



Calcium metabolism – a review of literature

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ABSTRACT

Osteoporosis is a disease of bones that leads to an increased risk of fracture. Osteoporosis is defined by the World Health Organization (WHO) as a bone mineral density of 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by dual-energy X-ray absorptiometry, and calcium metabolism plays a very important role in such bone diseases. Calcium metabolism or calcium homeostasis is the mechanism by which the body maintains adequate calcium levels. Derangements of this mechanism lead to hypercalcemia or hypocalcemia, this article highlights majorly on the calcium metabolism and its effects on our health.

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Introduction

Osteoporosis, the thinning of bone due to the net loss of calcium and bone structure, occurs primarily with ageing.¹ The rediscovery of earlier information that calcium deficiency led to the development of osteoporosis (not rickets and osteomalacia) in experimental animals² resulted in a re-examination of osteoporosis in humans, notably in postmenopausal women. This re-examination yielded evidence in the late 1960s that menopausal bone loss was not due to a decrease in bone formation but rather to an increase in bone resorption³⁻⁶; this has had a profound effect on our understanding of other forms of osteoporosis and has led to a new paradigm that is still evolving.

Changes in bone metabolism following the cessation of ovarian function at the time of menopause are characterized by an increased resorption without a commensurate rise in formation.⁷ This accelerated bone remodeling leads to progressive deterioration of bone micro architecture^{7,8} decreased skeletal strength^{9,10} and increased risk of fragility fractures with aging.¹¹

In the light of the above factors an attempt is made to review the literature on calcium metabolism.

Chemistry and distribution of calcium

Calcium is a divalent cation with an atomic weight of 40. In the elementary composition of the human body, it ranks fifth after oxygen, carbon, hydrogen, and nitrogen, and it makes up 1.9% of the body by weight.¹² Carcass analyses show that calcium constitutes 0.1–0.2% of early fetal fat-free weight, rising to about 2% of adult fat-free weight. In absolute terms, this represents a rise from about 24 g (600 mmol) at birth to 1300 g (32.5 mol) at maturity, requiring an average daily positive calcium balance of 180mg (4.5mmol) during the first 20 years of growth.

Nearly all (99%) of total body calcium is located in the skeleton. The remaining 1% is equally distributed between the teeth and soft tissues, with only 0.1% in the extracellular fluid (ECF). In the skeleton it constitutes 25% of the dry weight and 40% of the ash weight. The ECF contains ionized calcium at

concentrations of about 4.8mg/100ml (1.20 mmol/l) maintained by the parathyroid–vitamin D system as well as complexed calcium at concentrations of about 1.6mg/100ml (0.4 mmol/l). In the plasma there is also a protein-bound calcium fraction, which is present at a concentration of 3.2mg/100ml (0.8 mmol/l). In the cellular compartment, the total calcium concentration is comparable with that in the ECF, but the free calcium concentration is lower by several orders of magnitude.¹³

Biological role of calcium

Calcium salts provide rigidity to the skeleton and calcium ions play a role in many, if not most, metabolic processes. In the primitive exoskeleton and in shells, rigidity is generally provided by calcium carbonate, but in the vertebrate skeleton, it is provided by a form of calcium phosphate which approximates hydroxyapatite $[\text{Ca}_{10}(\text{OH})_2(\text{PO}_4)_6]$ and is embedded in collagen fibrils. Bone mineral serves as the ultimate reservoir for the calcium circulating in the ECF. Calcium enters the ECF from the gastrointestinal tract by absorption and from bone by resorption. Calcium leaves the ECF via the gastrointestinal tract, kidneys, and skin and enters into bone via bone formation. In addition, calcium fluxes occur across all cell membranes. Many neuromuscular and other cellular functions depend on the maintenance of the ionized calcium concentration in the ECF. Calcium fluxes are also important mediators of hormonal effects on target organs through several intracellular signalling pathways, such as the phosphoinositide and cyclic adenosine monophosphate systems. The cytoplasmic calcium concentration is regulated by a series of calcium pumps, which either concentrate calcium ions within the intracellular storage sites or extrude them from the cells (where they flow in by diffusion). The physiology of calcium metabolism is primarily directed towards the maintenance of the concentration of ionized calcium in the ECF. This concentration is protected and maintained by a feedback loop through calcium receptors in the parathyroid glands¹⁴, which control the secretion of parathyroid hormone. This hormone increases the renal tubular reabsorption of calcium, promotes intestinal calcium absorption by

stimulating the renal production of 1,25-dihydroxyvitamin D or calcitriol

[1,25-(OH)₂D], and, if necessary, resorbs bone. However, the integrity of the system depends critically on vitamin D status; if there is a deficiency of vitamin D, the loss of its calcaemic action¹⁵ leads to a decrease in the ionized calcium and secondary hyperparathyroidism and hypophosphataemia. This is why experimental vitamin D deficiency results in rickets and osteomalacia whereas calcium deficiency gives rise to osteoporosis.^{12,16}

Determinants of calcium balance

Calcium intake

In a strictly operational sense, calcium balance is determined by the relationship between calcium intake and calcium absorption and excretion. A striking feature of the system is that relatively small changes in calcium absorption and excretion can neutralize a high intake or compensate for a low one. There is a wide variation in calcium intake between countries, generally following the animal protein intake and depending largely on dairy product consumption. The lowest calcium intakes occur in developing countries, particularly in Asia, and the highest in developed countries, particularly in North America and Europe.

Calcium absorption

Ingested calcium mixes with digestive juice calcium in the proximal small intestine from where it is absorbed by a process which has an active saturable component and a diffusion component.¹⁷⁻²¹ When calcium intake is low, calcium is mainly absorbed by active (transcellular) transport, but at higher intakes, an increasing proportion of calcium is absorbed by simple (paracellular) diffusion. The unabsorbed component appears in the faeces together with the unabsorbed component of digestive juice calcium known as endogenous faecal calcium. Thus, the faeces contain unabsorbed dietary calcium and digestive juice calcium that was not reabsorbed. True absorbed calcium is the total amount of calcium absorbed from the calcium pool in the intestines and therefore contains both dietary and digestive juice components. Net absorbed calcium is the difference between dietary calcium and faecal calcium and is numerically the same as true absorbed calcium minus endogenous faecal calcium. At zero calcium intake, all the faecal calcium is endogenous and represents the digestive juice calcium which has not been reabsorbed; net absorbed calcium at this intake is therefore negative to the extent of about 200mg (5mmol).^{21,22} When the intake reaches about 200mg (5mmol), dietary and faecal calcium become equal and net absorbed calcium is zero. As calcium intake increases, net absorbed calcium also increases, steeply at first but then, as the active transport becomes saturated, more slowly until the slope of absorbed on ingested calcium approaches linearity with an ultimate gradient of about 5–10%.^{17,18,23,24} True absorption is an inverse function of calcium intake, falling from some 70% at very low intakes to about 35% at high intakes. Percentage net absorption is negative at low intake, becomes positive as intake increases, reaches a peak of about 35% at an intake of about 400 mg, and then falls off as intake increases further. True and net absorption converge as intake rises because the endogenous faecal component that separates them becomes proportionately smaller.

Many factors influence the availability of calcium for absorption and the absorptive mechanism itself. In the case of the former, factors include the presence of substances which

form insoluble complexes with calcium, such as the phosphate ion. The relatively high calcium–phosphate ratio of 2.2 in human milk compared with 0.77 in cow milk¹² may be a factor in the higher absorption of calcium from human milk than cow milk. Intestinal calcium absorption is mainly controlled by the serum concentration of 1,25-(OH)₂D. The activity of the 1- α -hydroxylase, which catalyses 1,25-(OH)₂D production from 25-hydroxyvitamin D (25-OH-D) in the kidneys, is negatively related to plasma calcium and phosphate concentrations and positively related to plasma parathyroid hormone concentrations.¹⁵ Thus the inverse relation between calcium intake and fractional absorption described above is enhanced by the inverse relationship between dietary calcium and serum 1,25-(OH)₂D.^{15,25,26} Phytates, present in the husks of many cereals as well as in nuts, seeds, and legumes, can form insoluble calcium phytate salts in the gastrointestinal tract. Excess oxalates can precipitate calcium in the bowel but are not an important factor in most diets.

Urinary calcium

Urinary calcium is the fraction of the filtered plasma water calcium which is not reabsorbed in the renal tubules. At a normal glomerular filtration rate of 120ml/min and an ultrafiltrable calcium concentration of 6.4mg/100ml (1.60 mmol/l), the filtered load of calcium is about 8mg/min (0.20mmol/min) or 11.6 g/day (290 mmol/day). Because the average 24-hour calcium excretion in subjects from developed countries is about 160–200mg (4–5mmol), it follows that 98–99% of the filtered calcium is usually reabsorbed in the renal tubules. However, calcium excretion is extremely sensitive to changes in filtered load. A decrease in plasma water calcium of only 0.17mg/100ml (0.043 mmol/l), which is barely detectable, was sufficient to account for a decrease in urinary calcium of 63 mg (1.51mmol) when 27 subjects changed from a normal- to a low-calcium diet²¹. This very sensitive renal response to calcium deprivation combines with the inverse relationship between calcium intake and absorption to stabilize the plasma ionized calcium concentration and to preserve the equilibrium between calcium entering and leaving the ECF over a wide range of calcium intakes. However, there is always a significant obligatory loss of calcium in the urine (as there is in the faeces), even on a low calcium intake, simply because maintenance of the plasma ionized calcium and, therefore, of the filtered load, prevents total elimination of calcium from the urine. The lower limit for urinary calcium in developed countries is about 140 mg (3.5mmol) but depends on protein and salt intakes. From this obligatory minimum, urinary calcium increases on intake with a slope of about 5–10%.^{23,24,28}

Insensible losses

Urinary and endogenous faecal calcium are not the only forms of excreted calcium; losses through skin, hair, and nails also need to be taken into account. These are not easily measured, but a combined balance and isotope procedure has yielded estimates of daily insensible calcium losses in the range of 40–80mg (1–2mmol), which are unrelated to calcium intake.^{29,30} Thus, the additional loss of a mean of 60mg (1.5 mmol) as a constant to urinary calcium loss raises the level of dietary calcium at which absorbed and excreted calcium reach equilibrium from 520 to 840 mg (13 to 21 mmol).

Conclusion

Calcium balance refers to the state of the calcium body stores, primarily in bone, which are largely a function of dietary intake, intestinal absorption, renal excretion, and bone

remodeling. Bone calcium balance can be positive, neutral, or negative, depending on a number of factors, including growth, aging, and acquired or inherited disorders. Calcium homeostasis refers to the hormonal regulation of serum ionized calcium by parathyroid hormone, 1,25-dihydroxyvitamin D, and serum ionized calcium itself, which together regulate calcium transport at the gut, kidney, and bone. Hypercalcemia and hypocalcemia indicate serious disruption of calcium homeostasis but do not reflect calcium balance on their own. Calcium balance studies have determined the dietary and supplemental calcium requirements needed to optimize bone mass in healthy subjects.

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