Calcium metabolism

Done by

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Introduction

Calcium

Calcium is a chemical element with a symbol Ca and atomic number 20. It has an atomic mass of 40.078. Calcium is a soft grey alkaline earth metal, and is the fifth most abundant element in the earth’s crust, and it is the most common metal in many animal and in the human body.

History

Calcium was known as early as the first century when the Ancient Romans prepared lime as calcium oxide. It was not isolated until 1808 in England when Sir Humphry Davy electrolyzed a mixture of lime and mercuric oxide. Davy was trying to isolate calcium; when he heard that Berzelius and Pontin prepared calcium amalgam by electrolyzing lime in mercury, he tried it himself. He worked with electrolysis throughout his life and also discovered/isolated sodium, potassium, magnesium, boron and barium.
Ca structure in the human body

Approximately 99% of total body calcium is in the skeleton and teeth and 1% in blood and soft tissues.

Sources

Calcium is present in variable amounts in all the foods and water we consume, although the main sources are dairy products and vegetables.
High Calcium Foods

Dairy products in general: Milk, yogurt, pudding, cheese and Sardines with bones.

**Calcium Functions**

- Calcium is responsible for construction, formation and maintenance of bone and teeth. This function helps reduce the occurrence of osteoporosis.
- Calcium is a vital component in blood clotting systems and also helps in wound healing.
- Calcium helps to control blood pressure, nerve transmission, regulates heart rhythm, and release of neurotransmitters.
- Calcium is an essential component in the production of enzymes and hormones that regulate digestion, energy, and fat metabolism.
- Calcium helps to transport ions (electrically charged particles) across the membrane.
- Calcium is essential for muscle contraction.
- Calcium assists in maintaining all cells and connective tissues in the body.
- Calcium may be helpful to reduce the incidence of premature heart disease, especially if adequate intakes of magnesium are also maintained.
- Calcium may help to prevent periodontal disease (gum disease).
- Calcium is important to normal kidney function and in the incidence of colon cancer.
- Reduces blood cholesterol levels.
### Calcium RDAs
(Recommended Dietary Allowances)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0 - 0.5 year</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>0.5 - 1 year</td>
<td>600</td>
</tr>
<tr>
<td>Children</td>
<td>1 - 3 years</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>4 - 8 years</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>8 - 10 year</td>
<td>800</td>
</tr>
<tr>
<td>Males</td>
<td>11 - 14 years</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>15 - 18 years</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>19 - 24 years</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>25 - 50 years</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>51+ years</td>
<td>800</td>
</tr>
<tr>
<td>Females</td>
<td>11 - 14 years</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>15 - 18 years</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>19 - 24 years</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>25 - 50 years</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>Over 65 years</td>
<td>1,500</td>
</tr>
</tbody>
</table>

### Normal ranges

The serum level of calcium is closely regulated with a normal total calcium of 2.2-2.6 mmol/L (9-10.5 mg/dL) and a normal ionized calcium of 1.1-1.4 mmol/L (4.5-5.6 mg/dL). The amount of total calcium varies with the level of serum albumin, a protein to which calcium is bound. The biologic effect of calcium is determined by the amount of ionized calcium, rather than the total calcium. Ionized calcium does not vary with the albumin level, and therefore it is useful to measure the ionized calcium level when the serum albumin is not within normal ranges, or when a calcium disorder is suspected despite a normal total calcium level.
P-type ion transporting ATPases are ATP-powered ion pumps that establish ion concentration gradients across biological membranes. Transfer of bound cations to the lumenal or extracellular side occurs while the ATPase is phosphorylated. Here we report at 2.3 Å resolution the structure of the calcium-ATPase of skeletal muscle sarcoplasmic reticulum, a representative P-type ATPase that is crystallized in the absence of Ca²⁺ but in the presence of magnesium fluoride, a stable phosphate analogue. This and other crystal structures determined previously provide atomic models for all four principal states in the reaction cycle. These structures show that the three cytoplasmic domains rearrange to move six out of ten transmembrane helices, thereby changing the affinity of the Ca²⁺-binding sites and the gating of the ion pathway. Release of ADP triggers the opening of the lumenal gate and release of phosphate its closure, effected mainly through movement of the A-domain, the actuator of transmembrane gates.

Proton pumps:
- electrogenic pump,
- electro-neutral pump,
- electro-neutral pump with calcium as its counterion,
- electrogenic proton transport
- electro-neutral anion/OH antiport (according to R.E. CLELAND, 1982).
Calcium pump-catalyzed 18O exchange between inorganic phosphate and water was studied to test the hypothesis that all P-type pumps bind Mg$^{2+}$ before Pi and validate utilization of the rate equation for ordered binding to interpret differences between site-directed mutants and wild-type enzyme. The results were remarkably similar to those obtained earlier with sodium pump (Kasho, VN; Stengelin, M; Smirnova, IN; Faller, LD (1997) Biochemistry 36, 8045–8052). The equation for ordered binding of Mg$^{2+}$ before Pi fit the data best with only a slight chance (0.6%) of Pi binding to apoenzyme. Therefore, Pi is the substrate, and Mg$^{2+}$ is an obligatory cofactor. The intrinsic Mg$^{2+}$ dissociation constant from metalloenzyme ($K'_M = 3.5 \pm 0.3$ mM) was experimentally indistinguishable from the sodium pump value. However, the half-maximal concentration for Pi binding to metalloenzyme ($K'_P = 6.3 \pm 0.6$ mM) was significantly higher (~6-fold), and the probability of calcium pump forming phosphoenzyme from bound Pi ($P_c = 0.04 \pm 0.03$) was significantly lower (~6-fold) than for the sodium pump. From estimates of the rate constants for phosphorylation and dephosphorylation, the calcium pump appears to catalyze phosphoryl group transfer less efficiently than the sodium pump. Ordered binding of Mg$^{2+}$ before Pi implies that both calcium pump and sodium pump form a ternary enzyme•metal•phosphate complex, consistent with molecular structures of other haloacid dehalogenase superfamily members that were crystallized with Mg$^{2+}$ and phosphate, or a phosphate analogue, bound
Proximal convoluted and straight renal tubule segments were studied to determine the effect of Ca on lumen-to-bath phosphate flux (JlbPO4). Increasing bath and perfusate Ca from 1.8 to 3.6 mM enhanced JlbPO4 from $3.3 \pm 0.7$ to $6.6 \pm 0.6$ pmol/mm per min in PC segments ($P$ less than 0.001) but had no effect in SR segments. Decreasing bath and perfusate Ca from 1.8 to 0.2 mM reduced JlbPO4 from $3.7 \pm 0.6$ to $2.2 \pm 0.6$ in S2 segments. These effects were unrelated to changes in fluid absorption and transepithelial potential difference. Increasing cytosolic Ca with a Ca ionophore, inhibiting the Ca-calmodulin complex with trifluoperazine, or applying the Ca channel blocker nifedipine had no effect on JlbPO4 in PC segments. Increasing only bath Ca from 1.8 to 3.6 mM did not significantly affect JlbPO4. However, increasing only perfusate Ca enhanced JlbPO4 from $3.4 \pm 0.7$ to $6.1 \pm 0.7$ pmol/mm per min ($P$ less than 0.005). Inhibition of hydrogen ion secretion, by using a low bicarbonate, low pH perfusate, both depressed base-line JlbPO4 and abolished the stimulatory effect of raising perfusate Ca. Net phosphate efflux (JnetPO4) also increased after ambient calcium levels were raised, ruling out a significant increase in PO4 backflux. When net sodium transport was abolished by reducing the bath temperature to 24 degrees C, JnetPO4 at normal ambient calcium was reduced and increasing ambient calcium failed to increase it, ruling out a simple physicochemical reaction wherein phosphate precipitates out of solution with calcium. The present studies provide direct evidence for a stimulatory effect of Ca on sodium-dependent PO4 absorption in the proximal convoluted tubule, exerted at the luminal membrane. It is postulated that Ca modulates the affinity of the PO4 transporter for the anion.
Dialysate calcium and calcium/phosphate balance in hemodialysis

The changing pattern of pharmaceutical use in dialysis patients has resulted in several alterations to dialysate calcium concentration over the past 40 years. Non-calcium-containing phosphate binders and calcimimetics are the most recent examples of drugs that influence the overall calcium balance in dialysis patients. Renal osteodystrophy, vascular disease, and mortality are believed to be linked in patients with chronic kidney disease (CKD), although to date most of the evidence is based only on statistical associations. The precise pathophysiology of vascular calcification in end-stage renal disease is unknown, but risk factors include age, hypertension, time on dialysis, and, most significantly, abnormalities in calcium and phosphate balance. Prospective studies are required before “cause and effect” can be established with certainty, but it is an active metabolic process with inhibitors and promoters. Serum calcium levels are clearly influenced by dialysate calcium and may therefore play an important role in influencing vascular calcification. Clinical management of hyperphosphatemia is being made easier by the introduction of potent non-calcium-based oral phosphate binders such as lanthanum carbonate. Short-term and long-term studies have demonstrated its efficacy and safety. Vitamin D analogs have been a disappointment in the control of serum parathyroid hormone (PTH) levels, but evidence is emerging that vitamin D has other important metabolic effects apart from this, and may confer survival advantages to patients with CKD. Calcimimetics such as cinacalcet enable much more effective and precise control of PTH levels, but at the cost of a major financial burden. While it is unreasonable to expect that any one of these recent pharmacological developments will be a panacea, they provide researchers with the tools to begin to examine the complex interplay between calcium, phosphate, vitamin D, and PTH, such that further progress is fortunately inevitable.
Calcium levels are regulated by two main hormones

Parathyroid hormone and Calcitotin

Parathyroid hormone (PTH), or parathormone, is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. It acts to increase the concentration of calcium ($Ca^{2+}$) in the blood, whereas calcitonin (a hormone produced by the parafollicular cells (C cells) of the thyroid gland) acts to decrease calcium concentration. PTH acts to increase the concentration of calcium in the blood by acting upon parathyroid hormone receptor in three parts of the body.
Its main function is raising serum calcium. And consequently has an effect on serum phosphate.

Effects on serum calcium (raising)

<table>
<thead>
<tr>
<th>Region</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Bones</td>
<td>It enhances the release of calcium from the large reservoir contained in the bones. Bone resorption is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH. Stimulation is indirect since osteoclasts do not have a receptor for PTH; rather, PTH binds to osteoblasts, the cells responsible for creating bone. Binding stimulates osteoblasts to increase their expression of RANKL, which can bind to osteoclast precursors containing RANK, a receptor for RANKL. The binding of RANKL to RANK stimulates these precursors to fuse, forming new osteoclasts which ultimately enhances the resorption of bone.</td>
</tr>
<tr>
<td>Kidney</td>
<td>It enhances active reabsorption of calcium from distal tubules and the thick ascending limb.</td>
</tr>
<tr>
<td>Intestine</td>
<td>It enhances the absorption of calcium in the intestine by increasing the production of vitamin D and upregulating the enzyme responsible for 1-alpha hydroxylation of 25-hydroxy vitamin D, converting vitamin D to its active form (1,25-dihydroxy vitamin D) which affects the actual absorption of calcium (as Ca²⁺ ions) by the intestine via calbindin.</td>
</tr>
</tbody>
</table>
**Effects on serum phosphate (decrease, with compensation)**

PTH reduces the uptake of phosphate from the proximal tubule of the kidney which means more phosphate is excreted through the urine. However, PTH also enhances the uptake of phosphate from the intestine and bones into the blood. Slightly more calcium than phosphate is released from the breakdown of bone, and the intestinal absorption of phosphate (mediated by an increase in activated vitamin D) is not as dependent on vitamin D as is that of calcium. The end result is a small net drop in the serum concentration of phosphate.

**Feedback regulation**

Increased calcium concentration in the blood acts (via feedback inhibition) to decrease PTH secretion by the parathyroid glands. This is achieved by the activation of calcium-sensing receptors located on parathyroid cells.

** Syndromes **

A high level of PTH in the blood is known as hyperparathyroidism. If the cause is in the parathyroid gland it is called primary hyperparathyroidism. The causes are parathyroid adenoma, parathyroid hyperplasia and parathyroid cancer. If the cause is outside the gland, it is known as secondary hyperparathyroidism. This can occur in chronic renal failure.

A low level of PTH in the blood is known as hypoparathyroidism. Causes include surgical misadventure (e.g. inadvertent removal during routine thyroid surgery), autoimmune disorder, and inborn errors of metabolism.
**Measurements**

PTH can be measured in the blood in several different forms: intact PTH; N-terminal PTH; mid-molecule PTH, and C-terminal PTH, and different tests are used in different clinical situations.

Calcitonin is a 32-amino acid polypeptide hormone that is produced in humans primarily by the parafollicular (also known as C) cells of the thyroid. It acts to reduce blood calcium ($Ca^{2+}$), opposing the effects of parathyroid hormone (PTH).

**Biosynthesis**

Calcitonin is formed by the proteolytic cleavage of a larger prepropeptide, which is the product of the CALC1 gene (CALCA). The CALC1 gene belongs to a superfamily of related protein hormone precursors including islet amyloid precursor protein, calcitonin gene-related peptide, and the precursor of adrenomedullin.

**Physiology**

In many ways, calcitonin has the counter effects of parathyroid hormone (PTH), to be specific, calcitonin reduces blood $Ca^{2+}$ levels in three ways:

- Decreasing $Ca^{2+}$ absorption by the intestines
- Decreasing osteoclast activity in bones
- Decreasing $Ca^{2+}$ and phosphate reabsorption by the kidney tubules
Actions

Its actions, in a broad sense, are:

**Bone mineral metabolism:**
- Prevent postprandial hypercalcemia resulting from absorption of \( \text{Ca}^{2+} \) from foods during a meal
- Promote mineralization of skeletal bone
- Protect against \( \text{Ca}^{2+} \) loss from skeleton during periods of \( \text{Ca}^{2+} \) stress such as pregnancy and lactation

**Vitamin D regulation**
- A satiety hormone:
  - Inhibit food intake in rats and monkeys
  - May have CNS action involving the regulation of feeding and appetite

Receptor

The calcitonin receptor is a G protein-coupled receptor, which is coupled by \( G_s \) to adenylyl cyclase and thereby to the generation of cAMP in target cells.

Pharmacology

Calcitonin is used for the treatment of:
- Postmenopausal osteoporosis
- Hypercalcaemia
- Paget's disease
- Bone metastases
- Phantom limb pain
Calcium metabolism disease

1) Osteoporosis
2) Osteomalacia
3) Rickets
4) Secondary nutritional hyperparathyroidism
5) Fibrous osteodystrophy

Osteoporosis
Osteoporosis leaves bones brittle and prone to fracture.

The bone factory

In osteoporosis, the cortex becomes thinner and more brittle, while the inner trabecular bone develops larger holes.

Mature adult bone is continually being remodelled. Specialised cells called osteoclasts absorb old bone and other cells called osteoblasts create new, strong, bone. In this way, bone retains its strength and density.
Normally in the adult skeleton, about 3% of 'cortical' bone – the outer hard part – and 25% of 'trabecular' bone – the inner, honeycomb part – is remodelled each year. For this process to work properly we need the minerals calcium and phosphorus from which bone is made (these come from our diet) and a range of hormones and vitamins which drive the process.

As we grow, our bone mass steadily increases; more bone is made than is absorbed. By early adulthood, we reach what is known as peak bone mass, which is the maximum density achieved by our bones. After about 35 years of age, even though bone formation still occurs, our bone mass slowly declines as more is absorbed than is added. The cortex becomes thinner and more brittle, while the inner trabecular bone develops larger holes.

In women after menopause, absorption and thinning of bones occurs even more rapidly. As bone is lost, the skeleton becomes progressively more and more osteoporotic and prone to bone fracture. While almost everyone loses bone, some people are less likely to suffer from osteoporosis until they are very old (if at all).

In some cases, osteoporosis is caused by a deficiency of these hormones or vitamins. Osteoporosis accelerates in women after menopause. That’s because after menopause, levels of the sex hormone oestrogen fall. Oestrogen is thought to play a role in maintaining bone mass by slowing the process of bone breakdown by osteoclasts.

People who don’t have enough calcium in the diet are prone to osteoporosis. Failure to absorb calcium properly from the gut can also play a role. This may be due to a disease of the small bowel (where calcium is absorbed) or a deficiency in vitamin D, which is needed for calcium absorption.

Osteoporosis isn’t an inherited disease, but it tends to run in families. So it’s more likely if there’s someone else in the family that has it.
**Symptoms**

The problem with osteoporosis is that it’s a silent condition; bone loss is gradual and invisible. People may not know they have osteoporosis until their bones become so weak that a sudden strain, bump, or fall causes fracture which wouldn’t have happened in a person with normal strong bones.

Fractures are most common in the wrist, hip, spine, pelvis and upper arm - but any bone can fracture. People with smaller, lighter frames are more likely to suffer a fracture than larger, taller people because they have less bone mass to start with, so are more likely to get a fracture for the same degree of bone demineralisation.

When a fracture occurs it can be quite serious. It often requires hospitalisation - in the case of a fractured hip for example - and then a prolonged period of rehabilitation.

Osteoporosis in the spine may cause collapse of the spinal vertebrae resulting in severe back pain, spinal deformities, loss of height, kyphosis of the spine or ‘dowagers hump.

**Rickets**

Rickets is a softening of the bones in children potentially leading to fractures and deformity. Rickets is among the most frequent childhood diseases in many developing countries. The predominant cause is a vitamin D deficiency, but lack of adequate calcium in the diet may also lead to rickets. Although it can occur in adults, the majority of cases occur in children suffering from severe malnutrition, usually resulting from famine or starvation during the early stages of childhood. Osteomalacia is the term used to describe a similar condition occurring in adults, generally due to a deficiency of vitamin D.
“rachitis” The “wrist widening” of rickets

Epidemiology

Those at higher risk for developing rickets include:

* Breast-fed infants whose mothers are not exposed to sunlight.
* Breast-fed infants who are not exposed to sunlight.
* Individuals not consuming fortified milk, such as those who are lactose intolerant.

Individuals with red hair have a decreased risk for rickets due to their greater production of vitamin D in sunlight.

Etiology

Vitamin D is required for proper calcium absorption from the gut. In the absence of vitamin D, dietary calcium is not properly absorbed, resulting in hypocalcemia, leading to skeletal and dental deformities and neuromuscular symptoms, e.g. hyperexcitability.
Radiograph of a two-year old rickets sufferer, with a marked genu varum (bowing of the femurs) and decreased bone opacity, suggesting poor bone mineralization.

**Signs and symptoms of rickets include:**

1) Bone pain or tenderness
2) dental problems
3) muscle weakness (rickety myopathy or “floppy baby syndrome”)
4) increased tendency for fractures (easily broken bones), especially greenstick fractures
5) Skeletal deformity
   * Toddlers: Bowed legs (genu varum)
   * Older children: Knock-knees (genu valgum) or “windswept knees”
   * Cranial, spinal, and pelvic deformities
6) Growth disturbance
7) Hypocalcemia (low level of calcium in the blood), and
8) Tetany (uncontrolled muscle spasms all over the body).
9) Craniotabes (soft skull)
10) Costochondral swelling (aka “rickety rosary” or “rachitic rosary”)
11) Harrison’s groove
12) Double malleoli sign due to metaphyseal hyperplasia
An X-ray or radiograph of an advanced sufferer from rickets tends to present in a classic way: bow legs (outward curve of long bone of the legs) and a deformed chest. Changes in the skull also occur causing a distinctive “square headed” appearance. These deformities persist into adult life if not treated.

Drug Regulating
Ca deficiency is regulated by the following drugs

Saline Diuresis:
In hypercalcemia of sufficient severity to produce symptoms, rapid reduction of serum calcium is required. The first steps include rehydration with saline and diuresis with furosemide. Most patients presenting with severe hypercalcemia have a substantial component of prerenal azotemia owing to dehydration, which prevents the kidney from compensating for the rise in serum calcium by excreting more calcium in urine. Therefore, the initial infusion of 500-1000ml/h of saline to reverse the dehydration and restore urine flow can by itself substantially lower serum calcium. The addition of a loop diuretic such as furosemide not only enhances urine flow but also inhibits calcium reabsorption in the ascending limb of the loop of Henle.

Biphosphonates:
Etidronate, 7.5mg/kg in 250-500ml saline, infused over several hours each day for 3 days, has proved quite useful in treating hypercalcemia of malignancy. More recently, Pamidronate, 60-90mg. infused over 2-4 hours, and Zoledronate, 4mg, infused over 15 minutes, have been approved for the same indication and appear to be more effective. This form of treatment is remarkably free of toxicity. The effects generally persist for weeks, but treatment can be repeated after a 7 day interval if necessary and if renal function is not impaired.
Calcitonin:
Calcitonin has proved useful as ancillary treatment in a large number of patients. Calcitonin by itself seldom restores serum calcium to normal, and refractoriness frequently develops. However, its lack of toxicity permits frequent administration at high dose. An effect on serum calcium is observed within 4-6 hours and lasts for 6-10 hours. Calcimar (salmon calcitonin) is available for parenteral and nasal administration.

Gallium Nitrate:
Gallium nitrate is approved by the Food and Drug Administration for the management of hypercalcemia of malignancy and is undergoing trials for the treatment of advanced Paget’s disease. This drug acts by inhibiting bone resorption. At a dosage of 200mg/m² body surface area per day given as a continuous intravenous infusion in 5% dextrose for 5 days, gallium nitrate proved superior to calcitonin in reducing serum calcium in cancer patients. Because of potential nephrotoxicity, patients should be well-hydrated and have good renal output before starting the infusion.

Vitamin D:
When rapidity of action is required, 1,25(OH)2D3(calcitriol), 0.25-1 microgram daily, is the vitamin D metabolite of choice, since it is capable of raising serum calcium within 24-48 hours. Calcitriol also raises serum phosphate, though this action is usually not observed early in treatment. The combined effects of calcitriol and all other vitamin D metabolites and analogs on both calcium and phosphate make careful monitoring of these mineral levels especially important to avoid ectopic calcification secondary to an abnormally high serum calcium phosphate product. Calcifediol (25[OH]D3) is less effective than calcitriol in stimulating intestinal calcium transport, so that hypercalcemia is less of a problem with calcifediol. Calcifediol requires several weeks to restore normocalcemia in hypocalcemic individuals with chronic renal failure. Presumably because of the reduced ability of the diseased kidney to metabolize calcifediol to more active metabolites, high doses (50-100 microgram daily) must be given to achieve the supraphysiologic serum levels required for therapeutic effectiveness.
**Raloxifene:**
It is a drug for treatment of osteoporosis and it appears to reduce the risk of breast cancer. Raloxifene protects against spine fractures but not hip fracture unlike biphosphonates. Which protect against both. To counter the reduced intestinal calcium transport associated with osteoporosis, vitamin D is often employed in addition to dietary calcium supplementation.

**Fluoride:**
Despite early promise that fluoride might be useful in the prevention or treatment of postmenopausal osteoporosis, this form of therapy remains controversial.

**References**
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- [http://www.naturalways.com/calciumResearch.htm](http://www.naturalways.com/calciumResearch.htm)
- [http://www.anapsid.org/mbd2.html](http://www.anapsid.org/mbd2.html)