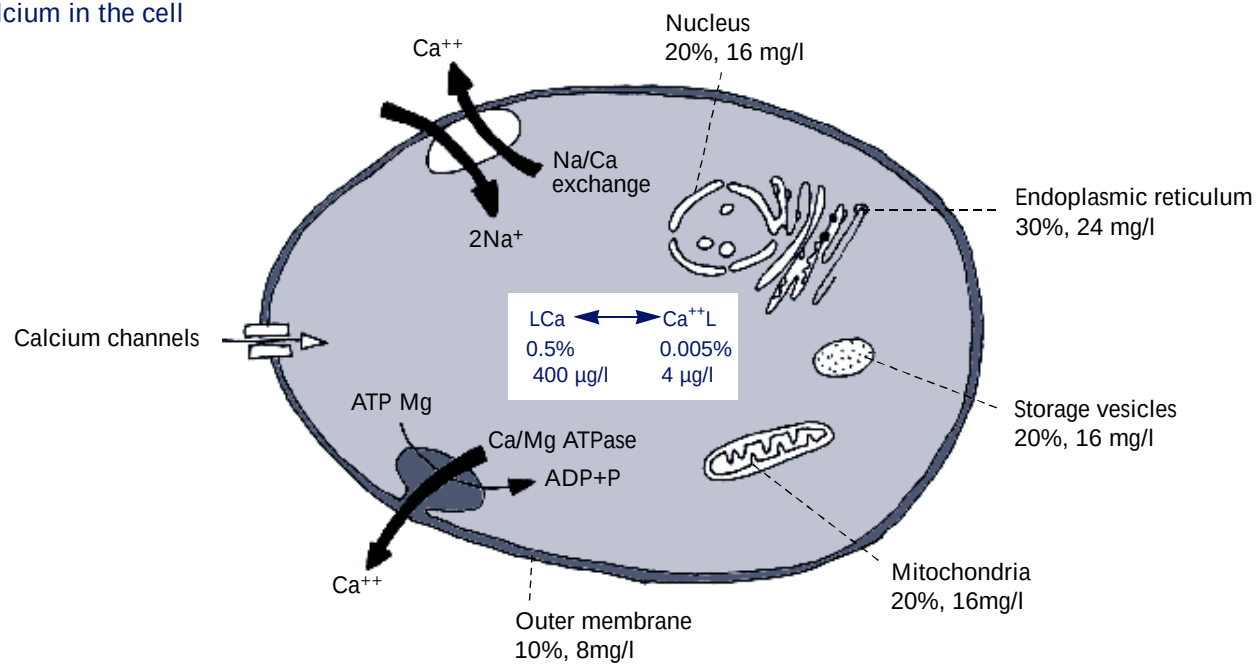
Calcium in the cells. In human cells the total calcium concentration can vary from as little as 0.8 mg/l in red blood cells to more than 200 mg/l in muscle cells or platelets with large intracellular stores. More than 99.9% of this intracellular calcium is bound to internal cellular structures including the nucleus, the mitochondria and a network of membranes called the endoplasmic reticulum (Figure 2). Some is present in specialized

FIGURE 1
Distribution and functions of calcium in the body



Most calcium in the body is present in the bones and teeth ("structural role"). Bone also provides a vast reserve of calcium for metabolic purposes. Less than 1% is present in the cells and body fluids, where it performs many metabolic and regulatory roles.

FIGURE 2
Calcium in the cell



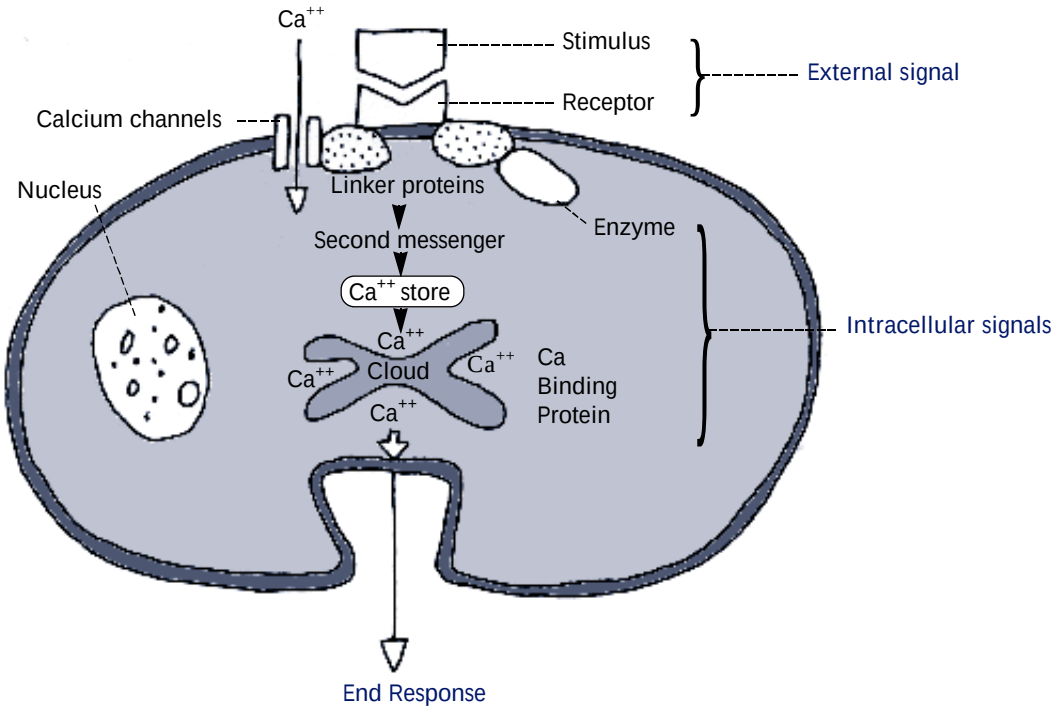
The absolute concentrations of cellular calcium are provided to indicate orders of magnitude and approximate proportions only. The calcium content differs appreciably among different types of cells. This cell's content is based on a total cell calcium concentration of about 80 mg/l. Parts of the cell membrane may be leaky to calcium ("calcium channels"), and this leakage is counter-balanced by metabolic pumps (Ca/Mg ATPase and Na/Ca exchange) which act to prevent the calcium concentration in the cell from rising too much. Calcium ions (Ca^{++}) may be exchanged for sodium ions ($2Na^{+}$) to maintain electrical neutrality. The L represents organic molecules (ligands) that form soluble complexes with calcium. These may be small molecules such as citrate or proteins.

storage vesicles. The concentration of free calcium in the cytosol (the cellular liquid as distinct from the membranous part) of a resting cell is only 4 µg / l, so that a difference in concentration of more than 10,000-fold can exist across the cell membrane.

Calcium in cell signalling. Important physiological events, such as muscle contraction, cell division, cell aggregation, enzyme secretion and many others, are brought about by a chain of cellular events that starts with a stimulus. This may be physical, such as a touch or an electrical potential, or chemical, such as a hormone or neurotransmitter. The stimulus acts at the cell membrane and transmits a signal through intracellular “chemical messengers” to structures and enzymes within the cell (Figure 3).

Calcium is one of the most important and widely occurring of these intracellular signals. Calcium that crosses the cell membrane by leakage through “calcium

FIGURE 3
Calcium as an intracellular signalling device



Calcium acts as an intracellular "messenger" in many different types of cells carrying out many different functions or "end responses". First, a stimulus or external signal is needed. The stimulus acts upon a receptor, which is a protein situated on the cell surface. In conjunction with various proteins and enzymes, the stimulus-receptor interaction results in the release, inside the cell, of a chemical substance sometimes called the "second messenger". This then amplifies the calcium content of the cell in the form of a "cloud" of calcium ions either by liberating calcium from internal stores or by enabling the calcium channels in the cell membrane to allow more external calcium into the cell. The calcium cloud then reacts at another point on the cell membrane to produce an end response, depending on the function of the cell. For example, in the cells of the adrenal gland, whose function is to make steroid hormones, the initial stimulus for the production of the steroid hormone aldosterone is the hormone angiotensin II. The end response is the production of aldosterone from cholesterol.

channels" or is released from intracellular stores can cause a very large proportionate rise in calcium concentration in the cell fluid. This can either activate the cell or, if too high, can injure it. The appropriate level of calcium in the cell is maintained by a pumping mechanism, which can counterbalance small leakages of calcium into cells. Excessive increases in intracellular calcium may injure the cell.

Defects in the calcium signalling system may occur in many diseases. Infectious agents, such as bacteria and viruses, can cause cells to become leaky to calcium, with

consequent increases in cellular calcium concentration. Malfunction of calcium-dependent processes also occurs in genetic abnormalities such as cystic fibrosis. Tissue calcification can arise after injury, so that dying cells may contain up to 10 times their normal calcium concentration. Many therapeutic agents have been devised to overcome these problems by, for example, blocking receptors and calcium channels and so preventing calcium from entering the cell.

CALCIUM METABOLISM

Because of calcium's vital role in cellular communication, it is essential that the concentration of ionized (electrically charged) calcium dissolved in the blood be regulated within narrow limits. This regulation is achieved by complex interactions between the processes of absorption and urinary excretion of calcium and bone remodelling, which are coordinated by several hormones.

Absorption

All calcium retained in the body after birth has to come from the diet. It is released from the food structure and is transferred through the gut wall into the bloodstream. This occurs either by simple diffusion or by a "pumping" mechanism that requires energy and the hormone calcitriol, which is derived by metabolism of vitamin D in the liver and kidneys (see Figure 4 and Box 1). Absorption efficiency can adapt to intake (greater at low levels of calcium intake) and physiological condition (higher during adolescence and pregnancy) and tends to decline with age.

Up to about a third of calcium from food is absorbed, the remainder being excreted in the faeces. The proportion absorbed from foods depends on how the calcium is chemically bound in the food and the presence of the many substances also present in the food, which may either enhance or inhibit absorption (see the section on *Calcium as a nutrient*).

Some calcium is lost from the tissues into the gut, for example, in secretions from the saliva, pancreas and bile duct, and from cells that are discarded from the intestinal lining. This is known as "endogenous secretion" (Figure 4). Because endogenously secreted calcium is not all reabsorbed, overall absorption is reduced: it is the net absorption that is nutritionally relevant.

BOX 1

Calcium absorption

Absorption processes

There are two main processes by which calcium is absorbed. First, there is a process of simple passive diffusion, whose rate depends mainly on the concentration of calcium in the lumen of the intestine and to some extent the rate of water absorption. The second, "active transport", is effectively a pumping mechanism that, unlike passive absorption, depends on a source of energy and a carrier molecule. Active calcium transport is regulated by a metabolic product of vitamin D (cholecalciferol). The vitamin is modified by metabolism, first in the liver, and then in the kidneys, to a hormone, calcitriol. (The widely used name "calcitriol" will be employed in this monograph instead of the more scientific, chemical term "1,25-dihydroxy-cholecalciferol".) Calcitriol stimulates the synthesis in the upper part of the small intestine of a calcium-binding protein, which carries the calcium across the gut wall. This process operates at very low concentrations in a specific part of the small intestine, whereas passive diffusion occurs in all parts of the gut and depends on high concentrations of calcium. It has been suggested that passive absorption in the colon may be important in salvaging calcium that has been prevented from being absorbed in the small intestine by the presence of, for example, phytic acid associated with dietary fibre. However, such absorption is minimal and may be offset by calcium in colonic cells shed into the large bowel.

In healthy people consuming amounts of calcium within the normal range, about half the absorption is active and about half passive. Kidney failure leads to deficiency of calcitriol and poor active transport of calcium. This can be overcome to some extent by increasing calcium intake. Calcium absorption efficiency declines with age, reflecting either reduced ability to make calcitriol or, more probably, lower vitamin D receptor activity.

Measurement of calcium absorption

A traditional method for the measurement of calcium absorption has been to measure calcium excreted in faeces over a defined period and to subtract this quantity from calcium consumed in the same time (the "metabolic balance" method). This provides a figure for "net absorption", since it includes endogenous secretion (i.e., calcium secreted from the body into the gut via the bile, pancreatic juices, etc.). This is a nutritionally relevant measurement, but it is technically difficult because of the problem of collecting faeces completely. Moreover, it provides an overall estimate of absorption from the whole diet but cannot provide information on absorption from individual foods. The best currently available method to study absorption employs either radioactive or stable isotopes of calcium. One is used to label the food under investigation; the other is injected intravenously. Urine is collected over a period exceeding 20 hours after dosing, and the amounts of the label excreted in urine are measured by a radioactivity counter (for radioisotopes) or by mass spectrometry (for stable isotopes). Alternatively, some research workers prefer to take a blood sample and measure the blood concentration of the isotope at specified times. The isotope that was injected intravenously represents a standard that is equivalent to 100% absorption, and the ratio of the ingested isotope to this standard enables gross absorption to be calculated. This method can be applied to individual foods and can be used with great precision.

Urinary excretion

Once calcium has been absorbed into the bloodstream, the main losses from the body are normally by excretion in the urine. (Very small losses also occur through the hair and skin and in sweat. However, losses in sweat may be proportionately much larger in athletes after strenuous exercise.) The kidney, which is an efficient device for filtering blood to remove unwanted substances, reabsorbs 98-99% of the calcium that it filters. There is considerable variation in the amount of calcium excreted daily in the urine of healthy men and women. The variation arises from differences in age (reduced excretion in very old age) and sex (greater excretion in men than in women, and greater in women at the menopause). Excretion also increases with high intakes of sodium and protein and, to a lesser extent with increasing intakes of calcium in the diet. It tends to decrease with high intakes of phosphorus (see Table 1).

Calcium in blood

Despite considerable variations in the intake, absorption and excretion of calcium, its concentration in the blood remains remarkably constant. This occurs because there are precise control mechanisms in place to ensure that calcium is always available to facilitate efficient communication between cells and to ensure that their behaviour is appropriately regulated. Calcium circulates in the blood in three main forms: (i) bound to proteins (about 45%), (ii) complexes with citrate, phosphate or bicarbonate (about 10%) and (iii) as free calcium ions (Ca^{++}, about 45%). The ionized form is physiologically important, and its concentration is regulated through the integrated actions of three hormones. The concentrations of these hormones, parathyroid hormone, calcitriol and calcitonin, respond to changes in concentration of calcium ions in the plasma by a process of "negative feedback" (Figure 4). In brief, when the blood calcium concentration is too low, parathyroid hormone and/or calcitriol bring blood calcium concentration up to the required level by mobilizing calcium from bone, increasing its absorption or encouraging its reabsorption from the kidneys. When the blood calcium concentration is too high, calcitonin ensures that calcium is shifted back into bone or excreted in urine (see Figure 4 and Box 2).

TABLE 1

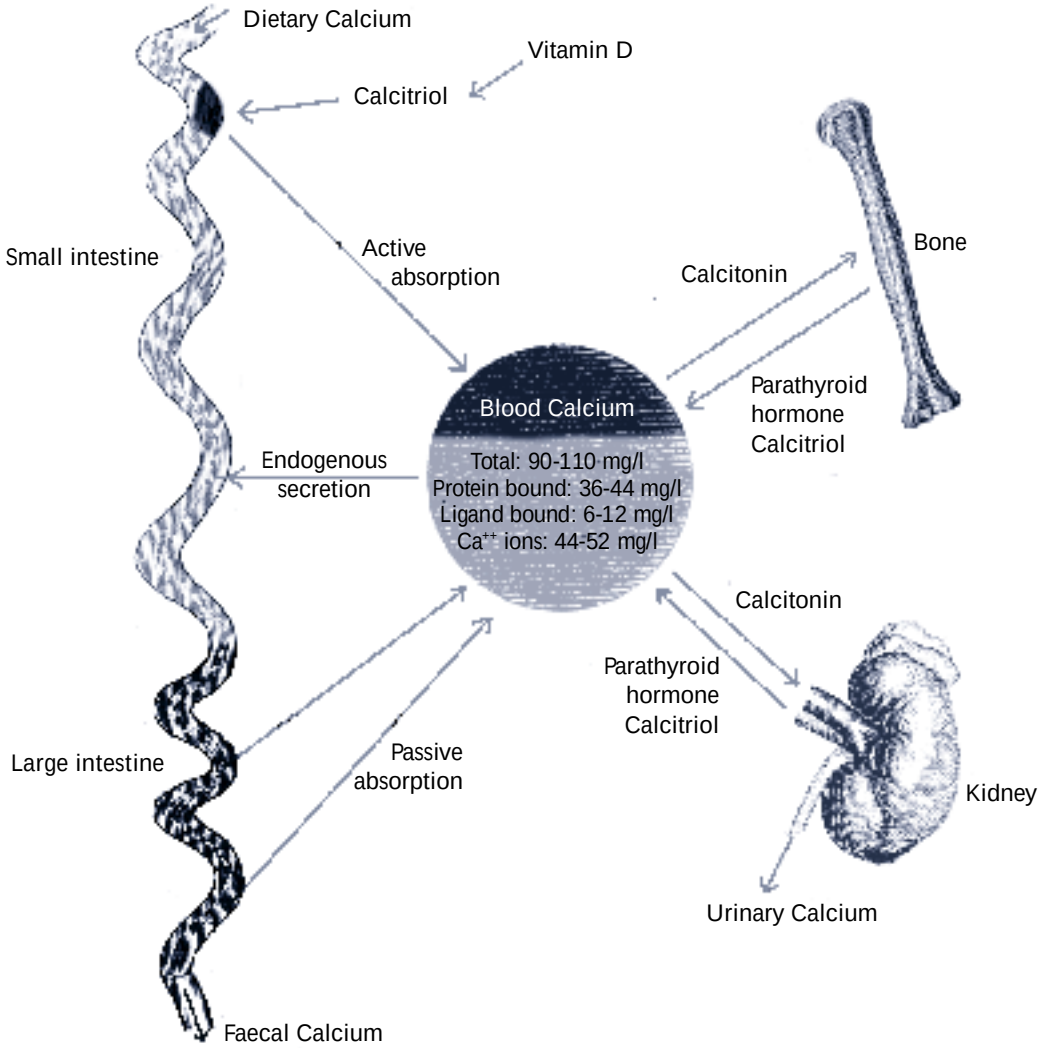
Dietary factors affecting calcium absorption efficiency

	Absorption	Urinary loss
Protein	0	+
Fat	–[a]	0
Lactose	+	0
Fibre		
Soluble	0	0
Insoluble	0	0
Phosphorus as:		
Orthophosphate	0	–
Phytate	–	0
Phosphopeptides	?	0
Oxalate	–	0
Caffeine	–[b]	+[c]
Sodium	0	+
Vitamin D	+	–
Alcohol	0	+

\+ Indicates that the substance increases absorption or urinary calcium loss.
– Indicates that the substance decreases absorption or urinary calcium loss.
0 Indicates no effect.

[a] Significant only in cases of fat malabsorption.
[b] Few studies; small effect.
[c] Few studies; short-term effect only.

FIGURE 4
Regulation of calcium levels in blood and tissues



The concentration of calcium in the blood is regulated within narrow limits. This is achieved in several ways. The amount absorbed from the intestine can be controlled by the hormone calcitriol, which is produced from vitamin D (see also Box 2). Bone represents a large store of body calcium. When blood calcium concentration is too low, it can be increased by mobilization of calcium from bone by the action of parathyroid hormone or calcitriol, or if too high, calcium moves into bone through the action of calcitonin. Calcium is filtered from blood in the kidneys and excreted in urine. Urinary loss is reduced mainly by the action of parathyroid hormone and calcitriol and may be increased by the action of calcitonin.

BOX 2

Hormones regulating blood calcium levels

Parathyroid hormone plays the key role. It is secreted from the parathyroid gland when the concentration of Ca^{++} ions falls below a certain "set point" and acts by controlling the amount of calcium excreted in the urine. It also promotes the metabolism of vitamin D to calcitriol in the kidney and thus indirectly affects intestinal absorption. Parathyroid hormone is also a key regulator of bone remodelling and, hence, the release of calcium from bone.

Calcitriol promotes the active absorption of calcium from the small intestine and enhances the reabsorption of calcium by the kidneys. Increases in dietary calcium lead to decreases in the concentration of calcitriol in the plasma, probably through the influence of parathyroid hormone. Calcitriol may also act directly on bone. Together, calcitriol and parathyroid hormone stimulate release of calcium from bone into blood (resorption) and its reabsorption from the kidneys, thus helping maintain the blood calcium concentration.

Calcitonin decreases the concentration of Ca^{++} ions in blood, in contrast to calcitriol and parathyroid hormone. Its secretion is stimulated by increases in blood Ca^{++} concentration, even within the normal range. It inhibits the release of calcium from bone and acts on the kidney to promote calcium excretion in urine.

Bone metabolism

Bone tissue is continuously being made and broken down by specialized bone cells in a process known as "turnover". Most bone turnover is accomplished by a process known as "remodelling", which is described in detail in a later section, *Calcium in bone*.

When bone mass is constant over a period of time (e.g., in middle age), the rate of bone formation is equal to the rate of loss because calcium and other bone constituents are continuously being incorporated into, and lost from, bone. During bone growth in early life, turnover continues all the time but the rate of bone formation exceeds that of bone loss (resorption), resulting in net accretion. Later in life, resorption exceeds formation, resulting in net bone loss.

The extent to which nutrition, including dietary calcium, influences bone turnover is an important area of current research and will be discussed in more detail in a later section. Briefly, increases in dietary calcium tend to depress bone turnover, whereas reduced intakes increase it. It is important to take into account dietary effects on remodelling when trying to interpret results of studies designed to investigate effects of dietary calcium on peak bone mass and on bone loss (see the sections on *Calcium in bone* and *Dietary calcium, bone development and maintenance of skeletal mass*).

CALCIUM IN BONE

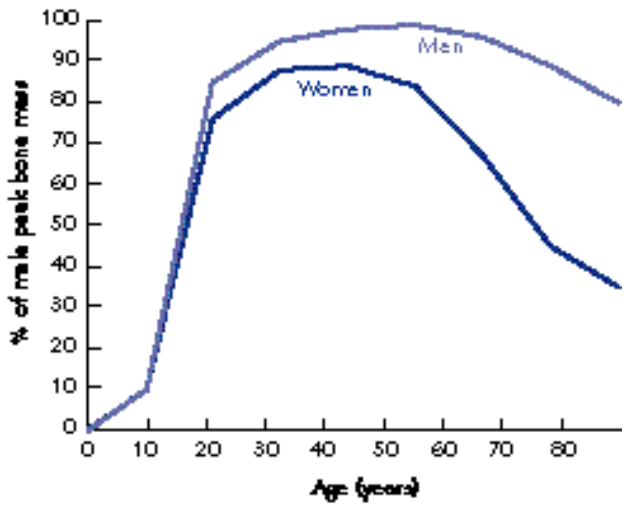
Calcium in skeletal growth

Infancy, childhood and adolescence are characterized by relatively rapid growth in which stature and body size progressively increase until adulthood. Growth occurs in all organ systems, but the most obvious is growth of the skeleton (Figure 5), of which calcium is an important constituent.

The nature of bone

Although it looks like an inert mineral substance, bone is a living, dynamic connective tissue. It contains cells and specialized collagen (protein) fibres encrusted with a crystalline mineral. The fibres are set in a ground substance composed mainly of mucopolysaccharides.

FIGURE 5
Growth of the skeleton



Together, the cells, fibres and ground substance form the organic "matrix" or "osteoid". Bone mineral is a complex salt of calcium phosphate and calcium hydroxide but also contains carbonate, citrate, sodium, magnesium and fluorine.

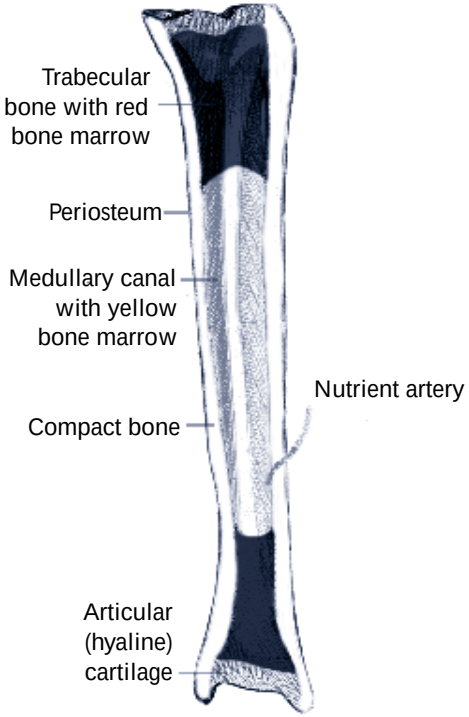
All bones in the skeleton contain two types of bone tissue (Figure 6). Compact bone (sometimes called cortical bone) forms the outer part of, for example, the shafts of the long bones. Trabecular (sometimes called cancellous) bone is a meshwork of tissue that forms the inner parts of the long bones and important parts of the vertebrae and pelvic bones. The specific arrangement of the trabeculae is important for the strength of bone. About 80% of total bone is the compact type.

The structure of bone is important for its strength and resistance to fracture. The fibrous protein collagen has great tensile strength, whereas the mineral calcium phosphate resists compression. If the protein fibres (which are normally protected by the mineral structure) are removed, bone becomes brittle. The composition of the material in bone and the way it is put together are both important. For example, the strength of the long bones is greater because of their cylindrical form, than if they were compact blocks. At the ends of the long bones and in bones such as the vertebrae, the material appears spongy in texture. Yet within this spongy tissue is a well-organized construction of narrow beams (trabeculae) joined by minor cross-struts, forming an intricate three-dimensional scaffolding. Together, these architectural features ensure that the forces due to body weight and movement are distributed optimally.

Peak bone mass

Bone growth is not a uniform process. Human stature follows a "sigmoid" curve between birth and adulthood, with the fastest rates soon after birth and in the prepubertal growth spurt (Figure 5). Peak bone mass is

FIGURE 6
Bone architecture



Compact bone occurs in the shafts of the long bones.
Trabecular bone occurs at the ends of the long bones.
Its network of beams ("trabeculae") is arranged to resist forces of compression and tension.

almost achieved between the ages of 20 and 25. After that a small increase in the amount of cortical bone takes place until the age of about 35. At the same time, body calcium content increases from about 28 g at birth to about 1.2 kg in adulthood, somewhat less for women than for men. After a decade or so in which bone mass remains more or less constant, loss of bone tissue and of calcium begins to occur and becomes significant as aging progresses. In particular loss of bone in women accelerates in the years immediately after the menopause.

The main influences on peak bone mass are sex (25-30% greater in men than in women) and race (10% greater in Afro-Caribbeans than in Caucasians). Within these groups there is wide individual variation as a result of genetic, hormonal and nutritional influences and of physical activity. The extent to which nutrient intakes influence peak bone mass is uncertain and is discussed in more detail in a later section on *Dietary calcium, bone development and maintenace of skeletal mass*.

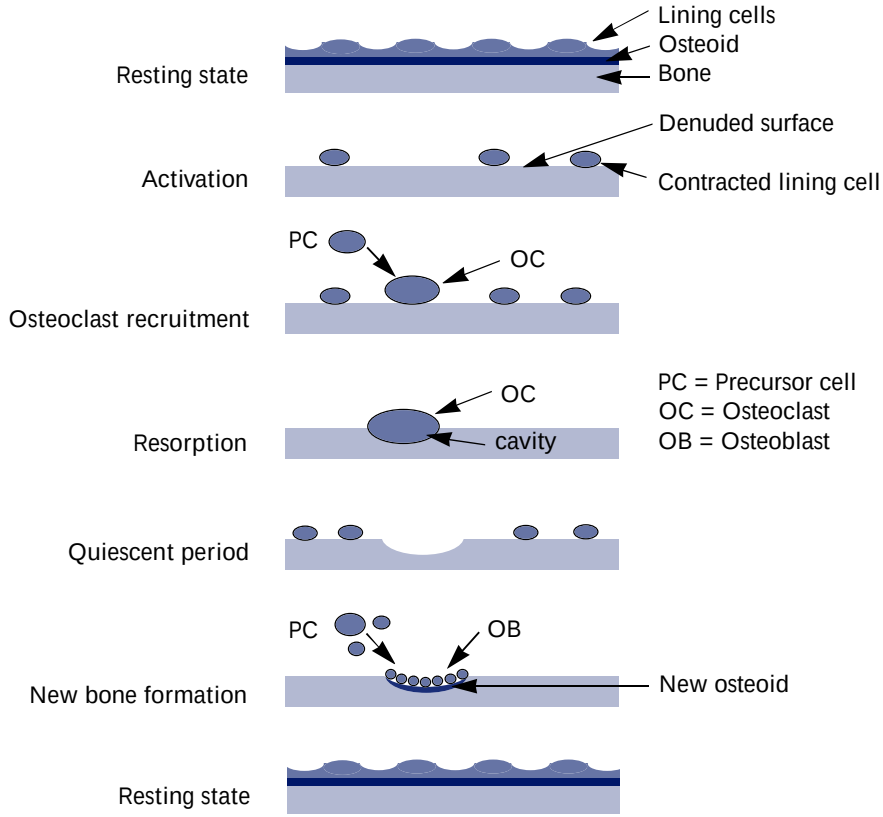
Methods of bone measurement

Some baseline data on skeletal weights at different ages are available from a limited number of studies of cadavers. A well-established method is radiography of single bones. Today the most commonly used techniques come under the heading of “absorptiometry” in which the body is scanned by beams of radiation (gamma rays or X-rays). The information on the attenuation of the radiation by bone is transformed by computer into measurements referred to as “bone mineral content” and “bone mineral density”. These are commonly used in epidemiologic and intervention studies, with the objective of relating dietary calcium to changes in bone mineral. Further details can be found in Box 3 and in the section on *Dietary calcium, bone development and maintenace of skeletal mass.*

Bone turnover and remodelling

New bone tissue is formed by specialized cells called “osteoblasts” and is broken down by other cells called “osteoclasts”. Removal of bone material is generally called “resorption” (see *Glossary*). The overall process of bone formation and breakdown is known as “turnover”. The specialized bone cells that carry out this process act at localized sites on the surface of the bone for limited periods of time; this is called “remodelling” (see Figure 7).

FIGURE 7
Bone turnover and remodelling



Turnover. Bone tissue is continuously being made and broken down by specialized bone cells. The overall process is called “turnover”.

Osteoblasts. Osteoblasts first make bone collagen fibres and other organic constituents of the bone matrix (“osteoid”) and then direct the second stage, which is the process of mineralization. Proteins made by these cells, osteocalcin and alkaline phosphatase, are released into the blood and can be used as biomarkers for bone formation.

Osteoclasts. By contrast, osteoclasts degrade the bone material in a single step, in which matrix and mineral are removed together (are “resorbed”). Peptides formed from collagen are released into the blood and urine and provide biomarkers for bone resorption.

Remodelling. Bone formation and resorption do not proceed continuously over the entire bone surface. Instead they are concentrated at localized centres of cellular activity called “remodelling units”. The cycle starts when macrophage-like cells become activated to form osteoclasts. These steadily erode the bone in a small area for about 4 weeks and then stop. After a quiescent period lasting about 2 weeks, osteoblasts are recruited into the cavity left by the osteoclasts and gradually build up new bone over a period of about 3 months.

Influences on remodelling. Factors that influence how many units are initiated have no effect on the lifespan of pre-existing units, which continue in a predetermined way. Bone formation is stimulated during periods of growth by the balance of circulating hormones and by physical activty. It is inhibited by undernutrition and by the glucocortico-steroid hormones. Resorption is increased by parathyroid hormone, which plays a major regulatory role in remodelling, and by immobility, and is inhibited by calcitonin. Other hormones, including oestrogens, can also affect bone remodelling through their stimulation of locally produced growth factors and by regulating the action of parathyroid hormone and calcitriol.

During the remodelling cycle there is a temporary net deficit of about 1.3% of total bone or 14 g of calcium in bone that is undergoing remodelling. Because resorption conditions vary, constant changes in the reversible calcium deficit act to minimize fluctuations in the calcium concentration of the extracellular fluid caused by dietary influences. Increases in dietary calcium tend to depress bone turnover, whereas reduced intakes increase it. Because bone remodelling is a relatively slow process (see Figure 7), the influence of dietary changes upon it may not be apparant for several months or even years. It is important to take into account dietary effects on remodelling when trying to interpret results of long term studies designed to investigate effects of dietary calcium on peak bone mass and on bone loss (see the section on *Dietary calcium, bone development and maintenance of skeletal mass*).

Research into the influence of nutrition on bone turnover has been stimulated by the development of several biomarkers to assess rates of bone turnover. For example, several characteristic peptides, derived specifically from the breakdown of bone collagen, can be measured in blood or urine and provide reliable markers for bone resorption. Osteocalcin is the principal protein of bone other than collagen. Although it is made in the osteoblasts, a proportion is released into the blood and can thus act as a "marker" for bone formation. Likewise, an alkaline phosphatase specific to bone and involved in the process of mineralization can also be detected in blood and provides a marker of bone formation. The use of bone markers is in its infancy, but with further development these markers may one day help provide a better picture of the state of bone turnover.

CALCIUM AS A NUTRIENT

Dietary sources of calcium

Calcium is present in small amounts in most foods but is present in large amounts in only a few (Table 2). The richest sources are milk and milk products, especially cheese. In some countries, for example, the United Kingdom, white flour is fortified with calcium and contributes substantially to total intakes. Whereas many vegetables are good sources of well-absorbed calcium (e.g., the Brassicas), some green vegetables contain substantial amounts of calcium but nevertheless are not good dietary sources because the calcium is hardly absorbed at all (e.g., spinach). Many nuts (e.g., almonds) and dried fruits (e.g., apricots and figs) are also good sources. Some commonly used cereal foods, such as pasta, are not rich in calcium in the raw state but when cooked may absorb substantial amounts from the cooking water. Some bottled mineral waters can also provide significant intakes, as can tap water in areas of hard water supply.

Calcium intakes

Because of large variations in food patterns, there are wide differences in both total calcium intakes and in the contributions of various foods to calcium intakes. Countries with high average consumption of dairy products tend to have higher average calcium intakes. There are considerable differences, too, between the sexes and between different age groups. In Europe average intakes range between 600 and 1500 mg per day, although these averages hide large differences between specific groups within European countries. Average intakes are also high in North America, Australia and New Zealand. In contrast, intakes are much lower in countries like China (380 mg / day) and The Gambia (350–400 mg / day).

TABLE 2

Calcium content of selected foods

	mg per 100 g
Cow's milk, full fat	115-120
Cheese, Cheddar	670-810
Cheese, Edam	677-896
Cheese, Emmenthal	970-1180
Cheese, cottage	75
Bread, unfortified	22-33
Bread, Dutch with milk	90
Bread, UK, fortified	100
Rice	10
Cornflakes	10-15
Potatoes	8-9
Carrots, raw	29-59
Lettuce	23-39
Watercress	180-250
Cabbage	30-59
Chinese vegetables	58
Bean curd	
Plain	150
Dried	284
Tofu	42
Soybean milk	19
Sesame paste	750
White fish	34
Sardines	330
Shellfish	83
Sharkfin	257

Compiled from UK, Dutch and German food tables and from Pun et al., Calcified Tissue International 1991;48:153-156.

Absorption efficiency

Because calcium is continually being lost from the body by excretion in the urine, and to a lesser extent through the skin, sweat and hair, sufficient calcium must be absorbed from the diet to compensate for these losses (Figure 8). Many authors have used the word "bioavailability" to denote the amount of absorbed calcium that is available for body processes after these losses have been taken into account. However, "bioavailability" will not be used in this monograph because it is used in different ways by different authors. Some consider it a property inherent in the food, whereas others regard it as a property of the subject who is absorbing. In this monograph, the term "absorption efficiency" is used instead.

Although about a third of the calcium in normal Western diets is absorbed on average, the efficiency of absorption can vary widely, depending on the nature and composition of the food (see Table 1) and on several non-dietary factors.

Dietary factors

The efficiency of calcium absorption decreases as the amount ingested increases. In general, calcium is absorbed best in soluble ionic form. Anything that enhances solubilization tends to increase absorption. Thus, gastric acid has an important solubilizing effect, and people with low acidity in the stomach may absorb calcium poorly. However, this is not an invariable rule. Calcium carbonate is insoluble but tends to be well absorbed, even by those with low gastric acidity. Even calcium oxalate, a very insoluble compound, can be absorbed to some extent. Calcium absorption is a complex process, and mechanisms currently poorly understood, must exist for the absorption of intact insoluble compounds. Compounds in foods that promote absorption may be the lactose in milk and the casein phosphopeptides derived from milk casein.

However, the effects are small and may be significant only when overall absorption is poor.

Substances in foods that form insoluble complexes with calcium in the intestine, such as phytic and oxalic acids, tend to reduce calcium absorption. Oxalates are present in significant amounts only in some vegetables, such as spinach and rhubarb.

Fibre-rich foods reduce calcium absorption when they contain high levels of phytic acid, which is frequently associated with fibre. Fermentation of fibre raises the acidity of the colon and increases calcium solubility; it also degrades phytic acid. Together, these changes may enhance absorption of calcium in the colon, thus counteracting adverse effects on absorption in the upper part of the small intestine.

In general, calcium is less well absorbed from plant foods than from milk, with the notable exception of the Brassica vegetables. The relative importance of inhibitory factors in vegetables and promotional factors in milk is uncertain. The presence of inhibitors in plant foods can also reduce the absorption of calcium from other foods. The absorption of calcium from most of its salts is similar to that from milk. Therefore, mineral waters rich in calcium generally provide a source of efficiently absorbed calcium.

Fatty acids released during fat digestion can form insoluble soaps with calcium, potentially reducing absorption. However, dietary fat level has no significant adverse effect on overall calcium absorption in healthy people and is a problem only when fat malabsorption occurs.

Non-dietary factors

Conditions in the gut affect the efficiency of calcium absorption. The rate at which food and digestion products pass through the gut can affect absorption by influencing the accessibility of calcium compounds to sites of absorption on the gut wall. Intestinal transit time is also influenced by the composition of the diet. The efficiency of “active” calcium absorption is influenced by the amount of calcium-binding protein on the absorbing surface and the extent to which the calcium-binding sites are occupied.

Calcium absorption efficiency tends to decrease with increasing age, which may relate to vitamin D status. Vitamin D synthesis in the skin, vitamin D absorption in the gut and the conversion to calcitriol all tend to become less efficient with age.

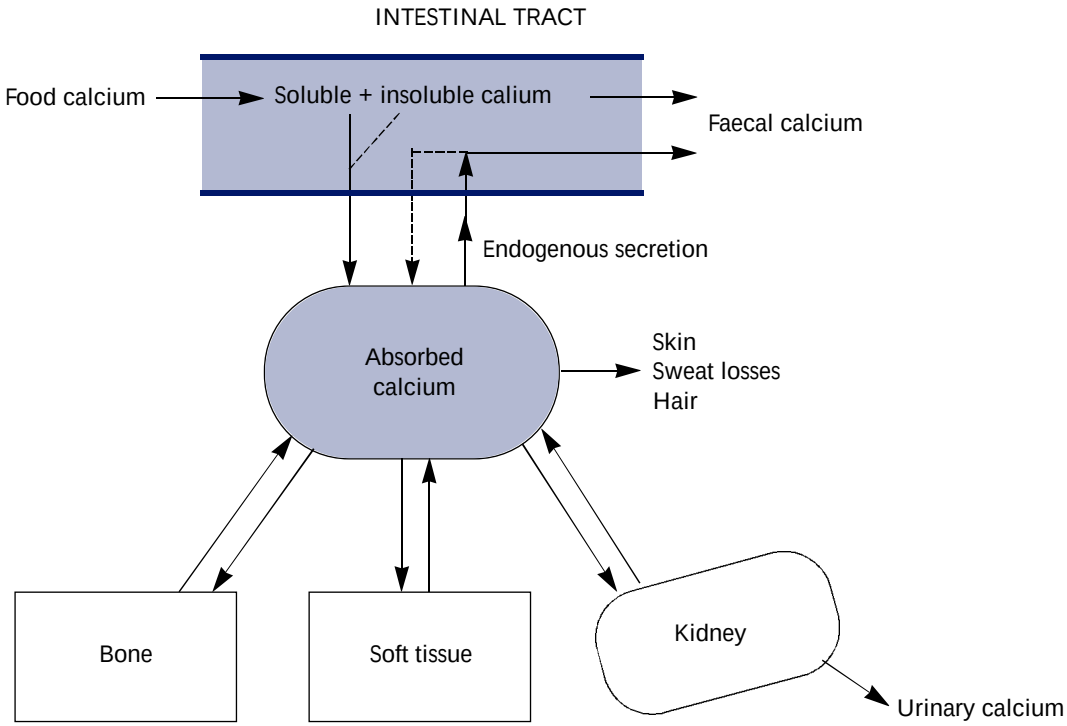
Physical activity increases local bone mass, reducing calcium excretion and raising absorption efficiency.

Calcium balance

Calcium enters the body from the diet and leaves it via the faeces and urine and, to some extent, from skin and hair (Figure 8). If intake equates with losses, the body is said to be “in balance”. Positive balance occurs during growth, when more calcium is being added to bone than is lost. Negative balance, when losses are not compensated by calcium absorbed from the diet, occurs with increasing age and in disease conditions such as osteoporosis, as discussed later.

Nutritionists measure calcium balance by supplying subjects with known amounts of food over a specified time and collecting faeces and urine during that period. All foods, faeces and urine are analysed chemically for calcium. Factors that influence calcium absorption efficiency or urinary excretion (Table 1 on page 8) can interact to produce a positive or negative calcium balance and thus influence requirements for calcium (see the section on *Calcium requirements*).

FIGURE 8
Calcium balance



Calcium from food enters the small intestine partly in soluble form and partly in insoluble form. Soluble calcium is well absorbed; a proportion of insoluble calcium (e.g., as oxalate) can also be absorbed. Calcium that is not absorbed is excreted in faeces. Net absorption is reduced because of so-called endogenous secretion. This refers to calcium secreted into the gut in bile or pancreatic juices, or in cells shed from the intestinal lining. As the amount of ingested calcium increases, the fraction that is absorbed decreases. Calcium is lost from the body mainly by excretion in the urine, although losses also occur through the skin, sweat and hair. Such losses must be compensated by absorption from the diet.

Calcium deficiency

Children who are malnourished grow slowly in weight and height and their bone growth and maturation is retarded. This results not simply from a lack of calcium for mineralization but also from a general lack of protein, energy and other nutrients. In one study, poorly nourished children in India grew somewhat better when given a calcium salt supplement but not nearly as well as when given milk, which contains a wide range of nutrients other than calcium. Paradoxically, improvements in nutrition, including better supplies of protein and vitamins, but where calcium is still limited, as is happening in parts of China, will lead to relative depletion in bone calcium without retarding growth.

A "deficiency" of calcium appears to occur after birth, since the ratio of calcium to nitrogen decreases. When infants are weaned and start to become mobile and their bones thus become weight bearing, rapid calcification of the bones takes place. Preterm babies are particularly at risk of not being able to absorb enough calcium for optimal bone growth. However, the reduced bone mineralization of prematurity is now regarded as predominantly due to a deficiency of phosphorus, not of calcium. Specialized formula milks for preterm infants are now routinely enriched with phosphorus.

In contrast, acute calcium deficiency can occur in special circumstances, for example, if term infants consume too much phosphorus in proportion to their calcium intake. This may happen if they are given unmodified cow's milk. Plasma calcium concentration falls and muscular convulsions occur (tetany). This can be overcome by giving breast milk or a modified formula milk.

Although some populations, for example, the Chinese, have very low intakes, this does not seem to cause problems and should not be regarded as deficiency. Whereas recent studies have revealed that bone mass is positively associated with calcium intake in mainland Chinese people, it has to be stressed that bone mass is not the only determinant of osteoporosis risk (see Box 4 and *Glossary*).

Because of changes in eating habits, changes in calcium intakes have been observed in many communities throughout the world over the past few decades. Certain subgroups within the population have particularly low intakes, which may be a cause for concern. Some experts regard the disease of osteoporosis, which is a substantial cause of disability in many industrialised countries, as due to a relative deficiency of calcium. This important topic will be discussed in detail in the section on *Calcium status and health.*

DIETARY CALCIUM, BONE DEVELOPMENT AND MAINTENANCE OF SKELETAL MASS

Observational studies have provided statistical associations between calcium intakes (assessed by questionnaires) and growth (measured as changes in height or as size, mass or density of the bones themselves). Intervention studies, in which the effects on bone of giving additional calcium in the diet are compared with a placebo treatment, give more direct information.

Children, adolescents and young adults

Scientific interest in the fastest rates of bone growth – in early infancy and puberty (Figure 5) – has focused on the maximization of bone growth at these times to achieve optimal peak bone mass. The idea is widely accepted that a greater reserve of bone during these times will attenuate the consequences of the inevitable bone loss in old age. Genetic background is an important determinant of potential bone mass, but diet and physical activity also play major roles. The important nutrients for bone health are now considered to be calcium, phosphorus, magnesium, potassium and vitamin D. There has also been interest in the potential role of vitamin K in bone health. However, although it plays a role in the formation of osteocalcin, vitamin K deficiency has not been shown to have adverse effects on bone health. Calcium has received by far the most research attention.

The main intervention studies in children and adolescents are summarized in Table 3. They are not entirely comparable because they involved children of

TABLE 3

Effect of calcium on bone growth in children and adolescents

Country	Sex	Age (years)	Length of study (months)	Calcium intake (mg per day) in diet	Calcium intake (mg per day) in supplement	Source	% Increase in bone mineral density
Australia[a]	F	10-17	12	700-800	750	Calcium salt	1.5
China[b]	M+F	7-9	18	300	300	Calcium salt	5.0
Switzerland[c]	F	6-9	12	900	850	Milk/milk products	5.0
United Kingdom[d]	F	12	18	740	386	Milk/milk products	2.9
United States[e]	F	12	18	960	354	Calcium salt	5.1
United States[f]	M+F	6-14	36	900	700	Calcium salt	5.1

[a] Nowson CA et al. Osteoporosis International 1997;6:219-225.
[b] Lee WTK et al. American Journal of Clinical Nutrition, 1994;60:744-750.
[c] Bonjour J-P et al. Journal of Clinical Investigation 1997;99:1287-1294.
[d] Cadogan J et al. British Medical Journal 1997;315:1255-1260.
[e] Lloyd T et al. Journal of the American Medical Association, 1993;270:841-844.
[f] Johnston CC et al. New England Journal of Medicine, 1992;327:82-87.

Note:

The numbers in each study varied from 84 to 159. The subjects in the Australian study and U.S. (1992) study were identical twins, one of each pair being supplemented while the other ate normally, acting as a control. This is a powerful way to minimize the effects of biological variation. All studies except the one in the United Kingdom employed double-blind placebo-controlled designs; that is, neither the subject nor the immediate investigators were informed of the treatment the subject was receiving. The increases in bone mineral density are expressed as the percentage increase in the supplemented group minus the percentage increase in the control group. In all studies except the Australian and the U.S. (1993) ones, bone mineral density was measured at more than one site. The figures quoted in this table are the maximum increases at any site.

different ages and with widely different habitual calcium intakes, subjects were given different amounts of calcium (sometimes as a calcium salt, sometimes in the form of dairy products) and different bone sites were studied. Nevertheless, there was a remarkable consistency in the results. Supplementation was associated with an increase in bone mineral density of between 1% and 5%, depending on the bone site.

A drawback was that supplementation did not continue until peak bone mass had been reached. Only then would it have been apparent whether calcium supplementation had been truly beneficial. The effect was greatest in the early months of supplementation and, where measured, tended to disappear once the supplement was withdrawn. Several scientists have interpreted these results as suppression by dietary calcium of the rate of bone remodelling (a process that takes several months), rather than a permanent increase in retention of calcium in bone. We do not yet know whether reducing the rate of bone remodelling in childhood is beneficial for the acquisition of optimal peak bone mass or long-term bone health. Nor do we know whether the apparent benefits of supplementation by calcium alone (as a salt) are equivalent to those obtained with a range of nutrients (as, e.g., when the additional calcium is supplied in dairy foods). Some problems involved in the interpretation of results from studies of bone density are outlined in Box 3.

Several studies found that peak bone mass did indeed seem to be higher in people who reported that they consumed more milk and dairy products in early life. These results have to be treated with caution because of the uncertainties of recalling food intakes over periods as long as 30 years or more.

Pregnancy and lactation

The body of a full-term infant contains about 30 g of calcium, which is derived from the mother's circulation during pregnancy. Pregnant women do not spontaneously increase their food intake. An increase in the absorption of calcium during pregnancy helps offset part of the deficit but much of the calcium required by the fetus is "borrowed" from the mother's "bone bank". This means that maternal bone mineral content decreases at this time.

On average 200–250 mg of calcium per day is secreted into breast milk during lactation, and the amount of calcium required for breast milk represents a considerable proportion of a woman's daily intake. Lactation, like pregnancy, is also accompanied by loss of calcium from bone. However, supplementation of the diet with up to 1 g of calcium a day has no detectable effect on either the loss from bone or the calcium content of the milk. This is equally true of African women with normal intakes of less than 300 mg per day and American women consuming up to 1300 mg per day.

This research challenges the usual assumption that women need extra calcium during lactation. It seems that it is a normal condition to "borrow from the bone bank" during pregnancy and lactation. In healthy women, the deficit is restored within a few months of completing lactation, and there is no evidence that bone health is in any way affected. There may be an exception to this rule, namely, when adolescent girls become pregnant and therefore have two risk factors for calcium deficiency: their own growth and their pregnancy. Research suggests that higher intakes may be advisable for these girls, preferably from foods that provide a wide range of other nutrients as well. As discussed earlier, phosphorus, potassium and magnesium are also essential constituents of bone mineral and vitamin K is involved in the formation of bone matrix material.

Older people

Additional dietary calcium cannot entirely prevent the inevitable loss of bone mineral that occurs in old age, but it can retard the losses from both cortical and trabecular bone. This topic is discussed in more detail in the section on *Calcium status and health*.

BOX 3

Assessing bone health

Modern methods to measure bone size and mass rely on the attenuation of a beam of radiation (gamma rays or X-rays) passed through the body. The radiation beams scan the body or the bone area of interest, and bone edges are detected from the rate of change of attenuation over a certain scan distance. The mass of bone can be computed, using dedicated software, by comparison with a calibration material of known absorption. Corrections can be made for overlying soft tissue by reference to the radiation attenuation in regions of soft tissue adjacent to the bone. These techniques have revolutionized bone measurement. They are quick and precise, are not traumatic for subjects and involve minimal radiation dose.

When these measurements are used in studies to investigate the effects of diet on bone mass, the following potential problems of interpretation need to be considered:

- Adaptation to changes in dietary intakes occurs over time periods that often exceed those under which many studies were conducted. Variation among individuals in adaptive response makes extrapolation from small, detailed studies to wider populations unsafe.
- Changes in bone mineral status as measured by techniques involving absorption of radiation may not necessarily relate directly to bone health, because the details of bone architecture, which are not generally observed, may be more crucial to health than bone mineral density itself.
- Different techniques give rise to different measurements. In methods involving single beams of radiation, results are expressed as bone mineral content per unit length of bone in the axial direction (g/cm). In dual-beam methods, bone mineral content often refers to an anatomical region (e.g., individual vertebrae) or even to whole-body bone mass. It is, confusingly, expressed in grams. By contrast, bone mineral density is not a true density but an "areal density" measurement, expressed in g/cm^2, and is derived by dividing bone mineral content by bone area.
- Expression of data as bone mineral density implies that bone mineral content is directly proportional to bone area, but many studies show that this is not always true. Uncritical use of bone mineral density in adults can lead to spurious associations with other variables, such as dietary intakes, energy expenditure and grip strength, which are themselves related to bone size through their dependence on overall body size. To minimise the potential for confounding by body size, bone area, body weight and height should be included as independent variables in all regression models involving bone mineral density. Unfortunately, this is rarely done, and therefore much evidence that relates bone mineral to dietary components is unreliable. Body mass index, which is often used as a means of standardizing in such studies, is not effective when adjusting for size in this context.
- During growth, however, bone mineral content rather than density, is the appropriate measurement.

Athletes: the role of physical activity

It is well recognized that regular weight-bearing exercise, including walking, during childhood and adolescence can increase peak bone mass substantially. Regular exercise during adulthood can improve bone strength. Bone mass in some skeletal sites is markedly higher in athletes than in sedentary people. Although the effects of exercise are not entirely linked to calcium, there appears to be an interaction between dietary calcium intake and exercise such that intakes above about 1 g per day are needed to achieve the maximum effect of exercise on bone development.

The main effects of exercise are a result of the stimulation by mechanical loading of new bone formation and the inhibition of bone loss. The effect is local, with changes occurring only at skeletal sites loaded in exercise. Exercise that is not weight bearing, such as swimming, does not influence bone mass. Regular physical activity during childhood and adolescence can increase peak bone mass substantially and, if continued into adulthood, can confer a significant advantage in later life, when bone loss begins. In the first 5 or so postmenopausal years, when the loss of bone is greatest because of oestrogen deficiency, physical activity may have little influence on bone loss. After this, exercise may be able to slow the rate of bone, and therefore calcium, loss.

CALCIUM STATUS AND HEALTH

Bone diseases

Several diseases affect bone function, the main ones being rickets, osteomalacia and osteoporosis. In rickets and osteomalacia, there is reduced mineralization relative to the organic bone matrix, resulting in soft, pliable bones that deform easily. Rickets is the childhood form of the disease, whereas osteomalacia affects adults. It is generally accepted that the condition results mainly from a deficiency in vitamin D rather than calcium. Since the discovery of vitamin D and its involvement in rickets and osteomalacia, these diseases have become much less common, although outbreaks are still seen even in affluent countries.

Osteoporosis

Osteoporosis, a disease in which bone becomes more fragile and more liable to fracture (see Box 4), is a major health problem in Western Europe and most affluent industrialized countries. It causes considerable pain, disability, disfigurement and loss of independence, and is a cost and burden to health services. Internationally, more than 1.5 million fractures occur every year as a result of osteoporosis, and some authors have predicted that this may increase fourfold by the middle of the next century.

Interest in the role that very low calcium intakes may play in the development of osteoporosis stems from early research that clearly showed that animals made calcium deficient developed osteoporosis. It is not surprising, therefore, that much research has been devoted to assessing the effectiveness of additional dietary calcium in preventing or reducing accelerated

BOX 4

Osteoporosis

What is osteoporosis?

Osteoporosis is a disease in which the bones become more fragile and susceptible to fracture with minimal trauma. It was once considered that with osteoporosis the composition of bony tissue remained normal but there was simply less of it. Now it is realized that the internal structure ("micro-architecture") changes. In 1990, a consensus conference redefined osteoporosis as "a condition of skeletal fragility due to decreased bone mass and to micro-architectural deterioration of bone tissue, with consequent increased risk of fracture". Two types of osteoporosis are recognized. The first typically occurs between the ages of 50 and 75 and affects six times as many women as men ("postmenopausal osteoporosis"). Bone loss is accelerated compared with normal losses associated with ageing. Most fractures occur in trabecular bone, especially the wrist and spinal vertebrae. It is generally thought that the main factor is oestrogen deficiency (as occurs, e.g., at the menopause in women), since oestrogen therapy is very effective in reducing bone loss and fracture risk. The second type affects men and women over 75 years of age and does not involve greater than normal bone loss ("senile osteoporosis"). Hip and spinal fractures are more common with this form of osteoporosis.

What causes osteoporosis?

It can be argued that osteoporosis is not a single disease with a single cause. After intense research, some of the many causes are now more clearly understood. Oestrogen deficiency, e.g., is clearly important in postmenopausal osteoporosis, but the disease is complex and other factors are involved. Osteoporosis is more common in white races than in black, in women than in men and in affluent than in underdeveloped countries. A sedentary lifestyle, smoking, very high caffeine and alcohol consumption, low body weight and low calcium intakes have all been implicated as risk factors. Osteoporosis is no longer regarded as due simply to a decrease in bone mass but can be considered a condition of increased skeletal fragility. Decreased bone mass contributes to but cannot fully explain this fragility. Thus, factors such as falls and the propensity to fall may perhaps explain up to half of all hip fractures.

Can osteoporosis be alleviated with extra dietary calcium?

At the present time there is no cure for osteoporosis, but with current knowledge much can be done to reduce the risk of debilitating disease in later life. One strategy is to ensure that, through good nutrition and regular exercise, optimal peak bone mass is developed in the early years. An additional (rather than an alternative) approach is to ensure adequate care later in life. Risk of osteoporosis is greatest in women in the first few years after the menopause as a result of oestrogen deficiency; the most effective therapy is oestrogen replacement but this should be under medical supervision as continued use may increase the risks of certain types of cancer. A few years after the menopause, the rate of bone loss slows; at this stage calcium intakes somewhat higher than normally found in Western diets may retard, rather than prevent, excessive bone loss. Relatively few studies have been conducted with men. Inconsistencies in the results of intervention studies with calcium in subjects with osteoporosis or at high risk of osteoporosis may be due to wide differences between subjects (age, state of health, aspects of lifestyle, habitual calcium intake, etc.) and design (whether a calcium salt or dairy foods were given, which bone sites were examined, whether other risk factors changed, the time scale of intervention, etc.). Some scientists reviewing these data have concluded that despite many differences, the results are consistent and that a significant reduction in the rate of bone loss can be achieved by calcium supplementation of the diet. Others have concluded that additional calcium has little effect. There have been fewer studies in which the measured endpoint was fracture rate. Some of them have shown reduced fracture rates after combined supplementation of the diet with calcium and vitamin D.

bone loss. The concept that osteoporosis is a result of calcium deficiency does not necessarily imply that there is insufficient calcium in the diet; poor absorption, defective bone metabolism or increased urinary excretion despite high calcium intakes may all be involved. Nevertheless, the focus has been on dietary intervention.

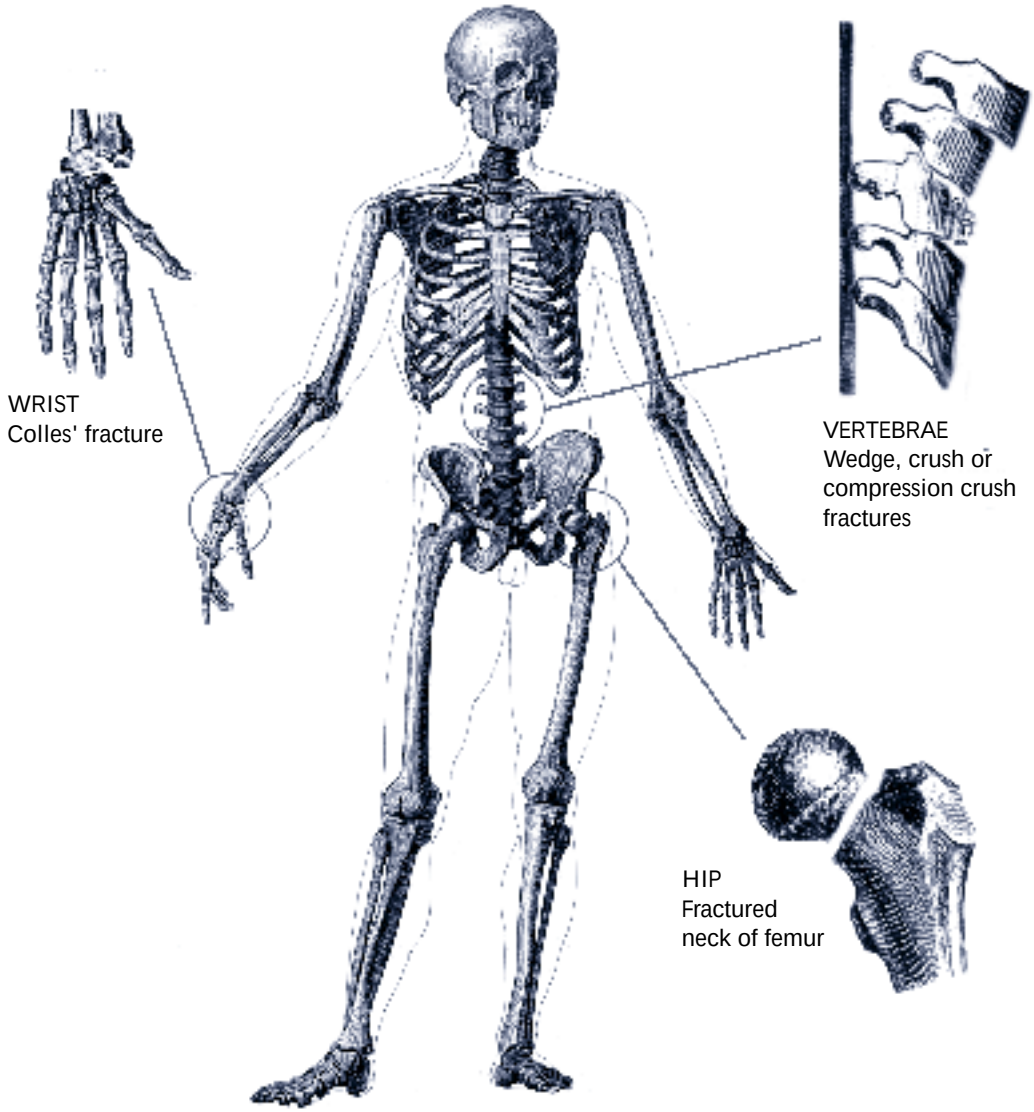
The results of such studies have been inconsistent (see Box 4). Overall, it seems that calcium cannot prevent bone loss but can reduce the rate of loss to some extent. It is more effective in reducing loss from cortical than from trabecular bone, especially in people who have had habitually low calcium intakes. However, the amounts of calcium used in intervention studies (often 1.5–2.2 g) were large in comparison with normal intakes or with intakes that can reasonably be expected from calcium-rich foods consumed in industrialised countries. (Afew communities with a "hunter-gatherer" lifestyle may consume as much as 2–3 g per day but such amounts are not readily attainable with Western-style diets.) Reservations about the interpretation of methods used to measure bone mineral content apply equally to these studies and to those discussed earlier, and are summarized in Box 3.

Although osteoporosis is usually defined in terms of bone mass, it is the end result – the greater tendency to sustain fractures – that is of major concern (Figure 9). People with osteoporosis find that they break bones after minor impacts that would go unnoticed in people with healthy bones. The greater ease of fracture is due in part to the decrease in mass but also to deterioration of the detailed structure and integrity of the bone architecture. Bone trabeculae become perforated, thereby weakening the structure and reducing the strength of the bones. However, people with reduced bone strength have widely different susceptibilities to fracture, and factors other than bone strength contribute to fracture rates. Thus, medical conditions causing dizziness, the use of certain medicines, abuse of alcohol, poor eyesight and inadequate lighting in the home all contribute in various ways to the risk of breaking bones. Measures to minimize the risk of falls or reduce the impact of falls can be useful in preventing osteoporotic fractures.

Just as there has been much research into the effect of additional calcium on bone mass, there have also been studies (although very few) on potential associations between calcium intake and fracture risk. Most case-control epidemiologic studies have found no association between calcium intake and fracture risk. Some, but not all, prospective studies found an inverse association between calcium intake and fracture rate, but confounding by other factors could not always be ruled out. Effects seemed to be most marked in populations with low habitual calcium intake. However, a 43% reduction in hip fractures in elderly French women was achieved by a combination of calcium phosphate and vitamin D supplements for 18 months.

In summary, research to investigate the effectiveness of additional dietary calcium in reducing bone loss or fracture risk has been mainly conducted in either healthy or osteoporotic women after the menopause. Calcium has little effect on the rapid loss of trabecular bone observed immediately after the menopause, but does seem to *retard* the loss from cortical bones some years after the menopause. Those most likely to benefit are those with habitually low calcium intakes, but the evidence does not suggest that amounts greater than 1.5 g actually prevent bone loss. The combination of calcium and vitamin D rather than calcium alone may be more effective in reducing risk of fractures. Comparisons of developing countries such as The Gambia, where average calcium intakes and bone mass are low, with Western European countries, where they are much

FIGURE 9
Main sites of bone fractures in people with osteoporosis



higher, suggest that bone mass is not the sole, or even most important, determinant of bone strength or fracture risk. Fractures due to minimal trauma are rare in The Gambia but are frequent and increasing in Europe. Other lifestyle factors that increase the risk of falls need more attention, as does the role of exercise.

Hypertension

Calcium in the body is involved in the maintenance of normal blood pressure; it works in conjunction with several other ions. Calcium and sodium are the predominant divalent and monovalent cations outside cells, whereas magnesium and potassium predominate inside cells. Together these ions influence blood pressure by affecting vascular tone (the normal state of balanced tension in muscles) through the regulation of contractile proteins and the transport of substances through membranes. They also regulate metabolic activities in the smooth muscles surrounding blood vessels, which in turn control the transmission of signals between cells and the generation of energy for muscular contraction.

People with raised blood pressure tend to have lower than normal concentrations of calcium ions in the blood, although this observation has not been confirmed in all studies. More consistently, high blood pressure is accompanied by higher intracellular calcium concentrations, especially in red blood cells, platelets and lymphocytes, higher circulating levels of parathyroid hormone and elevated excretion of calcium in urine. These observations suggest that at least some people with hypertension have a defect in their ability to use calcium in normal cellular functions.

An impaired ability to utilize calcium will not necessarily be normalized by increasing calcium intake. However, many studies have investigated whether there is a link between calcium intake and blood pressure or whether additional dietary calcium will prevent the development of hypertension or reduce existing high blood pressure. As in the studies of osteoporosis, these have included observational studies between and within countries as well as case-control, prospective cohort and intervention studies. Also, like the studies of osteoporosis, the results have been inconsistent. This is partly because of deficiencies in the design of many studies and the difficulties in comparing studies that are so different in many features.

An important consideration is that there are several different types of hypertension, which can be characterized by the level of the enzyme renin in the person's blood (low, normal or high). Renin is an enzyme originating in the kidney and is involved in blood pressure regulation. Each subgroup of hypertensive patients has different proportions of sodium, potassium, magnesium and calcium in the extracellular fluid, and their blood pressure responds differently to high salt intakes. It is quite possible that they also respond differently to dietary calcium and that the inconsistency in the outcomes of studies of dietary calcium and blood pressure is due to the fact that the study populations contained different types of hypertensive subjects.

Observational studies of large populations have generally shown an inverse association between calcium intake and blood pressure. However, there is not enough evidence to support a conclusion that calcium deficiency causes hypertension, but it may exacerbate the hypertension associated with sodium sensitivity. In intervention studies, calcium supplementation has been most effective in hypertensive patients with intakes lower than about 600 mg per day. It has been especially effective in women with hypertension of pregnancy, a

condition in which the high blood pressure develops over a short time and which is well characterized by reduced urinary calcium excretion and elevated intracellular free calcium concentrations.

It is important not to focus solely on calcium, since many other nutrients are clearly involved. In all populations studied, reduction of body fat has been the most consistent non-pharmaceutical method for controlling blood pressure, and this fact has to be kept in mind when formulating dietary advice.

Colon cancer

Colon cancer is the second most common type of cancer in industrialized countries. Although the precise causation is uncertain, it is generally believed that a toxic agent or agents cause epithelial cells that line the colon to divide at a faster rate. This allows more opportunities for carcinogenic substances to cause changes in the DNA of colonic cells that eventually lead to cancer. There is much evidence to suggest that agents that cause increased cell division are bile acids and fatty acids, which tend to be present in higher concentrations in the colon when dietary fat intakes are high. One theory for which there is much experimental evidence but no conclusive proof is that the cancer-inducing effects of bile acids and fatty acids can be reduced by the presence in the colon of calcium phosphates. These act by forming insoluble complexes with the bile acids, thereby reducing their toxicity.

Overall, the results of epidemiologic studies as well as a few intervention studies are moderately consistent, suggesting that higher intakes of calcium are associated with a lower risk of colon cancer. This may reflect consumption of calcium-rich foods, principally dairy products, rather than calcium alone.

Cardiovascular disease

Many years ago it was observed that in countries that had a high prevalence of coronary heart disease, lower rates of the disease tended to occur in areas of “hard” water supply where the concentration of calcium in the water was high. Since then, a protective role for calcium in cardiovascular diseases has not been given much prominence. Because high blood pressure is regarded as an important risk factor for cardiovascular disease, the tendency for higher calcium intakes to result in lower blood pressure might contribute, at least in part, to the “hard water effect”. At present this is speculative, and hard scientific data are needed.

Are there adverse effects of high calcium intakes?

Calcium levels in the body are so closely controlled that an excessive accumulation in blood or tissues arising from overconsumption is virtually unknown. Abnormally high blood calcium concentrations occur not from overconsumption of calcium but secondary to diseases such as bone cancer, hyperthyroidism and hyperparathyroidism. They also occur in prolonged immobilization (e.g., in hospitalized patients), as a result of over-consumption of vitamin D and in the so-called milk-alkali syndrome. The latter is now extremely rare and arose from specific treatments given to combat gastric ulcers.

Accumulation of calcium in tissues does undoubtedly occur in some instances; it results from failure of control mechanisms and has little relevance to dietary intake. A common example of accumulation of calcium in a body tissue is kidney stones. These occur when the urine becomes supersaturated with calcium oxalate or phosphate and these salts form large crystals. In “stone formers”, the excretion of calcium in urine is usually high, but stones are formed only if other risk factors are

present in susceptible people. Thus, some people absorb more oxalate from the diet than others and some produce more oxalate metabolically. Low intakes of dietary fibre, high environmental temperature and low humidity are also risk factors. Low to normal dietary intakes of calcium in the absence of high intakes of protein and oxalate appears to be beneficial for people who are susceptible to stone formation. However, one epidemiologic study found that high dietary calcium intake *reduced* the risk of symptomatic kidney stones.

Dietary calcium interferes with the absorption of iron, and concern has been expressed that high calcium intakes may compromise iron status, especially in women, who are more prone to iron deficiency than men. There is good experimental evidence that iron absorption from a meal can be markedly reduced even in the presence of normal amounts of calcium. However, it is now equally clear that when measured over an extended time period rather than after an individual meal, dietary calcium over a very wide range of intakes has little influence on overall iron absorption. Similar concerns have also been expressed about adverse effects of high intakes of calcium on magnesium and zinc absorption and metabolism. Current opinion is that caution may be needed with regard to very high intakes from non-food supplements.

CALCIUM REQUIREMENTS

Defining requirements

Dietary requirements for a nutrient differ from one individual to another and from one period of life to another. They also depend on the nature of the diet itself, which affects the efficiency with which nutrients such as calcium are absorbed or utilized. An individual's requirement for a nutrient was traditionally based on the amount of that nutrient required to prevent clinical signs of deficiency. However, societies increasingly think in terms of more than the basic need to avoid deficiency, because higher levels of a nutrient may be associated with optimal health. It is a matter of debate, however, whether the very high levels of calcium intake that have been claimed to have especially beneficial or therapeutic effects should influence estimates of requirement. Current differences in philosophy concerning the definition of calcium requirements are discussed in Box 5.

Calcium requirements through life

Requirements for calcium have generally been based on balance data or on a "factorial approach" that uses information on the calculated needs for growth and maintenance, taking into account absorption efficiency and obligatory losses. In general, these estimates agree with observations of average intakes in populations with no apparent calcium deficiencies.

Infancy

Calcium requirements in infancy are usually calculated from knowledge of normal daily intakes and the average composition of human milk.

Childhood and adolescence

Through childhood and adolescence, when most bone growth takes place, it is also possible to estimate

BOX 5

The scientific basis for defining calcium requirements

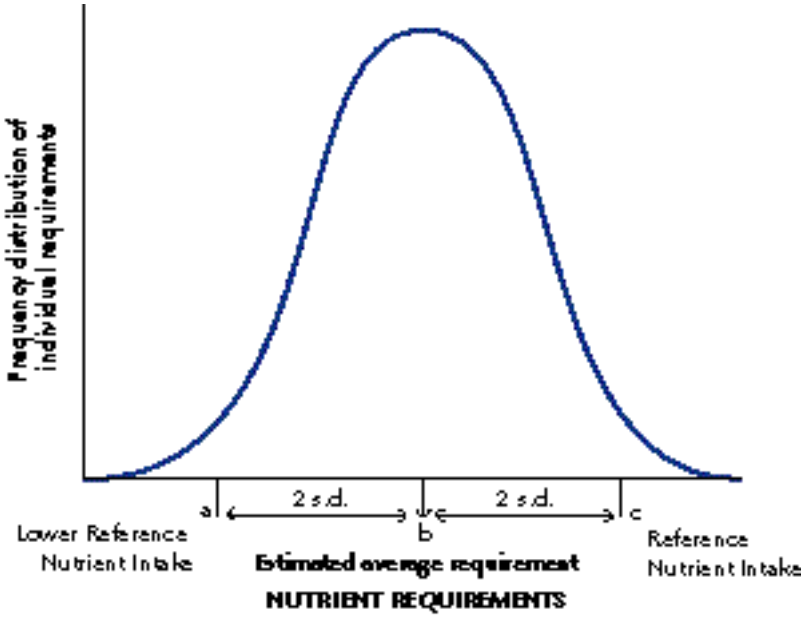
Calcium presents a problem in defining requirements because of the diversity of its functions and because bone represents a large body store of this nutrient. There is not yet general agreement about whether calcium requirements should be set at a level that aims to prevent loss of calcium from bone in most circumstances. The alternative view is that temporary withdrawal of calcium from the "bone bank" is a normal physiological event that does not warrant higher calcium intakes. However, intakes should clearly be high enough to avoid chronic as distinct from temporary loss.

Different approaches to defining requirement are apparent in the United States and Europe. In the United States, emphasis has recently been placed on the concept that calcium is a "threshold nutrient", meaning that calcium consumed in excess of need cannot be retained. The Food and Nutrition Board of the U.S. Institute of Medicine (1997) attempted to calculate "maximal calcium retention", namely, the highest retention that can be achieved by manipulating steady-state intake. Such maximal retention will be positive during growth, zero in healthy adults and often negative in the elderly. The point where retention stops as intake rises is defined in the United States as the requirement for calcium. Such an approach leads to somewhat higher estimates for calcium requirements of adults (other than pregnant or lactating women) than in most other countries (see Table 4).

The more conservative factorial approach (see the foregoing section on Calcium requirements through life) has been adopted in Europe (in the Further reading section see Commission of the European Communities, 1993; Department of Health, 1991, 1998). A recent U.K. publication (Department of Health 1998) reviewed scientific publications since U.K. Dietary Reference Values were last set, in 1991, and found no scientific basis for revising upwards their previous estimates for calcium requirements. European scientists have not specifically rejected the concept of thresholds but argue that accurate threshold values have not yet been determined because "maximal retention" has been measured only in short-term, but not in long-term experiments. Future research (see the final section of this monograph) needs to take account of these differences in philosophy and provide information on maximal calcium retention at different stages of life. Readers who wish to study the counter-arguments in more detail are referred to the publications cited in this Box.

requirements from knowledge of normal retention of calcium in bone. However, it is a matter of debate whether the values obtained should be amplified on the basis that greater (some say "optimal") growth could be achieved by consuming more calcium (see Table 3 on page 19). A firm conclusion on this issue requires more studies in which additional calcium has been given until peak bone mass has been reached.

FIGURE 10
Dietary reference values – definitions



Adults

The balance method has frequently been used to assess the requirements for adults who are no longer gaining bone; the factorial method gives similar results.

As discussed earlier, there still is controversy about the need to increase reference nutrient intakes for pregnant and lactating women and for elderly people.

Dietary reference values

Those charged with the responsibility for public health need to ensure that people are well nourished. For this purpose, individual dietary requirements are not very useful even if they could be determined accurately. Therefore, health authorities in many countries have traditionally published recommendations for dietary intakes of nutrients commensurate with the needs of a well-nourished population. Such recommendations may be useful for:

- assessing the adequacy of diets of groups of people
- prescribing diets or supplying food
- labelling food
- assessing the adequacy of individuals' diets (where the utmost caution must be used when applying such data to individuals).

TABLE 4

Reference nutrient intakes for calcium around the world

(mg/person/day)

	Children age 4-6	Adults	Pregnancy	Lactation
Australia	700	800	1100	1300
France	700	800	1000	1200
Germany	700	700F, 800M	1200	1200
India	450	450	1000	1000
Mexico	500	500	1000	1000
Netherlands	400-600	700-900	800-1000	900-1100
Scandinavia	600	600	1000	1000
United Kingdom	450	700	700	1250
United States*	800	1000*	1000	1000

* The U.S. Dietary reference intakes for adults over age 50 is 1200 mg/day.

Recommendations on nutrient intakes differ between countries and are variously called RDAs (recommended daily, or dietary, allowances, or amounts), RDIs (recommended daily, or dietary, intakes) or RNIs (reference nutrient intakes). They are defined in such a way (Figure 10) that they are likely to meet the nutrient needs of practically all members of a population. They are therefore considerably higher than estimated average requirements. The meaning of RDA has been widely misunderstood, and it has frequently been interpreted as meaning that each individual should receive at least the recommended amount to maintain health. In fact, most people should be perfectly healthy on intakes considerably less than the RDA. As the percentage of people with intakes below the RDA becomes larger, the risk of deficiency in the group increases.

Table 4 indicates some differences between authorities around the world in setting requirements. Such differences are usually due to different philosophies about whether additional calcium is of benefit in giving better bone growth (see Box 5). One argument is that dietary reference values apply only to groups of healthy people and are not necessarily appropriate for those with different needs arising from disease. Others argue that, because of the interaction of many lifestyle factors (which may include, e.g., high alcohol and salt consumption, low levels of activity and excessive smoking), the whole population in affluent developed countries is at high risk of osteoporosis. Therefore, the requirement for calcium is higher and should be reflected in higher recommendations. In less-developed countries, requirements seem to be lower and recommendations have been set at a lower level.

However, as lifestyles change in these countries during the course of economic development, changing risk factors may require a revision of calcium intake recommendations.

Controversy exists about whether guidance is necessary to the public about possible adverse effects of high intakes. Certainly there is little scientific evidence that amounts higher than 2 g per day are beneficial in any way.

Finally, in devising requirements for a specific nutrient such as calcium, it is assumed that requirements for energy and all other nutrients are met. It is important that future research fully takes into account important interactions between calcium and other nutrients as well as interactions with non-dietary lifestyle factors that may determine the level of an individual's or a population's requirement for calcium.

FUTURE RESEARCH NEEDS

The following suggestions are not meant to be exhaustive, but they do summarize the topics identified in this monograph as needing further elucidation.

Food sources of calcium and absorption efficiency

Dairy products account for a very large proportion of food calcium intake in some countries but a small or negligible proportion in others. When recommendations are made to increase calcium intakes and dairy foods are not a practical option, more information is needed on the content and absorption efficiency of calcium in non-dairy foods. More information is also needed on non-traditional sources of calcium in populations with limited access to dairy products.

Calcium absorption efficiency

Research is needed to determine the mechanistic basis for differences in the efficiency of calcium absorption in different people. What is the quantitative contribution of passive versus active absorption in different physiological (e.g., growth, pregnancy, lactation) and dietary conditions? What are the mechanisms by which absorption efficiency adapts to changes in intake, and what is the time scale range over which such adaptive changes occur? More information on the efficiency of absorption of calcium from plant foods and new ways of increasing absorption efficiency would be valuable.

Dietary calcium, skeletal mass and bone loss

Controversies about the extent to which "optimal" skeletal growth can be affected by additional dietary calcium have been highlighted here. At what levels of calcium intake are these effects apparent and over what time scales? Are there well-defined thresholds above which no further effect occurs? Before further progress can be made in understanding the role nutrition might play in either the prevention or treatment of osteoporosis, more information is needed on what causes the abnormal loss of bone in this disease. In some studies, additional calcium in the diet has retarded calcium loss from bone in later life. Is there a threshold above which further calcium is ineffective? It is important to know whether calcium works most effectively in conjunction with other nutrients and whether energy intake is important.

Bone remodelling

Some effects of dietary calcium on bone may be relatively short-term effects on bone remodelling. How does calcium intake influence the remodelling process? Are other nutrients involved, and how do they interact? What is the significance for peak bone mass of diet-induced changes in remodelling in young people?

Bone strength

Calcium intake affects bone mineral content, but how does it affect the structure and physical characteristics of bone? Research is needed on the interactive effects of nutrients other than calcium. How is bone structure related to bone strength? What is the relative influence of calcium compared with other factors such as hormones and physical activity?

Research methods

Much research into links between dietary calcium intakes and bone mineral content depends on modern techniques based on the absorption of radiation. Yet, as made clear in this monograph, lack of awareness of problems associated with uncritical use of such techniques and errors in the interpretation of data generated give concern and may account in part for inconsistencies reported in the literature. International agreement about standardization of the technique(s) and the basis for expression of data would be invaluable.

Blood pressure

There is epidemiologic and experimental evidence for a role for dietary calcium, but the extent to which such an effect operates within the range of normal dietary intakes is uncertain. Research is needed on whether the influence of calcium is measurable only in those with habitually low intakes, whether calcium is effective only in those who are salt sensitive and whether there is a threshold above which no further effect is apparent. How does the influence of calcium compare with non-dietary factors?

Colon cancer

There is evidence for a significant beneficial effect of dietary calcium. Research is needed into whether this is operative within the normal range of intakes. Is there a threshold above which no further effect is apparent? Does the mechanism involve complex formation with bile acids or fatty acids? It is important to know whether calcium alone is effective or only in combination with other nutrients found in calcium-rich foods.

Dietary requirements for calcium

Of all the nutrients, calcium is one of the most difficult for which to determine requirements, for reasons outlined in the section on *Calcium requirements*. Ultimately, answers to the research questions outlined above are required to increase the scientific database on which human requirements for calcium can be based. More information on the basis for racial and sex differences in calcium metabolism and requirements would also be valuable.

SUMMARY

Calcium, the most abundant mineral element in the body, has two key functions. More than 99% is present in the bones, where it plays an important role in their structure and strength. A very small proportion is involved in the regulation of critical functions including the transmission of nerve impulses, the contraction of muscles and the activities of enzymes.

Calcium enters the blood circulation by absorption from food; that which is not absorbed is voided in the faeces. Calcium can be lost from the body through the skin, sweat and hair, but the main losses occur in the urine. The fraction of calcium absorbed decreases as intake rises, and there is evidence that the body adapts to increase the efficiency with which it absorbs calcium when intakes are particularly low. Efficiency also increases in periods of high demand, such as the adolescent growth spurt or in pregnancy.

Within the body, there is a constant flow of calcium between the circulation and the tissues, especially the bones, which act as a kind of buffer to dampen the increase in circulating calcium that would normally occur after meals. So important is calcium in metabolic regulation that its concentration in blood needs to be maintained within a fairly narrow range. This is achieved by the coordinated actions of parathyroid hormone, calcitonin and calcitriol (derived from vitamin D) regulating absorption, urinary excretion and the flow of calcium between bone and circulation.

The concentration of calcium in cells is also highly regulated to prevent excessive concentrations in cells, which can cause injury. Many cells are “switched on” to perform their functions (e.g., the generation of electrical impulses by nerve cells) by release of free calcium from

stores within the cell. Once the function is performed, excess calcium is removed into the extracellular fluid by metabolic pumps in the cell membrane.

Calcium is essential in the diet to compensate for daily losses from the body and to provide for increases in skeletal mass during periods of growth. Most foods contain some calcium, but the richest sources are milk and milk products, root vegetables and some green vegetables. Cereals do not generally have high calcium contents except where foods made from them are fortified. The calcium content of water varies widely. Some plant foods contain substances (e.g., phytic and oxalic acids) that bind strongly to calcium and restrict its absorption. Thus, vegetables like rhubarb and spinach contain substantial amounts of calcium but are not good food sources because little is absorbed.

The calcium in bone is in the form of calcium phosphate combined with small amounts of other minerals. Bone is a living tissue encrusted in this crystalline material and is subject to continual processes of breakdown and renewal. Bone growth is fastest soon after birth and during the prepubertal growth spurt. Peak bone mass is achieved in the mid-20s. After a period of constancy, gradual loss of bone occurs from late middle age onwards. It is particularly rapid in women in the few years after the menopause, due to oestrogen deficiency. Several diseases affect bone function. In rickets and osteomalacia, reduced mineralization leads to soft, pliable bones, due mainly to vitamin D deficiency. In osteoporosis, loss of both organic and mineral components results in changes in internal architecture, leading to fragile bones that fracture easily.

There is currently much discussion about the daily intakes needed to provide maximal retention in bone during early growth so as to achieve optimal peak bone mass, and about the optimal amounts needed to minimize bone loss later in life. For example, the risk of osteoporosis, which some authorities regard as a calcium deficiency disease, might be minimized by ensuring optimal peak bone mass by appropriate calcium intakes in early life as well as by reducing losses later. In judging requirements for calcium, one must take into account other dietary and non-dietary (e.g., genetic and lifestyle) factors that interact with calcium. Thus, adequate physical activity as well as appropriate calcium intake influences bone strength. There are wide differences between recommendations in different parts of the world. This is due partly to differences in the factors that influence calcium requirements and partly to differences in the interpretation of the scientific evidence.

Future research should be aimed at increasing the knowledge base on which requirements for calcium can be based. More information is needed on differences in calcium metabolism by race (which may include genetic and lifestyle factors) and sex and on the factors that determine the body's ability to adapt to low or high intakes.

FURTHER READING

Allen LH. Calcium bioavailability and absorption: a review. *American Journal of Clinical Nutrition*, 1982;35:783-808

British Nutrition Foundation. *Calcium: The Report of a Task Force*. London: British Nutrition Foundation, 1989

Commission of the European Communities. *Nutrient and energy intakes for the European Community*. Reports of the Scientific Committee for Food (31st Series). Luxembourg: Office for Official Publications of the European Communities, 1993

Department of Health. *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. Report on Health and Social Subjects, 41. London: Her Majesty's Stationery Office, 1991

Department of Health. *Nutrition and Bone Health: with particular References to Calcium and Vitamin D*. Report on Health and Social Subjects, 49. London: The Stationery Office, 1998

Food and Nutrition Board of the Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academy Press, 1997

Hamet P. The evaluation of the scientific evidence for a relationship between calcium and hypertension. *Journal of Nutrition*, 1995;125(Suppl 2S):311S-400S

Heaney RP. Nutrition and risk for osteoporosis. In *Osteoporosis*. New York: Academic Press, 1996;Chap 22

Heaney RP. Calcium. In: *Principles of Bone Biology*. New York: Academic Press, 1996;Chap 72

Nilas L. Calcium intake and osteoporosis. *World Review of Nutrition and Dietetics* 1993;73:1-26

Nordin BEC. ed. *Calcium in Human Biology*. ILSI Human Nutrition Reviews. London: Springer-Verlag, 1988

Prentice A. Calcium requirements of children. *Nutrition Reviews* 1995;53:37-45

Prentice A. Is nutrition important in osteoporosis? *Proceedings of the Nutrition Society* 1997;56:357-367

Prentice A. Calcium requirements for breast-feeding mothers. *Nutrition Reviews* 1998;56:124-130

Schaafsma GJ. ed. *Dietary calcium in health*. International Dairy Federation Bulletin 322. Brussels: International Dairy Federation, 1997

Whiting SJ., Wood RJ. Adverse effects of high calcium diets in humans. *Nutrition Reviews* 1997;55:1-9

GLOSSARY

Absorptiometry: Technique used to measure the quantity of matter (e.g., bone) by passing electromagnetic radiation (e.g., light, gamma rays, X-rays, etc.) through the tissue and computing the degree of absorption of the radiation compared with a standard material.

Absorption: The passage of materials, mainly nutrients originating from the diet, from the gastrointestinal tract through the wall of the intestine into the blood. This is termed gross absorption. Net absorption takes into account the secretion of specific nutrients which may sometimes occur in the reverse direction.

Alkaline phosphatases: A group of enzymes that split phosphate from compounds that contain it. A specific alkaline phosphatase in bone aids the process of mineralization. Its presence in blood provides a biomarker for bone formation.

Biomarkers: Measurements in the human body or its products. They may provide indices of nutritional status, of disease risk or, in relation to bone, of the extent to which bone formation or breakdown is occurring.

Bone: Dense, hard but slightly elastic connective tissue contributing to the skeleton. Bone comprises cells, collagen fibres and an organic ground substance, encrusted in a crystalline mineral. The mineral is mainly a complex calcium phosphate salt, but other mineral elements are present. In general, compact (or cortical) bone forms the outer part, and trabecular (or cancellous) bone forms the inner part of the bones.

Bone mineral content: The amount of bone mineral present (usually expressed as g/cm) in a given piece of bone as measured by scanning with an absorptiometer.

Bone mineral density: The bone mineral content per unit area of bone (g/cm^2).

Calcitonin: A protein hormone involved in blood calcium homeostasis. It inhibits the release of calcium from bone and promotes urinary excretion, thereby tending to reduce blood calcium concentration.

Calcitriol: A steroid hormone that promotes active absorption of calcium from the small intestine and enhances the reabsorption of calcium from the kidneys, thereby tending to increase blood calcium concentration. It is formed from vitamin D, and its chemical name is 1,25-dihydroxycholecalciferol (sometimes called 1,25-dihydroxyvitamin D).

Calcium: An abundant element with an atomic weight of 40 denoted by the symbol Ca. It forms positively charged ions (Ca^{++}) and has several stable and radioactive isotopes.

Cancellous bone: *See* Bone.

Cardiovascular disease: Any one of numerous abnormal conditions characterized by dysfunction of the heart and blood vessels.

Collagen: A fibrous protein characteristic of connective tissues, including bone.

Compact, cortical bone: *See* Bone.

Dietary Reference Values (DRVs): A set of recommendations for nutrient intakes of population groups to ensure that deficiency is unlikely or that intakes are safe. *See* also Reference Nutrient Intake.

1,25-Dihydroxy-vitamin D: *See* Calcitriol.

Endogenous: From within the body; thus, endogenous secretion refers to the excretion of body substances (e.g., bile, pancreatic juices) into the gastrointestinal tract.

Enzymes: Proteins that catalyse the reactions of metabolism, speeding them up without themselves being used up. Each enzyme is specific for a given substrate and/or reaction.

Epidemiology: The study of the distribution and determinants of disease in human populations and the application of this study to control health problems.

Extracellular: Inside the body but not within the cells.

Gastrointestinal tract: The organ along which food travels from the mouth until the undigested remnants emerge as stools. Mixing and some digestion occur in the stomach, where the environment is acidic. Most digestion and absorption of nutrients occurs in the small intestine. The large intestine, principally the colon, contains very large numbers of microorganisms capable of fermenting food components that have escaped digestion in the small intestine.

Homeostasis: A relative constancy in the internal environment of the body naturally maintained by adaptive responses that promote healthy survival.

Hormone: A chemical substance produced in one part or organ of the body that initiates or regulates the activity of an organ or group of cells in another part of the body.

Hypertension: A disorder characterized by elevated blood pressure persistently exceeding systolic/diastolic pressures of 140/90 mm mercury.

Intervention trial: A study in which exposure to the factor under investigation is modified by the investigator; an experimental study.

Intracellular: Within cells.

Ion: An electrically charged form of an element or compound (e.g., Ca^{++}).

Kidney stone: An agglomeration of a calcium salt (usually either phosphate or oxalate) that occurs when urine becomes supersaturated as a result of the failure of metabolic control mechanisms.

Matrix: The organic, as distinct from the mineral, part of bone; sometimes called “osteoid”.

Metabolism: Complex interacting network of biochemical reactions within living organisms.

Mitochondria: Small organelles in cells in which cellular respiration occurs, providing the principal source of cellular energy.

Osteoblasts: Cells in bone responsible for bone formation.

Osteocalcin: The second most abundant protein in bone after collagen. It binds strongly to the bone mineral, and its synthesis is dependent on the presence of vitamin K.

Osteoclasts: Cells in bone responsible for the breakdown (resorption) of bone.

Osteoid: *See* Matrix.

Osteomalacia: A disease in which bones are softened and weakened as a result of reduced mineralization due to inadequate availability of calcium and phosphorus.

Osteoporosis: A disease in which bones become more fragile and susceptible to fracture with minimal trauma. There is less total bone, and the micro-architecture of the bones is altered.

Parathyroid hormone: A protein hormone that tends to cause a rise in blood calcium concentration. It acts by promoting the conversion of vitamin D into calcitriol, thereby increasing the efficiency of calcium absorption and by reducing urinary calcium excretion.

Phytic acid: A hexaphosphate of inositol found in many vegetables and often associated with dietary fibre. It binds calcium strongly and inhibits its absorption.

Recommended Dietary Allowance (RDA): Also called Recommended Daily Allowance (or Amount). *See* Reference Nutrient Intake.

Reference Nutrient Intake (RNI): An amount of a nutrient that is enough, or more than enough, for about 97% of people in a population group. The terms Recommended Daily Allowance (or Amount) (RDA) and Recommended Daily Intake (RDI) are similarly defined. If the average intake of a group is at the RNI, the risk of deficiency in the group is very small.

Remodelling: A process that contributes to bone turnover. A small area of bone (“remodelling site”) is degraded by osteoclasts (is "resorbed”); osteoblasts subsequently create new bone to restore the bone that was previously resorbed.

Renin: An enzyme that acts in blood vessels to form a substance that regulates blood pressure.

Resorption: The removal of bone mineral and matrix together, either as a new physiological process (as in bone remodelling) or a pathological condition.

Risk factor: Physical condition or lifestyle that in epidemiologic studies appears to increase susceptibility to a particular disease.

SI units (Système internationale d’unités): A coherent system of measurement based on seven base units (metre, kilogram, second, ampere, kelvin, mole, candela). In SI units, 1 mole of calcium is equivalent to 40 g.

Trabecular: *See* Bone.

Turnover: The simultaneous formation and breakdown of a part of the body, e.g., bone.

Urinary excretion: Urine is a fluid secreted by the kidneys, stored in the bladder and voided through the urethra. It is a means by which water, salts (including calcium salts) and various small organic substances are excreted from the body.

Vitamin D: A fat-soluble vitamin with a steroid structure that is present in a limited number of foods and also formed in the skin from cholesterol by the action of ultraviolet light. It is converted by a series of reactions in liver and kidney to calcitriol, which is the active form.

Vitamin K: A group of fat-soluble vitamins known chemically as menaquinones that are essential for the formation of various proteins involved in blood clotting and of osteocalcin.

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