

## Calcium

**C**alcium is the fifth most abundant element in the body with >99% residing in the skeleton as hydroxyapatite, a complex calcium phosphate molecule. This mineral supplies the strength to bones that support locomotion, but it also serves as a reservoir to maintain serum calcium concentrations. Calcium plays a central role in a wide range of essential functions. Its metabolism is regulated by 3 major transport systems: intestinal absorption, renal reabsorption, and bone turnover. Calcium transport in these tissues is regulated by a sophisticated homeostatic hormonal system that involves parathyroid hormone, and 1,25-dihydroxyvitamin D in response to decreased serum ionized calcium, detected by the calcium-sensing receptor (1).

### Deficiencies

The only source of calcium is from the diet which must be supplied daily to suppress bone resorption to replace obligatory losses. Calcium insufficiency manifests as decreased bone mass and osteoporotic fracture. However, calcium and vitamin D supplementation does not reduce fracture risk in community-dwelling and institutionalized middle-aged to older adults (2). In the rapidly growing child, calcium deficiency causes rickets. Low concentrations of intestinal calcium resulting from low dietary intakes have also been associated with increased risk of kidney stones and colon cancer (3). This is probably due to the decreased binding and increased absorption of oxalic acid (the main constituent of kidney stones) and of carcinogens such as bile acids.

### Diet Recommendations

The DRIs for calcium were updated in 2010 (4). The RDA is 700 mg/d for children aged 1–3 y, 1000 mg/d for children aged 4–8 y, 1300 mg/d for adolescents, 1000 mg/d for younger adults, 1200 mg/d for women over age 51 y, and 1200 mg for men and women over the age of 70 y. The mean  $\pm$  SD prevalence of US adults consuming below the Estimated Average Requirement for calcium from food only is  $37.7\% \pm 1.4\%$ , but supplement use decreases that to  $19.6\% \pm 1.3\%$  (5). Adolescents and older individuals are the most likely groups to be deficient in calcium in the United States (4). Prevalence of calcium intakes below the Estimated Average Requirement is higher for blacks ( $48.2\% \pm 1.4\%$ ) and Asians ( $47.0\% \pm 2.6\%$ ) than for Hispanics ( $30.1\% \pm 2.0\%$ ) and least for whites ( $24.2\% \pm 0.7\%$ ) (6). Socioeconomic status also influences calcium adequacy; fewer US adults who are not poor are below the Estimated Average Requirement than those considered poor or nearly poor (7).

### Food Sources

Natural food sources of calcium are primarily dairy foods. A cup (240 g) of milk or yogurt provides  $\sim$ 300 mg calcium. A

plethora of calcium-fortified foods are available to consumers. The fortified food with the most similar nutrient profile to dairy is calcium-fortified soymilk. Calcium-fortified orange juice also has many of the same nutrients as milk. Because milk provides a substantial portion of the calcium, phosphorus, riboflavin, and vitamin B-12 in the diet, it is difficult to meet nutrient needs without 3 servings (240 g milk or equivalent)/d of dairy foods as recommended by the Dietary Guidelines for Americans (8). Plant-based milk alternative beverages are becoming more popular, but except for fortified soy (9), the others have not been evaluated for calcium bioavailability.

### Clinical Use of Calcium

Calcium used clinically is usually prescribed as a dietary supplement. Various salts are in common use and include carbonate, phosphate, citrate, and citrate malate. These are usually consumed in the form of pills, but a number of calcium-fortified juices are available, which, in general, are easier to consume and are more digestible. Diseases treated with calcium supplements fall into 3 categories. The first are diseases in which the supplement is used to overcome calcium malabsorption by increasing the diffusion component of absorption. The supplement (expressed as grams of elemental calcium) is most effective when consumed frequently and between meals. The diseases include hypoparathyroidism, malabsorptive bowel disease, and osteoporosis. Calcium supplements ( $\leq 2$  g/d) are given in hypoparathyroidism to alleviate the hypocalcemia. However, because hypocalcemia is due to decreased renal calcium reabsorption, a dietary supplement has only marginal effects on increasing fasting serum calcium. A greater effect probably arises from chelation of dietary phosphate, which reduces the hyperphosphatemia and promotes an increase in fasting serum calcium (see below). In malabsorptive bowel disease, such as may occur with small bowel resection and celiac disease, calcium supplementation is used to optimize calcium absorption. The most common use of calcium supplementation ( $\leq 1.5$  g/d) currently is for the prevention of age-related osteoporosis (10). It is given to increase calcium absorption and thus decrease bone resorption. At best, the calcium supplement prevents bone loss but has no effect on bone gain (11). The second category is comprised of diseases in which the calcium supplement is used to chelate certain dietary anions, particularly phosphate. This use is largely restricted to chronic renal failure in which a reduction in phosphate absorption, and thus in serum phosphate, is the goal of treatment (12). In chronic renal failure, calcium supplements have been given to bind phosphate. However, calcium carbonate did not lower phosphorus balance in patients with stage 3–4 chronic kidney disease (13). The third category includes diseases with symptomatic gastric

acidity. Calcium carbonate (Tums is the best known) is used as an antacid between meals to neutralize gastric acidity in gastroesophageal acid reflux disease and peptic ulcer disease.

## Toxicity

The tolerable daily dietary upper intake level for calcium is set at 2500–3000 mg for adolescents and adults, 2500 mg for children, and 1000–1550 mg for infants (4). Intakes above these levels are considered to increase the risk of adverse effects, which are hypercalcemia and hypercalciuria, renal stone formation, vascular and soft tissue calcification, interactions with zinc and iron absorption, and constipation. These upper intake levels are about 2–3 times the RDA.

Sustained fasting hypercalcemia does not arise from calcium supplementation if the calcium–parathyroid hormone–1,25-dihydroxyvitamin D axis is intact and renal function and acid–base balance are normal. However, abnormalities in these systems in combination with high-calcium dietary supplements or intakes may lead to hypercalcemia. It also occurs if high calcium intake is given with high intakes of alkali that alter renal calcium reabsorption, as seen in milk alkali syndrome (14). Hypercalciuria, high calcium excretion in the urine, arises from the renal excretion of the absorbed calcium that is in excess of the needs of the body stores, the major site being in bone. Hypercalciuria is a risk factor for renal stone formation owing to the precipitation of calcium oxalate and calcium phosphate salts in urine. However, for calcium oxalate stones, an increase in urine oxalate is a much greater risk factor and for calcium phosphate stones, an increase in urine pH is a greater risk factor for stone formation (15).

Mineralization in bone, soft tissues, and blood vessels is a complex process (16). Although a supply of calcium and particularly phosphate are required, the relation between the serum calcium and phosphate activity product and the presence of mineralization is never simple. Thus, the supply of calcium in the diet is only a weak determinant of soft tissue mineralization. Concern over calcium supplementation and soft tissue calcification led to development of a systematic review to inform a position paper by the National Osteoporosis Foundation and American Society for Preventative Cardiology concluding lack of evidence for such a relation (17).

Binding of essential micronutrients such as iron and zinc is of concern in individuals at risk of these deficiencies. Constipation is said to be a complication of high-calcium dietary supplements, but it affects only some individuals and its pathophysiology is obscure.

## Recent Research

Studies of calcium interactions with other nutrients, i.e., protein, sodium, and phosphorus, are an active area of research. For example, the interaction of dietary protein and calcium determines the risk of fracture (18). Vitamin D status, as assessed by serum 25-hydroxyvitamin D concentrations, continues to be seen as a target for bone health (19) despite lack of benefit of vitamin D supplementation to fractional calcium absorption or other functional measures (20). Interventions

to improve the utilization of calcium such as prebiotics are currently being investigated (21). As with other nutrients, more attention is being given to dietary patterns and matrix effects of the major food sources such as dairy for calcium, rather than the nutrient in isolation (22).

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