19. Calcium

Physiology

The adult male contains approximately 1.2 kg calcium (i.e. 1.5-2 % of the body weight), about 99 % of which is in the skeleton and the teeth; the residual 1 % is distributed between soft tissues (0.6 %) and the extracellular fluid (ECF) (0.06 %) including plasma (0 03 %). The intracellular concentration of calcium ranges from 15 mmol/kg in muscle and platelets to as little as 0.02 mmol/kg in erythrocytes. Plasma and ECF calcium concentrations are 2.0-2.5 mmol/L; of this approximately 10 % is complexed with citrate, phosphate, bicarbonate, and 45 % is bound to circulating proteins of which 80-90 % is bound to albumin. About 45 % is present as free calcium ions – this is the functionally active pool, and it is far in excess of the intracellular activity of free calcium, which is only about 0.1 µmol/L [1,2].

Calcium in bone has a structural function as a component of calcium hydroxyapatite, the principal bone mineral, which is complexed within the glycosaminoglycan ground substance and collagen fibres of the organic matrix.

Calcium has an important regulatory role; the thousand fold gradient between extra- and intra-cellular ionic calcium concentrations is fundamental to cellular signal transduction and amplification. An induced influx of calcium triggers and activates a variety of cellular physical and metabolic events such as enzyme activation, muscle contraction, neurotransmission, vesicular secretion, cellular aggregation, transformation and cell division.

Although some calcium is absorbed in the distal bowel most is taken up in the proximal intestine via a carrier-mediated pathway and by diffusion which may be paracellular. The former involves a calcium-binding protein which transfers the element across the enterocyte to the baso-lateral membrane where it is extruded by Ca-Mg ATPase. When calcium requirements are increased, circulating concentrations of calcitriol (1,25-dihydroxycholecalciferol) increase, upregulating the carrier-dependent absorption of calcium.

Within the intestinal lumen dietary components such as phytate, oxalate, alginate, uronate, phosphate, and unabsorbed lipids may bind calcium and reduce its absorption. On the other hand the luminal availability and absorption of the element is enhanced by lactose, phosphatidic acid, amino acids, sucrose, and increased intraluminal pH [3].

Calcium excretion occurs via both the gastrointestinal tract and the kidneys. The urinary content of calcium is related closely to the dietary intake of the element. Up to 97 % of the calcium entering the renal glomerular filtrate can be reabsorbed. The remaining 3 % may represent an 'obligatory' urinary loss of calcium which is considered as a significant determinant of calcium requirements. Urinary calcium loss rises with increasing intakes of sodium and protein; however the latter effect may be offset by the accompanying high phosphorus intakes in the protein sources.

Calcium homoeostasis controls and protects the metabolically vital plasma pool of ionised calcium by simultaneously modifying its absorption, renal excretion and turnover in the mobilisable pool in bone. The principal regulators of these processes are parathyroid hormone, calcitonin, and calcitriol [4].

The secretion of parathyroid hormone is increased in response to low plasma ionised calcium concentrations and, possibly, low plasma magnesium concentrations. Initially this increased secretion is effected by increased cellular production of the hormone itself but with chronic hypocalcaemia parathyroid hyperplasia sustains the increased secretion of hormone. Parathyroid hormone increases renal excretion of phosphate and retention of calcium. It also stimulates the 1 α-hydroxylation of calcidiol (25-OH cholecalciferol) to calcitriol; thereby having an indirect effect on the intestinal absorption of calcium. Parathyroid hormone may also have a direct effect on the enterocyte. The hormone increases bone turnover and the release of calcium from the freely exchangeable calcium pools. It does this first via the surface osteocytes and in the long term by increasing the number of basic multicellular units (BMU) which mediate and coordinate bone turnover.

Calcitriol stimulates intestinal calcium uptake by increasing the enterocytic production of calcium-binding protein. It also induces the maturation of osteoblasts thereby stimulating calcification of bone matrix, whilst simultaneously blocking bone resorption by inhibiting parathyroid hormone production. Calcitonin is secreted by the thyroid C cells in response to high plasma ionised calcium activity, which it reduces by increasing the renal excretion of calcium and reducing osteoclastic activity.

Other hormones including the female sex hormones, mineralocorticoids, the thyroid hormones, and parathyroid hormone-related protein have a direct or indirect effect via the BMU on skeletal mineralisation and calcium metabolism but the precise mechanisms are not clear.

Deficiency and excess

Acute calcium deficiency arising from dietary origin is rare, the exception being young infants fed infant formulas with an inappropriately low calcium:phosphorus ratio. The features are muscular weakness and tetany resulting from reduced ECF ionised calcium activity. Thus features of calcium deficiency are commonly seen in severe systemic alkalosis in which ionised calcium levels are reduced.

Chronic calcium deficiency causes a reduction in bone density in children and may contribute to an increased fracture rate; it is debatable whether or not it causes growth retardation in children. Similarly the role and importance of an inadequate calcium intake in the pathogenesis of osteoporosis is not clear. Adequate bone formation depends on many nutrients and similarly the aetiology of osteoporosis is probably multifactorial [4]. It is uncertain that current calcium intakes play a major role in the pathogenesis of osteoporosis [5,6]. Although calcium supplements (1 g calcium/d) slow the loss of bone density in established post-menopausal osteoporosis, this needs to be further evaluated in the context of the similar, or possibly extra, benefits which can be achieved by exercise, vitamin D or hormone replacement therapy [7,8,9,10,11,12] or by changes in lifestyle and calcium intakes in earlier life.

Calcium excess arising from dietary intake is rare because of the effectiveness of the homoeostatic mechanisms. In healthy individuals, intakes of 2.5 g (62.5 mmol) are tolerated. At intakes above this, as may occur with ingestion of supplements of calcium (and sometimes of vitamin D) or of antacids, there is a risk of renal stones, hypercalcaemia and impaired renal function.

Requirements

Adults

Since plasma ionised calcium activity is maintained by mobilisation of skeletal calcium stores, as well as by increased net intestinal absorption and renal conservation of the element, if the dietary intake of calcium is inadequate the plasma ionised calcium can be maintained for a long time at the expense of the skeletal pool. The approximately thousand fold bigger size of this endogenous resource of calcium compared with ingested amounts (500-1000 mg daily) makes it difficult to establish reliable conditions under which obligatory losses of calcium can be gauged against dietary intakes. Although metabolic balances have been used to analyse the adequacy of calcium requirements, experience has shown that few studies allowed

sufficient time for systemic and intestinal adaptation to altered dietary intakes to occur or measured simultaneously the systemic hormonal homoeostatic adaptation. The prolonged studies of Malm [9] suggest that with time adult men can adapt to a calcium intake of 400 mg/d, but most metabolic studies have used intakes in excess of this and extrapolation of the data is limited also by the variable bioavailability arising from the various diets used.

Bone density or the incidence of osteoporosis were not considered suitable measurements for determining calcium requirements because they are both subject to many physical, genetic and nutritional influences [4,5].

Requirements have been estimated on the assumption that the principal determinant is the obligatory loss of the element via skin, faeces and urine, with additional estimated increments for skeletal growth and consolidation. In adults the needs for bone growth are minimal even though some 10 % of bone consolidation occurs during the third decade. No reliable data are available on losses via sweat and the integuments although these may not be negligible [6]. A level of such nonfaecal losses including 'obligatory urinary loss' has been taken as 160 mg/d. Assuming conservatively an absorptive efficiency of 30 % this translates to an average requirement of 530 mg/d (rounded to 550 mg/d) which with a 2SD distribution comes to 700 mg/d as a PRI with the LTI being set at 400 mg/d. [This may be a generous recommendation, and at an alternative, and not unlikely, absorptive efficiency of 40 % the average 'systemic need' would be met by an intake of 400 mg (+2SD = 520 mg)].

An upper limit of intake of 2.5 g/d is advised.

Children

Between the ages of 1 and 10, the average daily calcium retention needed for skeletal growth has been estimated to rise from 70 to 150 mg/d [13]. The PRIs given are based on the assumption that there is a net absorption of 35% of dietary calcium, with 30% (considered as equivalent to 2SD) being added to the calculated amount to allow for individual variation.

In the absence of reliable information, the PRI for 6-11 months old infants was taken as the same as for 1-3 year olds.

PRIs for adolescents are raised above those for adults to reflect the increased requirements for skeletal development. They are derived from a mean retention of 250 mg/d in girls and 300 mg/d in boys, assuming net absorption of 40% of dietary calcium, again with 30% being added to cover individual variation.

Pregnancy

There appears to be no spontaneous increase in calcium consumption by pregnant women. The physiological way of obtaining the calcium required for fetal growth includes an increased efficiency of dietary absorption and the mobilization of calcium from maternal bone [14]. There seems to be no need to increase the dietary calcium intake during pregnancy.

Lactation

The calcium required in the milk is normally obtained from the spontaneous increase of food intake by lactating women. On the assumption of an absorption efficiency of 40%, plus an allowance for 2SD, an extra 500 mg/d is proposed for lactating women.

Summary

Adults	mg/d
Average Requirement	550
Population Reference Intake	700
Lowest Threshold Intake	400

Population Reference Intakes of other groups

Age Group		PRI (mg/d)
	6-11 m	400
	1-3 y	400
	4-6 y	450
	7-10 y	550
Males	11-14 y	1000
	15-17 y	1000
Females	11-14 y	800
	15-17 y	800
	Pregnancy	700
	Lactation	1200

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