CHAPTER 3

BIOAVAILABILITY OF CALCIUM

M. de Vrese, K. Scholz-Ahrens & C.A. Barth
Institut für Physiologie und Biochemie der Ernährung, Bundesanstalt für Milchforschung,
Postfach 6069, 2300 Kiel 14, Germany F.R.

ABSTRACT

Interest in an adequate dietary intake of calcium has increased because of its reputed prevention of osteoporosis. As there is evidence of a generally suboptimal calcium intake, it does not suffice to consider the total amount of calcium from dietary sources or in the form of supplements. This chapter examines the bioavailability of calcium and its dependence on nutritive and non-nutritive factors.

INTRODUCTION

Although the hypotensive effect of calcium (1, 2) and potential protection against colorectal cancer (3, 4) have attracted increasing attention in recent years, an adequate calcium intake has, above all, attracted interest because of its reputation to prevent osteoporosis (5). From relatively constant daily calcium losses of 200 mg, an intestinal fractional absorption rate of 25-50% and an adequate safety margin, recommendations for the daily calcium intake have been derived which are in most countries in the order of 800 mg/day (6, 7) but higher for adolescents and pregnant or nursing women. On the basis of the results of balance studies on pre- and postmenopausal women (8) markedly higher calcium intakes of 1 g and 1.5 g/day were then recommended in the USA for both groups (9). Actually adolescents and particularly elder women ingest calcium at levels which are far below these standards (10). The 1989 US RDA now remains at 1200 mg for adolescents and young adults (to the age of 24). In previous editions the 1200 mg RDA extended only to the age of 19.

Hence, because of a generally suboptimal calcium intake there is reason to consider not only the total amount of calcium from dietary sources or ingested in the form of supplements, but also its bioavailability and its dependence on nutritive and non-nutritive factors. In the literature bioavailability is not a clearly defined notion, it is mostly held to be the proportion of a nutrient ingested which is adequately utilized in the organism.

3.1. NON-NUTRITIVE FACTORS

3.1.1 Vitamin D status and intestinal absorption

Unlike other work, this paper deals with vitamin D as a non-nutritive factor for two reasons:

1) Vitamin D per se is biologically inactive, the primary regulator of active calcium transport in the intestine is the hormonal vitamin D metabolite 1,25-dihydroxycholecalciferol (calcitriol) (11).
2) Dietary vitamin D normally contributes less to the maintenance of an adequate vitamin D status than endogenous synthesis (12), from which originates up to 80-90% in human metabolism (13). Upon UV irradiation in the skin provitamin D_3 is converted to vitamin D_3 (Cholecalciferol) and to inert isomers (14). Cholecalciferol is hydroxylated in the liver to 25-hydroxycholecalciferol and the latter in the kidney to calcitriol.

The vitamin D status deteriorates with aging because of the reduced synthesis of vitamin D in the skin and a decline in renal synthesis of calcitriol. Further, the elderly generally ingest less vitamin D from dietary sources and are less exposed to sunlight (12). Vitamin D is certainly a nutrient in the elderly who have a compromised ability to synthesize vitamin D in the skin and/or who are house-bound.

Vitamin D displays part of its activity directly during intestinal calcium absorption but is not directly necessary for bone growth and mineralization (15). The underlying mechanisms concerning calcium absorption were studied mainly in rats using the "ligated loop" and the "everted sac" technique (16). The results can be summarized as follows (16-25).

There are two mechanisms by which calcium is absorbed from the gut: the passive, vitamin D-independent and non-saturable transport is based on diffusion, follows a paracellular pathway and has a similar activity throughout the whole small intestine. The active, saturable calcium transport can be increased by calcitriol-enhanced synthesis of the calcium-binding protein, is transcellular, acts already at low calcium concentrations and displays its main activity in the upper small intestine.

In adult rats or men fractional absorption decreases with increasing intestinal calcium concentration due to saturation of the active transport in adults. This active transport in the duodenum is almost saturated at a calcium intake of 120 mg/meal. At this low calcium intake the passive calcium transport tends toward secretion, at a higher intake level of 300 mg/meal toward absorption (26).

Normally there is no or only ineffective calcium absorption from the colon (27). However, a considerable colonic absorption of calcium can be observed in calcium deficiency due to lacking or reduced absorption in the small intestine. Colonic absorption can be increased by vitamin D (20, 27-30).

Effective calcium absorption requires an adequate vitamin D status (5, 12, 31). Although calcium can also be absorbed when the vitamin D status is poor, absorption is, in any case, higher when vitamin D is supplied in sufficient amounts (12). Particularly when the diet is low in calcium, sufficient vitamin D levels should be available in order to maintain calcium homeostasis (12). The daily administration of 1000 mg calcium and 25 µg vitamin D increased significantly the gastrointestinal calcium absorption in healthy adults (32). Also in the elderly and in patients with osteoporosis calcium absorption was improved by vitamin D administration (33).

3.1.2 Infancy

In suckling rats there is exclusively passive absorption of calcium. At the end of the 3-week suckling period, when calcium levels are decreasing in the diet, this mechanism in the duodenum and ileum is replaced more and more by the active saturable process, whereas the efficiency of the passive transport decreases (19, 21, 22, 34). Related events are the appearance of receptors for vitamin D in the mucosa and higher concentrations of calcium-binding protein (19). Total calcium absorption reaches a maximum in 5-week-old animals and decreases slowly thereafter (19).

In piglets calcium transport from the gut during the first 2-4 weeks is independent of vitamin D (35). Calcium absorption in the human newborn is also assumed to be passive (36).

3.1.3 Pregnancy and nursing

The mother covers the fetal calcium requirements by mobilizing calcium from the bones (37, 38), by an up to two-fold increase in calcium absorption throughout pregnancy (39) and by reducing renal calcium excretion (39). Normally bone loss during nursing is negligible (40, 41) except in young mothers (38) and long nursing mothers with 4 or more children (42). By increasing the daily calcium intake to 1600 mg, which is the recommended dose for nursing mothers in the USA (43), prevention of bone demineralization has been reported (37).

3.1.4 Elderly people

In aging, in particular beyond the age of 60, intestinal calcium absorption and utilization are decreasing and calcium balance becomes negative, indicating bone loss (44, 45). In the age group from 70 to 90 absorption is lower by 2/3 if compared with the age group from 20 to 59. Simultaneously, the ability of the organism to adapt to reduced calcium intake is decreasing (44-46). The possibility to improve calcium balance by a calcium-rich diet or by calcium supplementation and to stop or slow bone loss is discussed in the next chapter.

3.1.5 Menopause

As a result of menopausal decreased estrogen levels, calcium absorption is markedly reduced as well as the capacity to respond to reduced calcium intake with increased absorption (8, 31, 33, 47, 48). A high renal calcium excretion and an impaired vitamin D status are other factors contributing to a lower calcium balance (49, 50).

In the first 6 years after menopause a rapid bone loss occurs (33). Here estrogen administration has proved to be the most efficient therapy (51-54). A matter of particular controversy is the effect of increased dietary calcium intake which is thought to be beneficial for two reaons:

1) to increase the peak bone mass between the ages of 25 and 35, and
2) to slow down the rate of age-related bone loss especially after menopause.

A positive correlation between bone mass and dietary calcium was shown in some studies (55-59) whereas others did not find such a relationship (60, 61) or showed even a positive correlation between calcium intake in several countries and the frequency of osteoporosis (62).

There was a significant negative relation between current dietary intake of calcium and the rate of bone loss or a significant reduction of bone loss by calcium supplementation only in 8 (51, 63-69) of 14 investigations (51, 52, 63-74). In some studies a slight reduction only of the cortical bone loss was found (52, 71) or the calcium effect was observed only in combination with estrogens (71). Some of the reasons for this inconsistency may be the complexity of age-related bone loss or the site and method of measurement.

3.1.6 Physical activity

It has been reported that physical activity increased the skeletal mass (75, 76), while inactivity and immobilization led to a loss of bone minerals (77).

3.1.7 Diseases and therapeutical measures

Diseases of the gastrointestinal tract such as malabsorption syndrome, celiac disease, Morbus Crohn or pancreatitis, as well as diabetes, renal diseases or alcoholism, can deteriorate calcium absorption and its balance (7, 78-80).

The consequences of small intestine resection and intestinal bypass surgery for calcium absorption and bone health have been the subject of detailed studies. After operation a reduction in calcium absorption (81-83) and partly masked bone malacia (84-86) was found depending on the remaining length of the small intestine. In the course of years calcium balances improved again as the result of an adaptive increase of calcium absorption in the small intestine and - as mentioned above - in the colon (81, 83). Absorption in the large intestine can also be regulated by the vitamin D status (82, 83, 87).

A number of drugs influence calcium balance mainly by increasing (corticosteroids, tetracyclines, laxatives, aluminium-containing antacids (44)) or reducing (thiazides (88)) renal excretion.

3.2. NUTRITIVE FACTORS

3.2.1 Quantity and physical form of calcium

The amount of calcium in the diet is only a weak indicator of how much is utilized because only about 30% of dietary calcium is absorbed, the remainder is excreted in the feces (7). An increased ingestion of calcium decreases its fractional absorption due to saturation of the active transport from the gut (see 3.1.1). For example, when 900 mg calcium/day were added to a basal diet containing 697 mg calcium/day, the apparent absorption rate decreased from 27% to 11-19% (89). This effect of quantity has to be taken into account when comparing experiments in which different amounts of calcium were consumed.

It is assumed that calcium is absorbed in its ionized form; therefore, easily soluble calcium salts are considered to have a better bioavailability (90). For example, it was possible to demonstrate a better absorption of calcium citrate or a calcium-citrate-malate complex if compared to calcium carbonate or calcium phosphate (90-93). Other authors did not find significant differences in intestinal absorption of several calcium salts exhibiting different degrees of solubility in men (94, 95) or rats (96).

Differences in solubility between calcium salts can be levelled out by gastric acidity: for example, calcium carbonate is significantly less absorbed than calcium citrate in patients with achlorhydria (97). Several investigations have shown that calcium supplements are better absorbed when ingested with a meal. This was explained by increased production of gastric acid and retarded gastric emptying during a meal (91). Other authors have not observed such effects by meals (98).

In milk and dairy products calcium occurs as colloidal calcium phosphate, a calcium-casein complex (micellar calcium) and ionic calcium (99). Colloidal calcium has been reported to be better absorbed than ionic calcium and differences in bioavailability of calcium from several dairy products have been explained with differences in their colloidal-to-ionic calcium ratio (100). However, there are no other investigations confirming this hypothesis. Two recent papers gave no evidence of a better bioavailability of calcium from milk products rich in colloidal calcium in rats (101, 102).

3.2.2 Lactose and other carbohydrates

Intestinal absorption of calcium can be increased by concomitant ingestion of several carbohydrates. Orally administered glucose (103, 104) or galactose (104) increased the fractional calcium absorption by up to 30% in healthy adults. However, there may be responders and non-responders (105).

In experimental animals (5, 31, 106-110) and children (111) the increase in calcium absorption by lactose is well documented. In adults the effect is not clear and is mainly dependent on intestinal ß-galactosidase activity of the subjects. In lactose absorbers, that is, people with a lifelong high ß-galactosidase activity, a positive lactose effect has been described in a number of papers (112-114). This effect is lacking, only minor or even negative in others (115-118). In subjects with lactose, malabsorption improved (115, 119) or impaired calcium absorption (112, 113) or no effect at all was established after lactose ingestion (117, 118). The cause for these different results is not always clear.

The lack of the positive influence of lactose on calcium absorption in lactose-intolerant subjects is, besides reduced milk consumption, held to be a further cause for the positive correlation between lactose intolerance and osteoporosis described in a number of studies (120-123).

It has not yet been possible to fully clarify the mechanism of lactose action (5, 124). Experiments with rats suggest that lactose increases the permeability of the brush border membrane by a change in polarization (108, 109, 124). This effect is independent of the vitamin D status (107). In subjects with normal lactase activity lactose prolongs the duration of absorption at a maximal rate, while it reduces the maximal absorption rate in subjects with lactose malabsorption, the duration of absorption remaining unchanged (112). A direct effect of intestinal ß-galactosidase on calcium absorption has not been established (117, 118, 120).

3.2.3 Fat

Fat does not influence calcium balance in healthy subjects (7), whereas in cases with fat malabsorption, or steatorrhea, calcium absorption is impaired due to the formation of insoluble soaps (125). With medium-chain triglycerides both fat and calcium are better absorbed, because they are more soluble than long-chain fatty acids (7).

3.2.4 Dietary fiber, phytic acid, oxalic acid

It is generally assumed that dietary fiber as well as phytic acid (in wheat bran) and oxalic acid (in spinach, rhubarb and cocoa powder) impair intestinal absorption of calcium and other minerals by formation of complexes of low solubility (31, 37, 126, 127). The calcium-binding potential of fiber correlates well with its content of uronic acids, which constitute 40% or 10% of the non-cellulose fraction of fiber in fruits and vegetables or cereals, respectively (7, 127). Further, dietary fiber is likely to contribute to lower calcium absorption due to accelerated intestinal passage and erosion of the intestinal mucosa and the associated loss in calcium-binding protein (128).

The effects of an enhanced ingestion of dietary fiber on calcium absorption and balance may be influenced by fiber particle size, calcium intake or adaptation to a high fiber diet and, hence, duration of balance measurement (5, 126, 128).

Further, numerous papers do not differentiate between the effect exerted by dietary fiber and phytic acid because wheat bran, no doubt the most often studied "roughage", contains both. For example, shifting from a low- to a high-fiber vegetable/cereal diet led to a significantly reduced calcium balance in humans, while calcium retention dropped from 35 to 11% (129). In primates, bran impaired calcium balance (130).

In a number of studies different types of dietary fiber have not been found to produce a significant effect on calcium absorption in men or experimental animals (128, 131-134). Even if many of these studies showed a slight decrease of calcium absorption this was, however, of no practical importance for calcium status.

In rats calcium bioavailability from spinach or calcium oxalate is significantly poorer than from kale (calcium-rich, oxalate-poor), $CaCO_3$ or $CaCl_2$ (135). Also in men calcium from spinach is less efficiently absorbed if compared with lactose-free and lactose-containing milk products (136, 137). However, oxalic acid in one food does not inhibit calcium absorption from another one. Although after addition of spinach to a meal only 5% of the calcium from spinach is available, total calcium absorption from the meal remains constant (135, 136).

In normal nutrition without excessive fiber-, phytate- or oxalate-ingestion the factors mentioned above are of minor importance for calcium balance in man (138, 139). Lacto-ovo-vegetarians have the same calcium status (139-140) and bone mineral content (141) as omnivores. Additionally calcium from a lacto-ovo-vegetarian meal seems to be better utilized by lacto-ovo-vegetarians than by omnivores (142).

3.2.5 Protein

A high protein intake leads to increased renal calcium excretion in experimental animals as well as in man (5, 143-147). This calciuretic effect, oberservable already after a small increase in protein ingestion (148), is not attributable to increased calcium absorption but is due to the protein-dependent significant increase in the glomerular filtration rate (143, 149) and a simultaneous decrease in renal tubular reabsorption (143, 149). The decrease in tubular reabsorption is dependent on the acid-forming components of dietary protein, especially the sulfur amino acids giving rise to sulfate when oxidized (150-152), while phosphate produces a hypocalciuretic effect in diets high in protein (153). In healthy subjects renal calcium excretion is higher after consumption of animal protein with a higher content of sulfur-containing amino acids compared with vegetable protein containing less sulfur (154). On the other hand, only about half of the calciuretic effect of increased protein intake can be explained by a corresponding increase in sulfur-containing amino acids alone (146).

High intake of isolated proteins leads to a negative calcium balance, and a relation with incidence of osteoporosis is under discussion (155, 156). In normal nutrition, protein has a less important effect if compared with isolated protein used in experimental diets. Here the duration of protein administration and phosphate contents in the diet have also to be taken into account (138, 144, 153, 157).

Even when the hypocalciuretic effect of phosphate cannot always fully compensate for the protein effect (146, 147), the phosphate content is held to be the main cause that, for example, meat consumption does not lead to a decreased calcium balance (5, 138, 153, 157-159). A recent investigation (160) has shown that protein-reduced milk causes less urinary calcium excretion. Some authors postulate that osteoporosis is rather a problem of calcium loss than of impaired calcium supply (161, 162).

3.2.6 Phosphopeptides

More than 30 years ago it was shown that orally administered calcium phosphopeptides caused an up to 80% increase in calcium absorption in rachitic newborns (163). Such phosphopeptides occur in casein and consist of phosphoserine-rich sequences particularly resistant to enzymatic hydrolysis. Since then it has been attempted in a number of studies, mainly performed in rats, to elucidate the underlying mechanisms of a stimulatory effect of phosphopeptides on calcium absorption. The results can be summarized as follows.

- After feeding casein higher amounts of soluble calcium are found in the distal small intestine of rats as well as higher rates of calcium absorption if compared to other proteins such as soybean or dephosphorylated casein (164-166).
- In vivo formation of phosphopeptides can be shown during casein digestion in the distal small intestine of rats (164, 166-168).
- Phosphopeptides obtained in vitro by tryptic digestion of casein prevent in vitro precipitation of calcium phosphates (164, 169) and increase calcium absorption both when orally administered (170) and directly injected into the small intestine of rats (164) or healthy and rachitic chicken (171).
- In pigs feeding on casein instead of whey protein (a protein not containing phosphoserine-rich sequences) did not cause an increase in absorption and retention of calcium (172).

3.2.7 Phosphate

Phosphate was *per se* believed to deteriorate calcium bioavailability and the reduction of the calcium-to-phosphate ratio in the diet by increased meat consumption or phosphate added to foods and refreshments (173) has been suggested to contribute to calcium loss. This could contribute to the development of osteoporosis (62, 174). In a number of investigations, however, the increased supply of phosphate did not impair significantly calcium absorption and balance independent of the amount of calcium ingested. Dietary phosphate causes a well-documented decrease in renal calcium excretion (5, 146, 153, 175-177). Diets with phosphate additions have not been found to change calcium bioavailability (138). Therefore less importance is attributed now to the dietary calcium-to-phosphate ratio as regards the prevention of osteoporosis (178).

3.2.8 Sodium and magnesium

Sodium chloride intake increases renal calcium excretion (179, 180) and - presumably parathormon mediated - serum calcitriol concentrations. The latter leads to an adaptive increase in intestinal calcium absorption (180) but also to mobilization of bone calcium.

Magnesium and calcium influence one another competitively in metabolism. With increased magnesium intake increased renal calcium loss was observed (181). On the other hand, magnesium deficiency leads to lower calcitriol levels and to corresponding effects on calcium metabolism (182, 183), because renal synthesis of calcitriol is magnesium-dependent.

3.2.9 Vitamin C

Whereas vitamin C increased the concentration of plasma calcitriol and calcium-binding protein in chicken (184), it neither influenced calcium retention in healthy adults (185) nor calcium bioavailability in rats (186).

3.2.10 Alcohol, caffeine

Alcohol impairs, at least when chronically abused, intestinal calcium absorption and increases both calcium excretion via the kidney and the risk of osteoporosis (5, 187). The following causes are being discussed: disturbance of pancreas function and steatorrhea leading to reduced absorption of calcium and vitamin D, decreased hydroxylation of cholecalciferol in the liver or increased lactate levels and acidosis (5, 188).

In healthy, young and perimenopausal women caffeine led to higher renal calcium losses and impaired calcium balance (189, 190) and bone mineralization. Following caffeine injection rats also showed increased renal excretion of calcium, although calcium balance was not influenced (191). Caffeine-fed rats had a higher calcium concentration in the tibia (192).

3.2.11 Milk and milk products

Having contents of 132 mg/100 ml, bovine milk contains, like most dairy products, high amounts of calcium. Milk is the food with the highest nutrient density for calcium (193). Half a litre of milk covers a recommended daily calcium intake of 800 mg by more than 80%. Moreover this calcium exhibits a good bioavailability. Of the calcium ingested with milk and dairy products, 25-45% are absorbed in the intestine (95, 106, 115, 118, 136, 194). In many countries milk and dairy products are the main source of dietary calcium. In the Federal Republic of Germany, for example, 59% of the daily calcium intake originates from milk and dairy products (10).

It is widely assumed that calcium bioavailability in milk and dairy products is markedly higher compared with other foods or inorganic calcium salts. This has been explained by the lactose content of milk, by the occurrence of casein phosphopeptides, by colloidal calcium contents, by a favorable calcium-to-phosphate ratio or by the lack of antinutritive factors. Further, it has been assumed that lactate causes a particularly high calcium bioavailability in fermented milk products (195).

But similarly, as with the earlier mentioned factors, differences which have been shown in isolated experiments cannot be reproduced if measured under free-living conditions. So, recent work did not reveal a higher calcium bioavailability from milk and dairy products, at least not of an order relevant to human nutrition in practice. Healthy adults absorbed calcium equally well from milk and different calcium salts (89, 91, 94, 95). Calcium absorption rate in postmenopausal women tended to decrease slightly in the following order: whole milk, yogurt, chocolate milk, cheese, an imitation milk and calcium carbonate, the differences being, however, not significant (194).

In experiments with rats fed milk, yogurt or cheese a higher calcium bioavailability was demonstrated than after feeding calcium carbonate (106, 196), the differences being of no great importance from a nutritional point of view (106). Other authors using rats did not find significant differences in calcium bioavailability between milk and dairy products on the one hand and several calcium salts from tofu and tortillas on the other (96, 186).

With one exception (197), a higher calcium bioavailability from yogurt than from milk could not be verified in rats (106) and lactose-tolerant adults absorbed calcium better from milk, whereas no differences were found in lactose-intolerant subjects (118).

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