Risk Assessment Calcium

General information

Chemistry

Calcium is an alkaline earth metal belonging to Group II of the periodic table. It is a divalent cation with an atomic weight of 40. Calcium shows a single oxidation state of +2.

Natural occurrence

Calcium does not exist freely in nature, but occurs abundantly as limestone ($CaCO_3$), gypsum ($CaSO_4.2H_2O$), and fluorite (CaF_2). Many calcium compounds (e.g. fluorspar and calcium carbonate) are almost insoluble in water, but there are exceptions (e.g. calcium chloride and calcium nitrate). Within this risk assessment, the word calcium refers to ionic calcium, except where specific calcium compounds are described.

Occurrence in food, food supplements and medicines

Foods particularly rich in calcium are milk (1200 mg/kg), cheese (730-12000 mg/kg) and other dairy products (except butter), green leafy vegetables (except spinach), soybean products, bread and other baked goods made from calcium fortified flour (variable levels), almonds (2400 mg/kg), brazil nuts (1700 mg/kg) and hazelnuts (1400 mg/kg). In the West, more than 70% of calcium intake is from milk and dairy products.

Fortified foods such as bread and baked products and some breakfast cereals now contribute significantly more calcium to the diet than would be the case without fortification. UK law requires that all flour, with the exception of wholemeal flour, be supplemented with 2350-3900 mg calcium carbonate (equivalent to 940-1560 mg calcium) per kg. Wholemeal flour contains naturally 380 mg calcium per kg.

Calcium in dietary supplements is available either alone or in combination with other minerals beneficial to bone health (such as vitamin D, magnesium and zinc) or in multivitamin preparations with added minerals. Concentrations typically range from 133 mg/tablet, taken once daily, to 800 mg/tablet, taken 3 times per day. Calcium in dietary supplements is available in many different forms, including calcium carbonate and various calcium chelates. Calcium carbonate contains the highest concentration of elemental calcium (400 mg/g), but is of low solubility and therefore less bioavailable than calcium chelates. Antacid preparations contain calcium carbonate (with a maximum daily dose of 4000 mg calcium).

Other sources of exposure

In different geographical areas, the concentration of calcium in drinking water varies from less than 100 mg calcium per litre in soft water areas, to up to 300 mg per litre in hard water areas. The calcium content of mineral water also varies widely ($<$10 mg/L to $>$ 300 mg/L).

Recommended amounts

Dietary Reference Values are based on calcium requirements for bone formation, minimised bone resorption and retention of calcium. Recommendations vary for different stages of growth and reproduction (COMA, 1998).

A Lower Reference Nutrient Intake (LRNI) of 240 mg/day has been calculated for infants. However, absorption from infant formula is less than from breast milk (40% as opposed to 66%) and so a RNI of 525 mg/day is recommended.

The calcium intake required for healthy bone formation and skeletal growth increases from the age of 1 to 10 years; RNIs of 350, 450 and 550 mg/day are recommended for children of ages 1-3, 4-6 and 7-10 years respectively. For adolescents (11-18 years) RNIs are 800 mg/day for females and 1000 mg/day for males, due to an increased requirement for calcium at a time of increased skeletal growth.

RNIs for adults are based on calcium loss and retention and are 700 mg/day. No additional intake is considered necessary for pregnancy, although an increase of 550 mg/day over the RNI is recommended during lactation.

Analysis of tissue levels and calcium status

Calcium in the body may be measured in the blood or in bone. However, blood calcium concentrations are tightly regulated and are not reflective of calcium status. Blood calcium levels are only seen outside the normal range in conditions such as severe malnutrition or hyperparathyroidism.

There are several techniques for measuring the amount of calcium in individual bones at different ages, but results from the different methods do not correlate very well. A recently developed technique, using neutron activation analysis, enables total body calcium to be measured in living persons. Bone mineral content (BMC), the concentration of mineral at a specific skeletal site, and bone mineral density (BMD), the bone mineral content per unit area of skeletal site, are used as indicators of calcium insufficiency and as predictors of increased risk of fracture, when compared to a reference range, adjusted for age and gender. Change in BMC and BMD are useful indicators of calcium status in adults; change in BMC is a useful indicator of calcium retention in children.

Brief overview of non-nutritional beneficial effects

In some, but not all studies, calcium supplementation at doses of approximately 1250-2000 mg/day, has been shown to reduce colonic and rectal epithelial cell proliferation in subjects at risk from developing colon cancer.

Epidemiological studies and clinical trials have suggested that dietary calcium may have a beneficial effect on primary hypertension (in non-pregnant women). Some studies have also indicated an association between calcium intake and decreased blood pressure in children.

Traditionally, calcium restriction has been advised in the prevention of calcium stones. However, recent evidence suggests that dietary calcium restriction may actually increase the risk.

Evidence from a limited number of studies has suggested that calcium supplementation may inhibit the development of breast cancer, particularly in the presence of vitamin D.

Function

In the vertebrate skeleton, calcium provides rigidity in the form of calcium phosphate ($Ca_{10}(OH)_2(PO_4)_6$, also known as hydroxyapatite), embedded in collagen fibrils. Calcium is also a key component in the maintenance of cell structure. Membrane rigidity, viscosity and permeability are partly dependent on local calcium concentrations.

Calcium fulfils important physiological roles as a cofactor for many enzymes (e.g. lipase), as an important component of the blood clotting mechanism and through an active role as an intracellular signal. Changes in intracellular calcium concentration, in response to a physiological stimulus, such as a hormone or neurotransmitter, can act as an intracellular signal. This signalling controls events such as cell aggregation, muscle contraction and cell movement, secretion, transformation and cell division, as well as muscle protein degradation.

Deficiency

A negative calcium balance occurs when net calcium absorption fails to compensate for urinary calcium losses. Calcium absorption is impaired in individuals with conditions of fat malabsorption (e.g. in syndromes such as pancreatic insufficiency, bile duct obstruction and coeliac disease) because of the lack of vitamin D as a transporter. Acute hypocalcaemia is frequently seen following parathyroid surgery and may occur during thyroid surgery through inadvertent interference with the parathyroid glands.

The possible effects of calcium deficiency are numerous and wide-ranging. Signs of calcium deficiency are manifest in the bones and teeth of all young animal species, including humans. Effects include stunted growth, poor quality bones and teeth, and bone malformation.

Interactions

Interactions between calcium and other dietary constituents may affect the efficiency of calcium absorption. Phytic acid (found in unleavened bread, raw beans, seeds, nuts and grains) can reduce calcium absorption by forming an insoluble salt, calcium phytate.

Calcium is thought to have an inhibitory effect on iron absorption from the diet, even at low levels. High calcium diets have also been shown to reduce net zinc absorption and balance.

The phosphate ion can form insoluble complexes with calcium, and therefore potentially decrease calcium absorption. It has been suggested that the dietary phosphate:calcium ratio has to be very high (exceeding 3:1) to interfere significantly with calcium availability. However, some studies have shown that phosphorus intake had little or no effect on overall calcium balance, and that variations in phosphorus intake were not associated with differences in calcium absorption. Complexation of phosphorus with aluminium inhibits phosphorus absorption, which increases excretion of calcium. Thus, long-term use of antacids can cause calcium loss.

Absorption and bioavailability

About 25-50% of dietary calcium is absorbed and delivered to the exchangeable calcium pool. Most of the calcium in food is in the form of complexes with other dietary constituents, which must be broken down and the calcium released in a soluble and ionised form before it can be absorbed.

Calcium crosses the intestinal mucosa by both active and passive transport mechanisms. The active transport mechanism is a saturable, transcellular process which involves the calcium-binding protein, calbindin. Calbindin is regulated by the active form of vitamin D (1,25-dihydroxy-vitamin D_3). The passive transport mechanism is a nonsaturable, paracellular process, which is of low efficacy and is unaffected by calcium status or parathyroid hormone. Both processes occur throughout the small intestine, although the efficiency of calcium absorption is much greater from the duodenojejunal segments of the intestine, than from the ileal segments.

During periods of additional calcium requirement, the absorptive capacity of the gut is increased, and renal excretion is regulated.

Distribution and metabolism

Total body calcium is about 30 mol (1200 g). Of this, 1% is located in the serum, lymph and other fluids, the remaining 99% being found in the bone and teeth. The concentration of ionised calcium in serum is closely regulated within 10% of approximately 100 mg/L.

Calcium circulates in the plasma in three forms: bound to plasma proteins (45%); in complexes with citrate, phosphate or bicarbonate (about 10%); and as free calcium ions (about 45%). Free ionised calcium is the most physiologically important form.

Excretion

Calcium excretion tends to equal intestinal calcium absorption in adults of a good nutritional state. Absorbed calcium is excreted in the urine, and to a lesser extent, in the sweat. Urinary calcium excretion varies widely among individuals, ranging from 100-200 mg/day. Faecal excretion of calcium consists mainly of unabsorbed dietary calcium, the remainder coming from shed epithelial cells and digestive juices.

Toxicity

Human data

Excessive calcium intake may lead to hypercalcaemia (serum calcium levels in excess of 10.5 mg/dl). Features of hypercalcaemia are progressive lethargy, confusion and ultimately coma (at serum calcium concentrations above 14 mg/dL). These effects are reversible and are directly related to the degree of hypercalcaemia. Headache, elevated cerebrospinal fluid protein and, rarely, convulsions, may also occur in patients with hypercalcaemia. However, hypercalcaemia more commonly results from an excessive ingestion of both calcium and alkali, such as antacid tablets, calcium supplements and milk (providing vitamin D which promotes calcium absorption), a condition which is known as milk-alkali syndrome (MAS).

Clinical signs of MAS are hypercalcaemia, alkalosis and renal insufficiency. MAS can be acute, intermediate (Cope's syndrome) or chronic (Burnett's syndrome) depending on the duration of exposure and symptoms. Hypercalcaemia, hyperphosphatemia and renal insufficiency are reversible after acute or intermediate exposure. However, chronic MAS is associated with irreversible or only partially reversible renal insufficiency and metastatic calcinosis (deposition of calcium in soft tissue). Historically, the majority of patients developing MAS have been middle-aged males ingesting milk and absorbable alkali, but this has decreased with the use of modern medication for peptic ulcer disease. More recently, case reports have described the syndrome occurring in predominantly female patients taking calcium-containing drugs for conditions such as autoimmune disease, organ transplantation, chronic renal failure and osteoporosis. The syndrome has been reported to occur at calcium carbonate intakes of 4000 mg/day and above.

Although MAS has usually been observed after ingestion of large quantities of antacid tablets or other calcium-containing medication with vitamin D, two cases of MAS have been described resulting purely from ingestion of food. Both cases arose from the practice of consuming betelnut paste containing calcium carbonate from oyster shells.

Hypercalcaemia commonly occurs as a result of hyperparathyroidism and malignancy. Breast cancer, lung cancer, and multiple myeloma are the neoplasias most commonly associated with hypercalcaemia, due either to osteolytic secondary deposits or to ectopic parathyroid-like hormone production, typically in lung cancer.

Supplementation studies

A range of supplementation studies have been reported with supplementary calcium doses of up to 2000 mg/day. These have generally failed to show adverse effects, but data on adverse effects are limited.

A study of supplementation of the diet of pregnant women with 2000 mg calcium/day (as calcium carbonate) showed no significant increase in the incidence of urolithiasis. Women with a history of, or high risk for, developing renal disease were excluded from the study (Levine *et al*., 1997).

In a randomised, double-blinded controlled clinical trial of pregnant adolescents, a reduced incidence of pre-term delivery and low birth weight was observed in the supplemented group receiving 2000 mg additional calcium/day (Bucher *et al*., 1996). No adverse effects were reported.

Numerous clinical trials have been reported in which patients with a history of adenomatous colonic polyps have received calcium supplements. These trials mainly consist of double-blind placebo-controlled studies, with patients receiving between 250 and 2000 mg calcium (usually in the form of calcium carbonate), over periods ranging from 4 weeks to 4 years. Few adverse effects have been reported in individuals participating in such trials, although this may be partly because the effects were not deliberately sought. A low incidence of gastrointestinal side effects, such as severe abdominal pain or diarrhoea, has been observed in studies where side effects have been actively ascertained.

Animal data

Limited animal data concerning calcium toxicity are available. In rodents and dogs, dietary administration of excess calcium leads to kidney calcification, enlarged kidneys and reduced glomerular filtration rate.

An investigation of the effect of providing pregnant mice with 8.2% calcium (as carbonate and lactate) in the diet (equivalent to an intake of approximately 12,200 mg/kg bw/day) compared to controls given diets containing 1.2% calcium (approximately 1800 mg/kg bw/day) on foetal development resulted in significantly decreased foetal weights, and retarded skeletal and dental calcification. No gross abnormalities were detected.

In rats maintained on a high calcium diet throughout pregnancy and lactation (providing an estimated calcium intake of 3790 mg/kg bw/day), offspring were born significantly hypocalcaemic and had lower growth rates and focal alopecia. These effects were reversible when the pups were weaned onto a normal diet. Hypercalcaemic lactating dams also produced milk with a higher calcium concentration than controls, which may have contributed to the response seen in the offspring.

Carcinogenicity and genotoxicity

No relevant data on carcinogenicity or genotoxicity have been identified.

Mechanisms of toxicity

Acute hypercalcaemia can impair renal function by causing vasoconstriction with consequent decreases in both the renal blood flow and glomerular filtration rate. Hypercalcaemia increases absorption of bicarbonate in the proximal tubule, thus predisposing the patient to metabolic alkalosis. Chronic hypercalcaemia, hyperphosphataemia and metabolic alkalosis promote irreversible renal calcification.

Dose response characterisation

No relevant data are available.

Vulnerable groups

Patients with renal failure are particularly susceptible to developing hypercalcaemia when taking calcium supplements. Individuals without renal failure taking diuretics may also be at increased risk.

Patients with absorptive or renal hypercalcuria, primary hyperparathyroidism and sarcoidosis may have a higher risk of renal stone formation following calcium supplementation.

Genetic variations

No data on genetic variations that increase the toxicity of calcium have been identified.

Studies of particular importance in the risk assessment

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD).

Human data

Kleibeuker et al., 1993

Calcium carbonate tablets were well tolerated by participants in this intervention study. No mention of side effects was made when individuals were specifically asked about them. Individuals received 1500 mg calcium/day for twelve weeks.

Wu et al., 1996

This paper reports two cases of milk-alkali syndrome. Both cases showed classic MAS symptoms, i.e. hypercalcaemia and renal insufficiency. The authors estimated that the patients had ingested 9000 mg and 6000 mg of calcium carbonate (3600 and 2400 mg calcium) per day, respectively. These are the first reports of MAS not caused iatrogenically.

Levine et al., 1997

Supplementation of 2,295 pregnant women with 2,000 mg calcium/day (as calcium carbonate) resulted in no significant increase in the incidence of urolithiasis. This study excluded women with a history of, or a high risk of, developing renal disease.

Hofstad et al., 1998

116 patients received 1,600 mg calcium/day (as calcium carbonate) or placebo for 18 months. Five patients in the treatment group experienced constipation compared to one in the controls. Diarrhoea was reported in 5 calcium and 7 placebo subjects and bloating (8 patients) was equally distributed between groups.

Baron et al., 1999

No toxicity was associated with calcium supplementation during a randomised double blind, placebo controlled trial on patients with a history of colorectal adenomas. The 930 received 3000 mg of calcium carbonate/day (equivalent to 1,200 mg calcium per day) and were examined after 1 and 4 years of treatment.

Bonithon-Kopp et al., 2000

665 adult patients with a history of polyps were randomised into 3 groups receiving 2000 mg calcium/day (as calcium gluconolactate and carbonate) fibre or placebo for 3 years. 552 patients completed the follow up examination after 3 years, although 94 of these had stopped treatment early. The total number of patients reporting side effects were 26/176, 19/198 and 12/178 in the calcium, fibre and control groups, respectively. Major side effects (severe abdominal pain or diarrhoea) were also reported to be more frequent (6/176) in the calcium group compared to the control (3/178) or fibre (3/198) groups, which might have been a chance finding.

Animal data

Fairney and Weir, 1970

The effect of maternal hypercalcaemia during pregnancy and lactation on the development of the offspring was investigated. Rats were maintained on high calcium diets, containing 3% calcium in diet and 4000 mg/100 mL drinking water (equating to an estimated total intake of 3790 mg/day), throughout pregnancy and lactation. In comparison to controls (receiving 0.8% calcium in diet and 1.1 mg calcium/100 mL drinking water), the offspring of treated rats were born with significant hypocalcaemia and had lower growth rates and focal alopecia. These effects were reversible when the pups were weaned onto a normal diet.

Shackelford et al., 1993

The effect of moderately increased dietary calcium on foetal development was investigated in pregnant rats. The doses were selected to resemble the increases recommended by the 1984 US National Institutes of Health Consensus Development Conference Panel on Osteoporosis. All animals were fed nutritionally adequate diets and received 0.5 (control), 0.75, 1.00 or 1.25% dietary calcium as calcium carbonate. Treatment was for 6 weeks prior to mating, during mating and for the first 20 days of gestation. Foetal bodyweights and lengths remained similar between treatment and control groups. There were no significant increases in external, visceral or skeletal variations of the foetuses, when compared to the control animals.

Exposure assessment

Total exposure/intake:

Food	Mean: 830 mg/day (from 1990 NDNS) 97.5th percentile: 1500 mg/day
Water	up to 600 mg/day (assuming 2L/day consumption at 300 mg/L)
Supplements	up to 2400 (3 x 800) mg/day (OTC, 2001)
Estimated maximum intake:	1500 + 600 + 2400 = 4500 mg/day

No potential high intake groups were identified.

Risk assessment

In humans, the main adverse effect associated with high levels of calcium intake is milk-alkali syndrome, resulting in hypercalcaemia, alkalosis and renal impairment. Symptoms can include abdominal pain, hypertension, headaches and tissue calcification. The condition has been reported in a small number of subjects taking calcium-containing medication. Previously, MAS was more common in males taking absorbable alkali and milk, but is now more common in females taking calcium-containing medication.

Data on the effects of high doses of calcium in animals are sparse. However tissue calcification and adverse reproductive effects have been reported.

ESTABLISHMENT OF GUIDANCE LEVEL

There are insufficient data from studies in animals or humans to establish a Safe Upper Level for calcium. High intakes of calcium in vulnerable human subjects can result in milk-alkali syndrome, a condition characterised by hypercalcaemia, alkalosis and renal impairment. This is associated with symptoms such as hypertension, neurological problems, abdominal pain and tissue calcification. Milk-alkali syndrome has not been investigated in controlled studies, but numerous case reports are available. The condition tends to occur as a result of consumption of large amounts of calcium via calcium-containing medication with or without vitamin D, with intakes of calcium carbonate as low as 4,000 mg/day (1,600 mg calcium) having been associated with this condition. However, since milk-alkali syndrome generally occurs in subjects taking medication or with underlying medical conditions, it is not considered relevant to the general population.

Numerous human trials have been reported in which calcium supplements have been given to subjects with colonic polyps or who are at risk of such polyps. Some investigations have reported gastrointestinal effects in small numbers of the many patients studied taking doses of 1600 or 2000 mg/day supplemental calcium, but many of the studies are limited by inadequate reporting of side effects. No uncertainty factor is needed because the assessment is based on studies of large numbers of people. Taken together the data suggest that, for guidance purposes, doses up to 1,500 mg/day supplemental calcium would not be expected to result in any adverse effect, but that higher doses could result in adverse gastrointestinal symptoms in a few people. An estimate for total calcium intakes has not been made as the effect is related to calcium in supplemental doses.

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