Calcium Revisited
by Dr. Bodean Gervang and Dr. Nigel Plummer

Introduction

Ask any household in the Western world, ‘What is the most important mineral for health?’, and the majority will answer ‘Calcium!’ Yet, despite this general knowledge about calcium, the average American female obtains well below the Recommended Daily Allowance (RDA) for calcium throughout the majority of her life. For men the figures are better, but their intake of calcium is still well below the RDA both during adolescence and when they are over 50 years old. See Figure 1. From this we understand that the modern diet is not supporting the body’s need for calcium, and perhaps the modern health care practitioner is mistakenly assuming that the general population has an adequate calcium intake, and hence has a tendency to focus more attention on less well known and/or more “interesting” nutrients. So how much might this seeming dietary complacency be costing human health?

There is no straight answer to this question, but what we do know is that calcium is not just for bones! Yes, it is the most abundant mineral in the body, due to being the main element in the skeleton, but it also has great importance in many biological controls in humans. Indeed its importance is reflected by the fact that the body maintains homeostasis of calcium in the plasma at the cost of bone integrity. The small variation in plasma concentration may be one of the reasons why many practitioners believe that their patients have sufficient calcium.

Whatever your current view on calcium, it is possible that calcium is not gaining the attention which it deserves. We think that it is well worth revisiting the facts about this mineral.

Distribution

Calcium is concentrated in the skeleton and teeth where more than 99% of the total body calcium is stored. Approximately 2% of the total body weight is calcium, leaving a 70 kg human with about 1400g (35mol) of calcium. Typically the content of calcium in an adult is 1000 to 1500g of which 6-8g is in tissues and about 1g is in plasma and extracellular fluid (ECF).

In circulating blood 45-50% of the calcium is dissociated as free ions, 40-45% is bound to plasma proteins e.g. parvalbumin, and 8-10% is complexed with ions such as citrate. (Weaver & Heaney, 1999) Due to the low concentration of proteins in the ECF the concentration of calcium is lower here than in the plasma. The lowest concentration is seen in the cytosol where the concentration of calcium ions, Ca²⁺, is 10,000 times lower than in the ECF.

Absorption

The absorption of calcium from the intestine involves both a transcellular and a paracellular transport. Transcellular absorption is the active, controlled pathway, whereas paracellular absorption is diffusion controlled. The active process takes place in the duodenum and proximal jejunum, whereas the passive (diffusion) transport takes place throughout the intestines. Absorption from the colon could account for about 5% of the whole absorption and may be of importance in individuals with small bowel resections. (Weaver & Heaney, 1999) Calcium absorption can vary enormously between individuals. Variation from 17-58% has been observed. (Wolf et al, 2000) The absorption of two calcium salts, calcium carbonate (CaCO₃) and calcium citrate-malate (CCM), was studied by Miller et al. (1988). In 12 healthy adolescents the average fractional absorption of elemental calcium from CaCO₃ and CCM was 26% and 36%, respectively. Assuming the fractional absorption value found for CCM is similar to the fractional absorption value for calcium citrate we can now calculate the amount of absorbed elemental calcium from one gram of respectively CaCO₃ and calcium citrate, knowing that 40% of CaCO₃ is elemental calcium and 24% of calcium citrate is elemental calcium. (See Table 1)

<table>
<thead>
<tr>
<th>Table 1. Estimated amount of absorbed calcium from two Ca salts.</th>
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<td>Ca salt</td>
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<tr>
<td>Fractional absorption of Ca</td>
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<td>Elemental Ca in compound</td>
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<td>Elemental Ca absorbed in 1g of compound</td>
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Table 1 indicates that CaCO₃ is a slightly better form of supplementing calcium than the compound calcium citrate. Its higher elemental value of calcium more than compensates for its lower absorption characteristics, indicating a better overall intake of calcium from 1 gram of raw material. The other factor, which sways the argument in favor of CaCO₃ supplementation, is that the raw material of CaCO₃ is approximately eight times cheaper than calcium citrate.

Figure 1. Mean calcium intake by age for U.S. males and females compared with 1997 Dietary Reference Intakes for calcium Adequate Intakes and the 1989 RDA. As seen from the graph females for most of life obtain less than 75% of recommended daily amount, a deficiency of approximately 200mg/day. Graph taken from Weaver and Heaney, (1999).
Transcellular absorption

Transcellular (through the cell) movement of calcium from the intestine to plasma involves three steps.

Step 1 – Luminal Absorption

Luminal transport involves a movement down a steep concentration gradient, (Wasserman & Fullmer, 1995). In order to maintain the concentration difference, the free calcium binds to a carrier. The carrier facilitates a fast transfer from the luminal side to the basolateral side of the epithelium. The binding to a carrier also lowers the concentration of free calcium thereby minimizing the risk of toxicity. The calcium carrier is the vitamin D-dependent enterocytic calcium-binding protein, calbindin-D_{28k}. The metabolically active form of vitamin D_{3}, called either 1,25(OH)_{2}D_{3}, cholecalciferol or calcitriol, acts via nuclear receptors (VDR) to induce the expression of the calbindin_{D_{28k}} mRNA and, subsequently, the translation into the functional calbindin_{D_{28k}} transport protein. (Civitelli & Avioli, 1994).

Step 2 – Diffusion through the Cytoplasm

The diffusion of calcium from the luminal side to the basolateral side of the cell, through the cytoplasm takes place through diffusion (by movement) of:

- Free calcium ions, (Ca^{2+})
- Calcium bound to calbindin_{D_{28k}}
- Calcium carried by lysosomes, (Nemere et al., 1986).

The diffusion of calcium in vesicles may involve the participation of microtubules, (Nemere et al., 1991). The diffusion of calcium using vitamin D-induced carriers increases the diffusion by 100-fold compared to free calcium ion diffusion, showing the importance of vitamin D-induced carriers.

Step 3 – Transport over the Basolateral Cell Membrane

The extrusion at the basolateral side occurs through two channels/pumps, which take calcium up a chemical gradient. The channels/pumps are:

- Ca^{2+}-ATPase pump
- Na^{+}/Ca^{2+} exchanger, (Civitelli & Avioli, 1994).

The extrusion process is also vitamin D dependent, probably because vitamin D increases the number of enzymes i.e. the number of pumps in the endothelial cell, (Bronner, 1998).

The affinity of the vitamin D receptor for calcitriol is 1000-2000 times higher than the affinity of the receptor for calcidiol. This reflects that calcitriol is the hormone principally responsible for the regulation of intestinal calcium absorption, despite the fact that the concentration of calcidiol is approximately 1000 times higher than calcitriol, (Devine et al., 2002).

Calcitriol, the bioavailable form of vitamin D_{3}, can be made in the body through a cascade of biosynthetic reactions in the skin, liver and kidneys, see Figure 2:

⇒ Cholecalciferol (vitamin D_{3}) can either be obtained directly from our diet or it can be formed in the skin by the action of ultraviolet light on its precursor, 7-dehydrocholesterol, which is derived from cholesterol.
⇒ Cholecalciferol is hydroxylated in the liver by adding hydroxyl (OH), to carbon number 25 to form 25-hydroxycholecalciferol, also known as calcidiol.
⇒ In proximal tubule cells of the kidney, a specific enzyme known as 1α-hydroxylase catalyses the conversion of calcidiol to 1,25-di-hydroxycholecalciferol (calcitriol).

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This conversion in the kidney is impaired in many elderly women, consequently lowering the concentration of the active hormone, calcitriol, (Fandellone et al., 1998).

Paracellular transport

Paracellular transport is mediated through the movement of calcium down a chemical gradient. The diffusion takes place through the tight and intermediate junctions, (Bronner, 1998), but paracellular movement takes place in both directions. The rate of transfer depends on calcium load and tightness of the junctions but since water and citrate may enhance paracellular transport, (Weaver & Heaney, 1999) other factors could be involved.
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Excretion
Calcium losses may be divided into three groups: fecal, sweat, and urine.

Loss of calcium in the faeces
Calcium loss through the faeces is mainly regulated through absorption and includes unabsorbed calcium from the diet, losses through endogenous secretion, and losses due to bidirectional paracellular transport.

Loss of calcium in sweat
Loss of calcium in sweat is 16-24 mg per day, (Jensen et al. 1983).

Loss of calcium in urine
Only free calcium ions, Ca²⁺, and calcium bound to anions are filtered in the glomeruli of the kidneys. The majority is reabsorbed in the proximal tubule, approx. 60%, by active transport and approx. 30% by passive transport. In the distal tubule, active transport regulated by both calcitriol and parathyroid hormone (PTH), contribute for approx. 9% of the reabsorption, leaving approx. 1% for excretion in the urine, (Rhoades & Pflanz, 1996).

Figure 3 shows the average daily flow of calcium in a person with no gain or loss of calcium, based upon estimated 33.3% absorption of dietary calcium.

Building and Maintaining the Calcium Reservoir
The function of calcium in the skeleton is often understood as being purely of structural significance. However, the bones are far more than that, they act as the body's huge reservoir of calcium for the body. The calcium in this reservoir can be released into the blood, under the instruction of PTH, should plasma levels of this mineral fall. In summary, the maintenance of plasma levels of calcium is at the cost of calcium from the bones, risking the bone integrity. This is one of the reasons why insufficient intakes of calcium can have a detrimental effect on health and why it is so important to maintain the levels of calcium in the skeletal reservoir.

Building our Calcium Reservoir
The age of peak bone mass varies a lot, and different bones achieve their peak at different ages. However, to ensure strong bones throughout life it is especially important that the intake of calcium is adequate during childhood and adolescence. This builds our reserves to account for our greater losses of calcium later in life. Nature plays a helping hand in building strong bones, at this time, as the rate of bone building is greater in children and adolescence. To correlate with this, calcium absorption is greater at this time and excretion is smaller, (Ievgarden et al, 1999).

Maintaining Our Calcium Reservoir
In Children
For years children have been encouraged by their parents to drink milk and take calcium supplements for their bones, which begs the question, "Does this help the child's bone mineral density (BMD)?" The large number of studies on this subject indicate that BMD does increase with supplementation. One study by (Wosje & Specker, 2000) showed that most of the increase was evidenced by increased density of cortical (compact) bone sites.

During Lactation and Pregnancy
Prentice, (2000A & 2000B) discusses the changes in calcium and bone metabolism during pregnancy and lactation. There is no evidence of loss of BMD 3-6 months after lactation compared to non-lactating women, however, large changes in bone remodeling markers take place. The remodeling process is the metabolic active bone tissue process that is turning over constantly. It could be that lactation actually strengthens the bones due to the high level of bone turnover.

The picture during pregnancy is less clear, both calcium absorption and urinary calcium excretion are greater. Markers for both bone resorption and bone formation increase but whether bone turnover is increased is not clear, since the placenta may take-up some of the markers, (Prentice, 2000A & 2000B). Calcium status during pregnancy clearly has an effect on the health of the child in terms of bone density and growth. A lowering of blood pressure has also been observed, Belizán, (1997).

Postmenopausally
Studies indicate that estrogen has a similar effect as calcitonin. There is a similar relationship between calcium and calcitonin as there is with calcium and estrogen. A review article (Nieves et al, 1998) concludes that there is a significant increase in bone mass when estrogen (HRT) is taken with high levels of calcium when compared with taking estrogen alone. There was little positive effect on bone health when taking estrogen alone.

Postmenopausal women are in the highest risk group for losing calcium. Many of the research studies on bone health in postmenopausal women do indicate that calcium is beneficial for bone remodeling but calcium taken alongside Vitamin D supplementation show the largest effect.
Parathyroid hormone (PTH) is the most important hormone involved in the regulation of plasma calcium concentrations. If the parathyroid glands are removed death appears within 48 to 72 hours caused by hypocalcemic tetany. (Rhoades & Pflanzer, 1996). PTH’s primary effect is to stimulate bone resorption. This is done by increasing the activity of:

- osteoclasts
- stimulating the maturation of osteoclasts
- decreasing collagen synthesis in osteoblasts (Rhoades & Pflanzer, 1996).

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Factors Influencing Homeostasis of Calcium

So, the homeostatic controllers of calcium are the three hormones calcitriol, calcitonin, and PTH, but there are other factors which can strongly influence the body’s calcium homeostasis.

Lifestyle and Genetics

When we consider that intake of calcium in Asian countries is lower than in the Western world, (Lau et al. 1988), but the number of bone fractures are smaller we have to ask ‘why?’ This could reflect a number of factors including genetics, the quality of the Asian diet and maybe the difference in amount of exercise.

Certainly, we know that weight-bearing exercise encourages the uptake of calcium in the bones and as such does positively affect calcium homeostasis. We also know that dietary habits are of great importance and not just in terms of calcium and Vitamin D intake. Some dietary factors which we do know strongly affect plasma calcium levels are phosphate, sodium, proteins, and phytase; all of which reduce the concentration of calcium if their ingestion is too great. It seems that the classic modern American lifestyle, with minimal exercise and diets high in phosphates, sodium, and protein make the maintenance of calcium optimal levels a very difficult task, even for those who do include calcium rich foods in their diets. This is one of the main reasons why many scientists feel that although there was no necessity to supplement calcium 50 years ago they now believe that calcium supplementation may be necessary for the health of modern day Westerners.

Magnesium

One mineral, which could positively affect BMD is magnesium. It has been argued that a high intake of calcium could have a negative effect on magnesium balance, and influence bone mass. However, in a study (Andon et al. 1996), it was shown that the plasma concentration of magnesium was not affected in adolescent females who consumed a low or high calcium diet (667 mg Ca or 1667 mg Ca). What seems to be of much greater importance is magnesium’s influence on PTH. In studies done on rats (Malthouse et al. 1982 & Shils 1980), it is shown that secretion of PTH decreases with decreasing magnesium concentration. This could indicate the importance of magnesium for this hormone’s synthesis. At low concentrations of magnesium, an increase in calcium suppresses PTH secretion. Normally, at marginally low plasma calcium concentrations PTH rises but when there are low levels of magnesium bone responsiveness is impaired. (Rude, 1986). The hypocalcemia which results from a deficiency of magnesium, causes an impairment of the calcium regulatory system and is unresponsive to calcium supplementation. This is a principal reason why magnesium is recommended with calcium supplementation for bone health. The potential importance of magnesium in calcium metabolism is further increased by the fact that magnesium level of intake is also below its optimal level. This is again a reason why

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Figure 4. Daily exchange of calcium in a person with bone loss, see also Figure 3.

Figure 5. The three hormones involved in homeostasis of calcium.
calcium and magnesium supplementation is best combined.

Functions and Effects of Calcium – Not just a bone builder
 Calcium plays many essential roles in our body and it has been shown to have positive effects on many of the common disease states which detrimentally affect Westerners, such as:
- blood pressure
- the risk of kidney stones
- the risk of colorectal cancer
- the risk of obesity
- symptoms associated with premenstrual syndrome
- the incidence of osteoporosis

The degree to which calcium has a positive effect on these health problems varies between playing a very large and significant role, to having a small role but significant effect. Calcium mediates these results by several known and probably many more unknown methods. Some of the methods are discussed below:

Calcium as a Second Messenger (intracellular signaling)
 Most of calcium’s roles are mediated by the action of calcium acting as a second messenger in targeted cells. What makes calcium unique from other second messengers is that most are enzymes and they therefore tend to have short lives. Calcium, by contrast, is not metabolized.

Its role as a second messenger is simple but fundamental to human physiological function. A stimulus, such as a hormone or a neurotransmitter, opens channels in the cell membrane causing the concentration of Ca²⁺ to increase above the resting level of 0.1μM. This activates the release of Ca²⁺ from the cell’s Ca²⁺ reserves, to increase the concentration to 10μM. The binding of Ca²⁺ to specific proteins produces a physiological response, for example, the contraction of muscle cells or secretion of intraneuronal transmission signals. After cell activation, calcium ions have to be stored. If it was not stored, the cell would be ‘turned on’ all the time, resulting in cell death. In addition, a high concentration of Ca²⁺ in the cell would precipitate phosphate – vital for energy production. (Rihodes & Flianzor, 1996) (Weaver & Heaney, 1999).

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Calcium Effects on Blood Pressure and PMS
 Many of the other regulatory systems of calcium result from the body’s strong homeostatic control of plasma calcium levels.

Research studies have shown a small but definitely significant effect of calcium on blood pressure, (Jorde & Benza, 2000), (Beltia et al., 1997), and also premenstrual syndrome (Thys-Jacobs et al., 1997). However, this effect of calcium may only be indirect. It is thought that the change in blood pressure and premenstrual symptoms could be due to the effect of the high concentration of PTH and/or calcitriol trying to sustain the plasma calcium concentration, (Heaney, 2000). It is speculated that if the intake of calcium is enough for plasma calcium levels to remain constant then the involvement of the endocrine system, to pull on the bone reservoir of calcium, should be unnecessary. The result is that related increases in blood pressure and premenstrual symptoms become less likely.
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Calcium and obesity

Calcium’s contribution to the reduction of obesity may also be due to a similar mechanism, as illustrated by (Zemel et al., 2009). The study shows that a high concentration of calcitriol, caused by high concentration of PTH and consequently low intake of calcium, causes a high concentration of free Ca²⁺ in the cytosol of adipocytes. The increase switches the cell from lipolysis to lipogenesis.

It is important to once again, keep in perspective that if the body’s calcium intake is insufficient, then calcium is obtained from bones to maintain plasma levels. This means that this strong regulatory system may induce osteoporosis.

Calcium and kidney stone

Despite the general advice to avoid calcium in the case of recurrent kidney stones, it seems that calcium may have benefit in this condition. The formation of kidney stones can occur with high oxalate intakes because calcium and oxalate can form insoluble complexes, which can deposit in the kidneys. However, adequate calcium could form insoluble complexes with dietary oxalate in the intestines. This eliminates the risk of kidney stones simply because the complexes cannot be absorbed. What is not clear is how much calcium is needed to form the complexes and should the calcium be taken at each oxalate containing meal?

Calcium and colorectal cancer

In a study by Garland et al., (1991) it was found that an intake of 1200mg calcium per day was associated with a 75% reduction in colorectal cancer. The beneficial effect of calcium on colorectal cancer is thought to be due to its reaction with fatty acids. It has been postulated that dietary fat could be a promoter of colorectal cancer by acting as a source of free fatty acids and by increasing bile acids in the faeces. A small amount of bile escapes daily into the colon where the microbial flora hydrolyses it to form free bile acids in the faeces. But fatty and bile acids in their soluble form damage the colonic epithelium, possibly by depleting the tissue of interstitial calcium and causing cells to detach themselves from the basal lamina, or by entering the lipid phase of cell membranes causing damage, (Aldred et al., 1998). Where calcium is believed to benefit this situation is that it may form soaps with the fatty acids, and salts with the bile acids, rendering fatty acids and bile acids inert.

Conclusion

There is no doubt that calcium is of exceptional importance in human biological function. To remind ourselves:

- Calcium is essential for maintaining our physical structure
- Calcium has a unique ability, as a mineral, to act as second messenger to many, if not almost all physiological functions.
- Due to the body’s tight control on plasma levels of calcium, we can assume that maintaining these levels is extremely important to human function. The body is prepared to sacrifice its physical structure for this!

There is also no doubt that the vast majority of the population, at most stages in their lives, are not consuming enough calcium. This is likely to be due to a greater body demand for this mineral at these stages and the negative influence of our modern lifestyle. Low exercise and diet, both what we are eating and are not eating, can negatively affect our calcium status.


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<th>Life-Stage Group</th>
<th>Calcium (mg/d)</th>
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<td>Infants (months)</td>
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<tr>
<td>0-6</td>
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