Calcium Supplementation in Clinical Practice: A Review of Forms, Doses, and Indications

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Invited Review

Calcium Supplementation in Clinical Practice: A Review of Forms, Doses, and Indications

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ABSTRACT: Most Americans do not meet the adequate intake (AI) for calcium; calcium supplements can help meet requirements. Calcium supplementation has been found to be beneficial for bone health in children, young adults, and menopausal women. In addition to calcium, vitamin D is necessary for bone health and is generally deficient in the industrialized world. Calcium from carbonate and citrate are the most common forms of calcium supplements. Calcium carbonate, the most cost-effective form, should be taken with a meal to ensure optimal absorption. Calcium citrate can be taken without food and is the supplement of choice for individuals with achlorhydria or who are taking histamine-2 blockers or protein-pump inhibitors. Calcium lactate and calcium gluconate are less concentrated forms of calcium and are not practical oral supplements. Research on hydroxyapatite as a source of calcium is limited, so this form of calcium is not recommended. The maximum dose of elemental calcium that should be taken at a time is 500 mg. U.S. Pharmacopeia–verified calcium supplements meet vigorous manufacturing and quality requirements. Absorption from calcium-fortified beverages varies and in general is not equal to that of milk. Potential adverse effects of calcium supplementation include gastrointestinal complaints. Renal calculi in most studies have not been associated with calcium supplementation. The risk of advanced and fatal prostate cancer has been associated with calcium intakes from food or supplements in amounts >1500 mg/d.

It is clear that Americans of all ages do not consume adequate dietary calcium when compared with the current recommendations issued by the Institute of Medicine (IOM). Osteoporosis is the result of inadequate calcium consumption over time and has a long latency period.[1] In other words, inadequate calcium intake early in life can have significant consequences later in life. In children 9–18 years of age, mean calcium intake using data from the Continuing Survey of Food Intake by Individuals (CSFII; 1994–1996, 1998) and the National Health and Nutrition Examination Survey (NHANES; 1999–2000) was 935 mg/d, significantly less than the adequate intake (AI) of 1300 mg/d for this age group.[2] In adults ages 51 and older, the mean calcium intake was 674 mg/d, significantly less that the AI of 1200 mg/d. In addition to calcium, vitamin D, which is necessary for bone health, is generally deficient in the diets throughout the industrialized world.[3] Low levels of vitamin D result in impaired calcium absorption, secondary hyperparathyroidism, bone loss, and osteoporosis. The purpose of this paper is to review the role of calcium supplementation in bone health and the practical considerations when making recommendations.

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Current Calcium Recommendations

An AI has been set for all age groups for calcium by the IOM[4] (Table 1). The AI for calcium is based on calcium balance studies, factorial estimates of requirements, and limited data on changes in bone mineral density (BMD) and bone mineral content. The AI is the level at which the needs of most individuals are met or exceeded in a specific life stage and gender group. The tolerable upper limit (UL)—the level that may cause adverse health effects—for calcium is 2500 mg/d for children ages 1 year and older and adults. The UL has not been established for children <1 year of age. The UL includes intake from food, supplements, and water. The risks associated with exceeding the UL for calcium include hypercalcemia, increased risk of kidney stones, renal insufficiency, and milk-alkali syndrome (hypercalcemia, metabolic alkalosis, renal failure). In addition, calcium intakes in excess of 2500 mg/d may interfere with the absorption of other minerals, including zinc, magnesium, and phosphorus.

Table 1
Recommended adequate intake for calcium for men and women

Age	Adequate intake (mg/d)	Upper limit (mg/d)
0–6 mo	210	Not determined
7–12 mo	270	Not determined
1–3 y	500	2500
4–8 y	800	2500
9–13 y	1300	2500
14–18 y	1300	2500
19–30 y	1000	2500
31–50 y	1000	2500
51–70 y	1200	2500
>70 y	1200	2500
Pregnancy ≤18 y	1300	2500
Pregnancy 19–50 y	1000	2500
Lactation ≤18 y	1300	2500
Lactation 19–50 y	1000	2500

Adapted from the Institute of Medicine, Washington, DC.[4]

Physiology

The skeleton accounts for 99% of total calcium stores in the form of hydroxyapatite. The primary function of calcium is to form the structure of bones and teeth. The remaining calcium stores are found in the cells of the soft tissue (0.9%) and in the bloodstream and extracellular fluid (0.1%). Calcium is involved in the function of the muscular, cardiovascular, endocrine, and nervous systems; homeostasis is maintained by the actions of several hormones, including parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D [1,25(OH_2)D].

Absorption

A number of factors affect calcium absorption in the gut.[5] Absorption is greatest when the intake of calcium is low and the need is high. Vitamin D levels, an acidic environment in the gut, age, estrogen levels, and dietary fiber intake all play a role in calcium absorption. Calcium absorption decreases with age, low vitamin D levels, hypochlorhydria, low estrogen levels, and a high-fiber diet.

Calcium is both actively and passively absorbed in the small intestines. Low vitamin D levels are associated with impairment of the active absorption of calcium. Low levels may be due to lack of dietary or supplemental vitamin D intake or lack of sun exposure. In individuals with gross vitamin D deficiency, only 10%–15% of dietary calcium is absorbed. Calcium absorption varies, depending on serum 25-hydroxyvitamin D [25(OH)D] levels. In 1 study, absorption rates of calcium were 65% higher at serum 25(OH)D levels of 86.5 nmol/L than at levels averaging <50 nmol/L.[6] Both of these vitamin D levels are within the current reference range, but these data suggest that the lower end of the reference range may be set too low.

In addition to dietary factors, genetics plays a role in bone density. Polymorphisms in vitamin D receptors (VDR) have been associated with variation in calcium absorption, although no consensus has been reached regarding their role in BMD.[7] In a study of 99 healthy women approaching menopause (mean age 47; range, 43–53), calcium absorption and bone density was highest in individuals with the bbaaTT haplotype and the aa genotype.[8] Dietary calcium was determined by a food frequency questionnaire, with absorption determined by a single-isotope radiocalcium test. Serum levels of 1,25(OH2)D levels were also measured. Calcium absorption was positively related to vitamin D levels and inversely related to dietary calcium intake.

Individuals vary in their ability to absorb calcium. Calcium absorption averaged 35% and ranged from 17% to 58% in a study of 142 healthy pre- and perimenopausal women.[9] In this study, calcium absorption was inversely related to total dietary calcium intake, dietary fiber, alcohol intake, and physical activity. Calcium absorption was also positively associated with body mass index, dietary fat intake, and serum 1,25(OH_2)D and PTH levels. Women who had the lowest ratio of fat to fiber intake had a 19% lower absorption of calcium when compared with women with the highest ratio of fat to fiber intake. Polymorphisms in VDR were not associated with differences in calcium absorption in this study.

Excretion

Calcium is excreted primarily in the urine and feces, with a number of factors thought to increase urinary calcium loss, including intake of caffeine, protein, and sodium, as well as low estrogen levels.

In a study investigating caffeine intake in 489 women aged 66–77 years, there was a positive association between caffeine intake and bone loss.[10] Bone loss at the spine was greater in women consuming >300 mg of caffeine per day than in women consuming <300 mg/d. Women with the tt genetic variant of VDR had significantly greater loss of bone at the spine than women with the TT genetic variant when their intake was >300 mg/d.

Protein is necessary for bone formation. Bone is approximately 50% protein by volume. Although increasing dietary protein increases calcium excretion, research has shown this may not necessarily have a negative effect on bone health. Dawson-Hughes and Harris[11] studied 342 healthy men and women aged 65 and older for 3 years in a randomized, placebo-controlled trial to determine the impact of calcium and vitamin D supplementation on the rates of change in BMD. Individuals were randomized either to the study group (which

received 500 mg of calcium citrate-malate and 700 IU of vitamin D daily) or to the double placebo group. Protein intake was determined by use of a food frequency questionnaire, and bone density was measured every 6 months by dual-energy x-ray absorptiometry (DXA). Urinary calcium increased slightly, but not significantly, with protein intake. The calcium-supplemented subjects gained bone density, but those with the highest protein intake (88.6 ± 29.3 g/d) had the greatest increase in total body and femoral neck bone density compared with those with the lowest protein intake (77.7 ± 25.7 g/d). Both animal and plant proteins had a positive effect on BMD. The control group lost bone density during the study. This study suggests that increasing protein intake in older men and women may have a beneficial effect on bone mass when supplemented with calcium and vitamin D.

Prevalence of Calcium Supplement Use in the United States

Calcium supplements are widely marketed in the United States and are readily available over the counter. According to data from the National Health Interview Survey (NHIS), calcium supplement use by US adults increased from 6.2% in 1992 to 11% in 2000.[12] In this survey, supplement use increased in all demographic groups, with the exception of younger individuals (age 18–24 years), those who had annual incomes of <$25,000, or underweight individuals.

Analysis of data from the 1999–2000 NHANES indicated that 10% of the population took a calcium supplement in the previous month.[13] This number increased to 25% when calcium-containing antacids were included. The prevalence of calcium use varied, depending on demographic and lifestyle characteristics; calcium supplement use was higher among: women *vs* men, participants aged 60 or older *vs* those 20–39 years old, non-Hispanic whites *vs* non Hispanic blacks and Mexican Americans, participants with more than a high school education *vs* less, those reporting moderate physical activity *vs* no physical activity, and for former smokers *vs* current smokers.

Indications for Calcium Supplementation

Calcium supplementation should be considered for individuals who fail to meet the AI for calcium, individuals with osteopenia or osteoporosis, perimenopausal and postmenopausal women, mothers who breastfeed multiple infants, vegans, amenorrheic women, residents of long-term care facilities, and in individuals who are lactose intolerant or receiving chronic corticosteroid therapy. Supplementation should also be considered for patients with inflammatory bowel or celiac disease. In addition to calcium, vitamin D supplementation should be administered concurrently.

Calcium supplementation is contraindicated in patients with hypercalcemia.[14] Hypercalcemia may be caused by sarcoidosis, hyperparathyroidism, hypervitaminosis D, and certain types of cancer.

Calcium Supplements and Bone Health

Childhood to Young Adulthood

There is little debate about calcium needs during childhood and young adulthood. During adolescence, 40% of total lifetime bone mass is accumulated. However, most older children and adolescents in the United States do not meet the AI for calcium.[2] Suboptimal calcium intake has been associated with replacement of soda for milk, especially during the early adolescent years.[15] Interventions to prevent this adverse trend include limiting the availability of soda and increasing the availability of milk at home and at school. The American Academy of Pediatrics issued a policy statement on soft drinks in schools in 2004.[16] The policy recommends that pediatricians work to eliminate soft drinks in schools and to educate parents about the health ramifications of soft drink consumption.

In 2006, the American Academy of Pediatrics published a clinical report providing guidelines for optimizing bone health in infants, children, and adolescents.[17] The report recommends that calcium intake be assessed using a simple questionnaire during pediatric office visits at 2–3 years, after the transition from breast milk or formula; at 8–9 years of age, during preadolescence; and during adolescence, when the peak rate of bone accretion occurs. The report also recommends that pediatricians encourage adequate calcium and vitamin D intake as established by the IOM. Dairy sources of calcium are recommended because of their prevalence in the diet and the other nutrients that they contain. Supplements are suggested as an alternative to dairy products. The expertise of a registered dietitian is suggested for a more thorough assessment of the diet and to make recommendations. Pediatricians are encouraged to discuss with the family the benefits of calcium and vitamin D in decreasing the risk of osteoporosis later in life and perhaps decreasing the risk of fractures in childhood and adolescence.

Calcium supplementation can significantly increase bone accretion in young women.[18] In a 4-year randomized, controlled clinical trial, 352 women in pubertal stage 2 were studied. The trial was optionally extended 3 years. The mean dietary calcium intake during the study was 830 mg/d. Calcium-supplemented individuals received an additional 670 mg of calcium per day as citrate. Vitamin D was not supplemented and serum levels were not measured. The calcium-supplemented group had a significant increase in bone accretion during the pubertal growth spurt. Supplementation during this period of life may have implications for

the primary prevention of osteoporosis, as well as preventing bone fragility fractures during growth. Furthermore, an analysis of investigator case-controlled and observational studies from 1975 to 1998 established that adequate calcium from dietary sources or supplementation increases bone gain during growth.[19]

In summary, AI of calcium and vitamin D is paramount in maximizing bone accretion during growth, preventing future osteoporosis, and perhaps preventing fragility fractures during growth. Calcium intake from dietary sources should be encouraged at home, school, and by pediatricians and registered dietitians. If adequate calcium cannot be achieved through dietary sources, supplementation is an effective alternative. Adequate vitamin D should also be ensured through diet or supplementation.

Peri- and Postmenopausal Women

Calcium requirements increase with menopause. Low estrogen levels lead to an increase in bone resorption, a decrease in the efficiency of intestinal calcium absorption, and a decrease in renal conservation of calcium. By age 65, calcium absorption is 50% of adolescent absorption levels.

Inadequate vitamin D status can also limit calcium absorption and have a negative effect on bone health. With aging, several factors can lead to inadequate serum levels including poor dietary intake, inadequate sun exposure, decreased renal efficiency in converting vitamin D to the active form 1,25(OH_2)D, and decreased intestinal responsiveness to vitamin D.

Osteoporosis is a mulitfactorial disease; calcium and vitamin D are key nutrients necessary for bone health. In addition to calcium and vitamin D, vitamin K, magnesium, potassium, and vitamin C may also play a role in optimizing bone health.[20]

The North American Menopause Society (NAMS) issued a position paper in 2006, supporting the role of adequate calcium in the presence of adequate vitamin D in reducing bone loss in peri- and postmenopausal women and in reducing fractures in women over the age of 60 with low dietary calcium intakes.[21] The society recommends 1200 mg of calcium/d and adequate vitamin D, defined as a serum level of 25(OH)D of ≥30 ng/mL. Food is recommended as the primary source of calcium, but supplements and fortified foods are recommended as alternative sources.

Calcium (1200 mg/d) and vitamin D (700–800 IU/d) are also recommended in the NAM's 2006 position paper on the management of osteoporosis in postmenopausal women.[22] Calcium and vitamin D are recommended as an adjunct to all types of pharmacotherapy used to treat osteoporosis.

Short clinical trials of calcium supplementation show that calcium reduces the loss of bone in postmenopausal women and the risk of fracture. A meta-analysis of 15 trials that included a total of 1806 participants randomized to either calcium supplementation or usual calcium dietary intake over a 2-year period showed an increase in bone density for the lumbar spine of 1.66%, 1.64% for the hip, and 1.91% for the distal radius in the calcium-supplemented group.[23] A trend toward a reduction in vertebral fractures was also noted. Inclusion criteria included calcium doses of at least 400 mg/d, with or without a maximum intake of 400 IU of vitamin D/d. Supplemental sources of calcium included carbonate, citrate, citrate-malate, gluconate, and lactate. An analysis of 20 major calcium trials in postmenopausal women also demonstrated that calcium supplementation (500–1200 mg/d) decreased bone loss.[24] Women who received calcium supplementation lost bone at the rate of 0.014% per year. Women who did not receive calcium supplementation lost bone at the rate of 1% per year. A review of both investigator-controlled calcium intervention trials and observational studies from 1975 to 1998 found that calcium from diet or supplements decreased age-related bone loss.[19]

Both vitamin D and calcium were found to be effective in decreasing bone loss and fracture risk in a 3-year, double-blind, placebo-controlled trial of 213 women and 176 men 65 years of age or older.[25] The subjects received either placebo or 500 mg of elemental calcium as calcium citrate-malate and 700 IU of vitamin D_3 per day. In the treatment group, bone loss was moderately reduced in the femoral neck, spine, and total body. The incidence of nonvertebral fractures was also reduced in the treatment group.

The Women's Health Initiative (WHI), a recent large randomized trial, studied >36,000 women ages 50–79 over a 7-year period and evaluated the effect of calcium and vitamin D on fracture rates.[26] Hip fractures were significantly reduced in women who were adherent to calcium and vitamin D treatment. A 29% relative decrease in hip fracture rates was found in women who were compliant with taking 1000 mg of elemental calcium as carbonate and 400 IU of vitamin D per day.

In summary, adequate calcium and vitamin D intake plays a key role in preventing menopausal bone loss and in decreasing the risk of bone fractures in women. Women should consume 1200 mg/d of calcium from food or supplementation. An adequate vitamin D level is defined as a serum level of 25(OH)D of ≥30 ng/mL.

Supplemental Sources of Calcium

The most common forms of calcium available to the consumer are calcium carbonate and calcium citrate. Other forms of calcium include lactate, gluconate, bone meal, and hydroxyapatite. Calcium supplements are available as capsules, tablets, chews, wafers, powders, and liquids. When recommending calcium supplements, the bioavailability,

presence of achlorhydria, use of H_2 blockers or protein-pump inhibitors, number of tablets needed to achieve the desired dose, size of the tablet, form of the calcium, and cost should all be considered. Many patients have difficulty swallowing large tablets or do not want to take multiple tablets to achieve the desired dose of calcium.

Calcium Carbonate and Calcium Citrate

Studies on the absorbability of calcium carbonate and calcium citrate have yielded varying results, which may reflect differences in methodology. The bioavailability of calcium carbonate *vs* calcium citrate was found to be identical in 23 vitamin D–sufficient postmenopausal women.[27] In this study, ionized serum calcium, total serum calcium, and PTH levels were measured over a 24-hour period. Urine calcium excretion was also measured. VThe cost-benefit analysis in this study favored the use of calcium carbonate. In another study, the absorption of calcium carbonate and calcium citrate was found to be equivalent when taken with a meal.[28] Absorption was measured in 37 healthy men and women using tracer appearance of calcium in the serum and by the absorptive increment in urinary calcium. Both salts were equally absorbed at 36% at a 300-mg load and 28.4% at a 1000-mg load.

The bioavailability of calcium carbonate was found to be equivalent to skim milk and orange juice fortified with calcium-citrate malate in 12 elderly subjects.[29] Changes in serum, urinary calcium, and PTH were not significantly different between sources including skim milk, calcium carbonate, or orange juice fortified with calcium citrate malate.

In contrast to these findings, calcium citrate was found to have better bioavailability in 25 postmenopausal women than calcium carbonate when given with a meal.[30] Serum calcium, PTH levels, and urinary calcium were measured. The increase in serum and urinary calcium was greater for calcium citrate than for calcium carbonate. The decrease in PTH was greater for calcium citrate than for calcium carbonate. These findings suggest that calcium citrate is more bioavailable than calcium carbonate when given with a meal. The authors suggest that one possible explanation for these findings is a low gastric acid output in some of the study subjects because the absorption of calcium from carbonate requires an acidic environment.

Calcium citrate should be the supplement of choice in patients with achlorhydria, a condition common in the elderly. In a study dating back to 1985, calcium carbonate was found to be poorly absorbed under fasting conditions in patients with achlorhydria, whereas the absorption of calcium citrate was significantly higher.[31] Of interest, calcium carbonate when taken with breakfast resulted in normal absorption in achlorhydric subjects.

Medications used to treat gastroesophageal reflux can interfere with the absorption of calcium carbonate.[14] Protein-pump inhibitors and H_2 blockers decrease stomach acidity. Therefore, because calcium carbonate requires an acidic environment for absorption, individuals taking these medications should use calcium citrate supplements.

Calcium carbonate is the most common and least expensive form of calcium. Cost is a consideration for many patients. A study assessing the cost of calcium from food and supplements found that calcium carbonate was the least expensive form of calcium, at approximately one-third the cost of the least expensive food source, which includes skim milk and calcium-fortified orange juice made from frozen concentrate.[31]

The concentration of calcium varies in supplements.[14] Calcium carbonate supplements contain 40% calcium, whereas calcium citrate supplements contain only 21% calcium. The only drawback associated with the use of calcium citrate supplements is the need to take more tablets or capsules to make the dose equivalent to that of calcium carbonate. A requirement for more tablets may affect compliance.

In summary, calcium carbonate is well-absorbed and tolerated in most individuals when taken with a meal. Calcium carbonate supplements provide greater amounts of elemental calcium and consequently require fewer tablets than other forms of calcium. Calcium citrate should be used in individuals with suspected achlorhydria, inflammatory bowel disease, or absorption disorders. Calcium citrate supplements should also be recommended for individuals treated with H_2 blockers or protein-pump inhibitors. Residents of long-term care facilities who may not be given their calcium supplements at mealtimes should be supplemented with calcium citrate. Additionally, busy individuals who find it difficult to supplement at meals should use calcium citrate, which can be taken with or without food.

Coral Calcium

Coral calcium became popular several years ago after infomercials featuring Kevin Trudeau and Robert Barefoot claimed that the longevity and health experienced by Okinawans was due to the coral calcium in their drinking water. Okinawa has the world's highest concentration of centenarians and low mortality rates from diseases common in the western world. The marketers of the supplement Coral Calcium Supreme claimed that their product could treat or cure cancer, multiple sclerosis, and other diseases. The supplements were supposedly made from marine coral from Okinawa, Japan. In fact, coral calcium is nothing more that calcium carbonate, the least expensive form of calcium in the marketplace.

In 2003, the Okinawa Centenarian Study (OCS) issued a position paper regarding the use of coral calcium.[32] The OCS clearly states that the longevity of the Okinawans is not due to the coral calcium in their drinking water but rather to their healthy lifestyle. Cost and the lack of scientific evidence to support health claims were additional factors considered in their lack of endorsement. Environmental concerns about the health of the world's coral reefs are also stated as a reason against the use of coral calcium.

The Federal Trade Commission (FTC) took legal action against Kevin Trudeau, Robert Barefoot, and their companies regarding the advertising and sales of Coral Calcium Supreme.[33] A federal court ruled in favor of the FTC against Robert Barefoot and his companies in January of 2004, prohibiting them from making unsupported health claims about coral calcium.

Calcium Lactate and Calcium Gluconate

Calcium lactate and calcium gluconate are less concentrated forms of calcium.[14] Calcium lactate contains 13% elemental calcium, whereas calcium gluconate contains only 9% elemental calcium; therefore, these forms are not considered practical for clinical practice. Because calcium lactate and calcium gluconate contain a small concentration of elemental calcium, many tablets have to be consumed to reach desirable doses. One popular brand of calcium lactate contained only 255 mg of elemental calcium in 3 tablets. To obtain 1000 mg of supplemental elemental calcium from this form, >12 tablets would need to be consumed.

Calcium From Bone Meal

Calcium supplementation from bone meal has fallen out of favor. In the 1980s, calcium from bone meal was found to be contaminated with lead, arsenic, mercury, and cadmium.

Microcrystalline hydroxyapatite is a "second-generation" calcium supplement derived from bovine bone. Manufacturers of this form of calcium claim that it is free of heavy metals. The organic component of this supplement consists of collagen and bone-specific growth peptides, which manufacturers claim are beneficial for bone health. The inorganic component provides calcium and phosphorus. Little recent research on this form of calcium is available in the peer-reviewed literature. Most of the research has been done in Europe. A 1995 randomized placebo controlled study that included 40 osteoporotic patients found that hydroxyapatite was more effective than calcium carbonate in slowing peripheral trabecular bone loss from the distal tibia and the distal radius.[34] Patients were followed up for 20 months, and bone densities were evaluated every 4 months using high-precision peripheral quantitative computed tomography. At the end of the study, the loss of trabecular bone was 0.8% in the hydroxyapatite group compared with 1.8% in the calcium carbonate group.

Currently, insufficient evidence is available to recommend using hydroxyapatite as a form of calcium supplementation. There are many other forms of calcium that are free of contaminants and have been shown to be well absorbed and efficacious.

Dosing

The dosing of calcium supplements can affect both the absorption of calcium and PTH levels. Absorption of calcium is greatest when taken in a dose of 500 mg or less.[35] In a study dating back to 1988, calcium absorption using 3 different doses was measured in 4 men and 17 women ages 22–60. Doses of 500 mg, 1000 mg, and 2000 mg of elemental calcium were given to all of the subjects. Calcium absorption was tested using a 200-mg dose in 9 subjects. Both calcium citrate and calcium carbonate were used. Urinary calcium was found to increase rapidly at the 200-mg and 500-mg doses, with only a slight additional increase after the 1000-mg and 2000-mg doses.

Timing, dosage, and whether small repetitive doses of calcium are more effective was studied in 30 healthy women ages 21–34.[36] PTH levels and markers of bone formation and resorption were measured. There was not a significant difference in PTH levels whether calcium was taken during the day or at night (9 AM *vs* 9 PM). The size of the dose did have a significant effect of PTH levels: the higher the dose of calcium, the lower the PTH level. Small 200-mg doses of calcium given 4 times per day also produced lower PTH levels. There was no significant effect on markers of bone formation or resorption in any of the dosing schedules.

In clinical practice, to obtain optimal clinical outcomes related to calcium supplementation, the dose of calcium should not exceed 500 mg at 1 time. It may be beneficial to supplement in smaller doses 4 times per day to lower PTH levels and decrease bone resorption. Compliance with this dosing schedule may be difficult but should be considered in motivated individuals with osteopenia or osteoporosis.

Quality Considerations and Product Testing of Calcium Supplements

The quality of the calcium supplement is as important as the form of the mineral. Consumers have multiple brands from which to choose but few assurances that the products are of high quality. There are, however, some guidelines that the consumer and health professional can use to ensure the purchase of a high-quality calcium supplement.

The US Pharmacopeia (USP) is a nongovernmental, nonprofit organization formed in 1820 to set standards for healthcare products.[37] Federal law recognizes the USP as the official body that sets standards for prescription drugs, over-the-counter medications, and dietary supplements. Manufacturers of dietary supplements are not required to comply with USP standards. Dietary supplements labeled *USP* represent the manufacturer's claim that the product meets USP standards, although verification is not required. In response to consumer demand for assurances about the quality of dietary supplements, USP has instituted a voluntary verification program. When the USP-verified symbol appears on a calcium supplement label, it assures the consumer that the label is accurate; the calcium is present in the stated amount; the product will dissolve; the products meets federal limits for heavy metals, pesticides, and microbes; and that good manufacturing practices (GMPs) have been followed. A list of USP-verified calcium supplements can be found at www.uspverified.org.[38]

ConsumerLab.com LLC (CL) evaluates consumer products relating to health, including dietary supplements.[39] Calcium supplements are purchased independently at the retail level and tested blindly at commercial or academic laboratories for dissolution, acceptable lead levels, and content. The results of the testing can be found at www.consumerlab.com and are available only to subscribers. Manufacturers whose products pass testing can have their products certified by ConsumerLab on acceptance of the CL Seal Use License Agreement. These products bear the CL seal. A listing of these products is available to nonsubscribers on the CL website, www.consumerlab.com.

Calcium-Fortified Beverages

Calcium-fortified beverages are increasingly available in the marketplace. They are a convenient and popular way to increase calcium intake and are especially helpful for individuals who have difficulty swallowing large tablets and for children, vegans, and individuals with dairy allergies or intolerances. Calcium-fortified foods include orange juice and soy and rice milk. The bioavailability of calcium from these fortified foods, however, varies considerably. When advising patients on the use of these foods, it is important to take into account bioavailability. Currently, information about the bioavailability of calcium-fortified products is not included on the nutrition label. Although consumers assume that calcium absorption from fortified foods is equal to that of milk, often it is not.

Orange Juice and Soymilk

Calcium absorption from 2 commercially available calcium-fortified orange juices was compared in 25 healthy premenopausal women.[40] Study subjects consumed fortified orange juice providing 500 mg of elemental calcium at breakfast after an overnight fast. Serum calcium levels were measured over a 9-hour period. The women drinking orange juice fortified with calcium citrate malate absorbed 48% more calcium than the women drinking the juice fortified with tricalcium phosphate/calcium lactate. The difference in absorption was highly significant.

The form of the calcium may not be the determinant of absorbability but rather the physical state of the calcium. Calcium in fortified beverages can precipitate out and settle to the bottom of the container, depending on the fortification system.

The degree to which calcium settled out of 14 calcium-fortified beverages was evaluated and compared with unfortified fat-free milk.[41] Each beverage was extrinsically labeled with a calcium isotope and allowed to equilibrate in the refrigerator for 17 hours. The calcium-fortified beverages were then centrifuged to separate the solid and soluble moieties. All of the soy and rice beverages had most of their calcium separate out in a particulate form. Of the total calcium found in these beverages, 82%–89% of the total calcium separated out of the solution. The calcium that separated out in orange juice ranged from 8.1% to 50.4%. Only 11% of the calcium found in cow's milk separated. Two of the orange juices were comparable to cow's milk, with very little calcium settling out of the solution.

Mineral Water

Analysis of the data from the USDA's Nationwide Food Consumption Surveys indicates that since the late 1970s to the mid-1990s, milk consumption decreased by 36%, whereas soda and fruit juice consumption doubled.[15] The trend in decreased milk consumption is particularly troubling in young girls between the ages of 12 and 19 years because it is during this time that bone density accretion rates are at their highest. Seventy-eight percent of girls drank milk at the age of 12 and had the lowest intake of soda, however by age of 19, only 36% of girls drank milk, and soda intake had increased.

Calcium-rich mineral water may provide a calorie-free, calcium-rich alternative to soda. Heaney found that the absorption of calcium from mineral water was equal or slightly better than the absorption of calcium from milk.[42] Biomarkers of calcium absorption indicated significant calcium absorption. Urinary calcium increased, whereas PTH and bone resorption markers decreased. In a meta-analysis of 6 studies, calcium absorption from mineral water was also found to be significantly higher than calcium absorption from milk.[43] High-calcium mineral water should therefore be considered as a source of highly bioavailable calcium.

Potential Adverse Effects of Calcium Supplementation

Gastrointestinal Side Effects

Calcium supplements are generally well tolerated; however, some patients complain of gastrointestinal symptoms, including constipation, gas, flatulence, and bloating. Although calcium carbonate is the form most often associated with these reported side effects, little information about how to avoid these symptoms is available in the scientific literature.

In clinical practice, calcium from food and supplementation should not exceed the current AI. Calcium citrate should be substituted for calcium carbonate in any patient complaining of constipation, gas, and flatulence or bloating in an attempt to see if symptoms improve. In addition, it is important to determine if lack of fluid or fiber is the cause of constipation. Other causes of gas and bloating, such as lactose or fructose intolerance, food sensitivities, dysbiosis, or celiac disease, should be investigated if symptoms do not improve after changing to calcium citrate.

Renal Calculi

Calcium once was thought to play a role in the formation of kidney stones, and patients with stones often began receiving a low-calcium diet. More recent studies now suggest that a low-calcium diet may actually increase the risk of developing kidney stones.[44] In a 5-year randomized trial, 120 men with recurrent calcium oxalate stones began receiving either a low-calcium diet (10 mmol/d) or a normal-calcium (30 mmol/d), low-sodium, low-animal-protein diet. Urinary oxalate excretion increased in the men receiving the calcium-restricted diet but decreased in the men consuming the normal-calcium, low-animal-protein (52 g/d), low-sodium diet (50 mmol/d sodium chloride). The risk of stone recurrence was decreased by 50% in the men receiving the normal calcium diet compared with those receiving the low-calcium diet. It is thought that dietary calcium binds oxalates in the gut, preventing absorption.

Dietary calcium intake was also inversely associated with the risk of kidney stones in the Health Professionals Follow-up Study.[42] A cohort of 45,619 men from 40 to 75 years of age, with no history of kidney stones, was followed for 4 years. No significant risk was associated between the risk of kidney stones and calcium supplementation. Additionally, in a study of 56 postmenopausal women, calcium carbonate supplementation with a meal or combined calcium supplementation with estrogen therapy did not increase urinary calcium oxalate excretion.[43] Conversely, results of the WHI raised some concerns regarding whether calcium and vitamin D supplementation together increases the risk of renal stones.[26] Women in the group randomly assigned to receive 1000 mg/d calcium and 400 IU/d of vitamin D_3 experienced a significant 17% increase in risk of renal stones compared with the placebo group. However, apparently the women in the supplemented group were also using self-selected supplements, which resulted in a calcium intake close to 2000 mg/d. Thus, further studies are needed to clarify this issue.

To reduce the risk for calcium oxalate stones, calcium supplements should be taken with food to allow calcium to bind with oxalates in the gut, and the UL should not be exceeded.

Prostate Cancer

Calcium intake from diet and supplementation in men is currently under scrutiny. Dairy intake has been associated with higher rates of prostate cancer in men.[45] Now, the most recent findings from the Health Professionals Follow-up Study have found that calcium from diet and supplements is not associated with total or nonadvanced prostate cancer, but rather is associated with a higher risk of advanced and fatal prostate cancer.[46] The increased risk for advanced and fatal prostate cancer was observed at intakes of 1500–1999 mg/d and was greatest at intakes >2000 mg/d. Dietary calcium and supplemental calcium were independently associated with increased risk. A mechanism has not been identified, but the authors theorize that high calcium intakes may lower vitamin D, which may protect against prostate cancer. Lowest risk for prostate cancer occurred in men whose calcium intake was 500–749 mg/d. No other health risks have been identified when calcium supplements are taken at recommended levels.

Drug and Food Interactions

There are multiple drug-nutrient interactions associated with calcium supplements. Calcium supplements are widely used, and the risk for interactions is therefore elevated. Patients should be asked about calcium supplement use and educated on potential drug-nutrient interactions. Tables 2 and 3 summarize some of the more common drug and food interactions.

Summary

Calcium supplementation can play a valuable role in bone health throughout the lifecycle. In bone health, it is paramount not only to ensure adequate calcium intake but also intake of adequate vitamin D and the other micronutrients important to bone health. Calcium from carbonate and citrate should be the forms of choice for supplementation. Calcium carbonate is cost-effective but should be taken with meals to optimize absorption, but is contraindicated

Table 2
Calcium-drug interactions

Levothyroxine	Administrations of calcium and levothyroxine should be separated by 4 h; calcium reduces levothyroxine absorption by forming insoluble complexes.
H_2 blockers and protein-pump inhibitors	H_2 blockers and protein-pump inhibitors decrease the absorption of calcium carbonate, which requires an acidic environment.
Tetracyclines	Tetracyclines should be taken 2 h before or 4–6 h after calcium supplements; calcium decreases the absorption of tetracycline by forming insoluble complexes.
Biphosphonates	Biphosphonates should be taken at least 30 min before calcium supplementation. Ideally, calcium should be taken at another time of day.
Quinolone antibiotics	Quinolone antibiotics should be taken at least 2 h before or 4–6 h after calcium supplementation; calcium decreases absorption of the drug by forming insoluble complexes.
Digoxin	Hypercalcemia increases the risk of fatal cardiac arrhythmias.
Thiazide diuretics	Thiazide diuretics decrease the excretion of calcium. Calcium supplementation in moderate doses increases the risk of milk-alkali syndrome. Serum calcium and PTH levels should be monitored regularly.
Corticosteroids	Corticosteroids in doses of 7.5 mg/d or more can cause significant bone loss, as they decrease calcium absorption, increase calcium excretion, and inhibit bone formation. Patients using these drugs should take calcium and vitamin D supplements.
Anticonvulsants, phenytoin, fosphenytoin, carbamazepine, phenobarbital	These anticonvulsants decrease calcium absorption by increasing the metabolism of vitamin D. Hypocalcemia and osteomalacia have been identified in patients receiving chronic therapy. Patients receiving these drugs should take calcium and vitamin D supplements.

Adapted with permission from the Natural Medicines Comprehensive Database.[47]
PTH, parathyroid hormone.

in patients with achlorhydria or those taking gastric acid suppression medications such as H_2 blockers or protein-pump inhibitors. Calcium citrate is recommended in these situations. There is insufficient evidence to recommend hydroxyapatite at this time as a reliable supplement. The dose of elemental calcium should not exceed 500 mg at a time. The absorption of calcium from fortified beverages is generally less than that of milk and cannot be considered a reliable source of bioavailable calcium. Mineral water, on the other hand, appears to be a good source of bioavailable calcium and should be considered a calorie-free alternative to carbonated beverages.

There are few adverse effects associated with calcium supplementation when taken in amounts below the UL set by the IOM. The exception to this is in men. Advanced and fatal prostate cancer has been associated with calcium from food and from supplements in amounts of ≥1500 mg/d.

Table 3
Calcium supplement interactions with food

Fiber	Phytic acid can decrease calcium absorption. Psyllium does not seem to significantly decrease calcium absorption.
Iron, zinc, magnesium	Calcium supplements may decrease the absorption of iron, zinc, and magnesium. There is little clinical significance in patients with adequate stores of these minerals. For compromised patients who are at risk for deficiencies of iron, zinc, or magnesium, calcium citrate should be take in between meals and at bedtime.
Caffeine	Caffeine intake >300 mg/d increases urinary excretion of calcium.
Sodium	Sodium increases urinary calcium excretion.

Adapted with permission from the Natural Medicines Comprehensive Database.[47]

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