

Calcium

Introduction

Calcium is a nutrient most often associated with the formation, metabolism, strength, and health of bones and teeth (Institute of Medicine [IOM] 2010). Over 99 percent of calcium in the body resides in bones and teeth as a complex calcium phosphate mineral crystal. Less obvious but equally important roles for calcium occur in the soft tissues where it mediates vascular contraction, vasodilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion functions, among others. In its structural roles, calcium has a substantial impact on presence or absence of osteoporosis. Calcium absorption and utilization may be dependent on and influenced by dietary intakes of phosphorus and vitamin D, as well as other factors such as parathyroid hormone, the peptide calcitonin, and estrogen.

The role of dietary calcium and vitamin D in reducing the risk or delaying the onset of osteoporosis is now well recognized (Food and Drug Administration [FDA] 1994). Because bone loss often accompanies the aging process, sufficient calcium intake during early adulthood increases peak bone mass, thereby reducing the risk of osteoporosis decades later (Heaney et al. 2000). Increases in calcium intake in postmenopausal women delay calcium loss from bone, thus lowering the risk of declines in bone mineral density to osteoporotic levels. Calcium intakes of 1,000 to 2,000 mg per day have been shown to increase or slow the decline in bone density and to reduce the risk of osteoporosis (FDA 1994).

Safety Considerations

A number of hypotheses for adverse effects of excess calcium intake have been investigated over the years, including kidney stones (nephrolithiasis) (Johnson et al. 1979), hypercalcemia with renal insufficiency (milk-alkali syndrome) (Junor and Catto 1976; Orwoll 1982), and harmful calcium interactions with other minerals (Spencer et al. 1965; Clarkson et al. 1967; Schiller et al., 1989). The evidence regarding a link to an increased risk of kidney stones with high calcium

intake from foods and supplements is inconsistent, with some studies associating higher calcium intakes with *decreased* risk of kidney stones (Curhan et al. 1993). High dietary calcium levels can influence the bioavailability and absorption of many trace elements—particularly the divalent cations, such as magnesium, manganese, and zinc—but it is unlikely that these effects are commonly severe enough to have clinical impact (Greger 1988). The intestinal interactions have been studied primarily in animals.

Official Reviews

IOM (1997, 2010). The IOM evaluated the various potential adverse effects of excess calcium intake and concluded that kidney stone formation was the only one with appropriate data to support a risk assessment (IOM 1997). The IOM identified the following tolerable upper intake level (UL) values for calcium: 2,500 mg for children up through 8 years of age, 3,000 mg for those ages 9 through 18 years, 2,500 mg for adults ages 19 through 50 years, and 2,000 mg for adults ages 70 years and older. There are some difficulties with these values, however, since the UL is based on a UF that varies from one example to another. The IOM recognized that the data from patients with kidney stones were not likely to be meaningful for normal adults and thus did not utilize the data of Burtis et al. (1994), which might have indicated a LOAEL of 1,685 mg per day.

Expert Group on Vitamins and Minerals (EVM 2003). The UK’s EVM published its findings on calcium in 2003. Concluding that the available data were insufficient to set a safe UL, they instead determined a guidance level of calcium intake at which milk-alkali syndrome, constipation, and bloating would be avoided. The report recognized that few side effects have occurred in clinical trials with 1,600 or 2,000 mg of supplemental calcium (Levine et al. 1997; Hofstad et al. 1998; Bonithon-Kopp et al. 2000). Based on a mean dietary calcium intake of 830 mg per day in the UK, the EVM set the guidance level for supplemental calcium at 1,500 mg per day, stating that such a supplemental level “would not be expected to result in any adverse effect.”

EFSA (2012). EFSA considered a number of human intervention studies in adults. These studies showed a lack of adverse effects associated with daily calcium intakes of 2,500 mg from both diet and supplements. Taken together with the robust database used by the European Commission's Scientific Committee on Food (EC SCF) to establish a UL of 2,500 mg in 2003 (based on a NOAEL of 2,500 mg and a UF of 1), EFSA also proposed a UL of 2,500 mg per day of calcium from all sources for adults.

Recent Concerns

Published results from numerous epidemiological studies and one meta-analysis of select randomized controlled clinical trials have prompted concern about possible associations between calcium use and a small increase in risk of adverse cardiovascular events. Because of significant limitations in design or interpretation, these reports do not provide strong evidence of harmful cardiovascular effects of calcium supplementation.

A subgroup analysis from a large clinical trial—the Women's Health Initiative (WHI)—played an important role in the meta-analysis. A number of limitations in the design and execution of this trial invalidate many generalizations based on it. These limitations include (1) inadequate monitoring and assessment of compliance with the treatment protocol, (2) use of nontrial calcium supplements by the majority of subjects in the placebo and calcium treatment groups, and (3) lack of information on and adjustment for known cardiovascular risk factors. With these limitations, confounding and bias cannot be excluded as explanations for the results (Bolland et al. 2011).

No suggestions of serious adverse effects from calcium supplements or calcium with vitamin D had been reported until Bolland, Reid, and coworkers raised the issue of possible increased risk of adverse cardiovascular events (Bolland et al. 2008; Reid et al. 2008). Although some of the data suggested a hazard ratio for calcium or calcium plus vitamin D as high as 1.43 (43 percent increase in risk), after adjustment for known cardiovascular risk factors, statistical significance was lost (Bolland et al. 2008).

Bolland, Reid, and colleagues followed these research articles with a meta-analysis from other clinical trials (Bolland et al. 2010), as well as the subgroup analysis from the WHI (Bolland et al. 2011). On the basis of this and a follow-up meta-analysis, these researchers concluded that calcium supplementation, with or without vitamin D, modestly increases the risk for myocardial infarction or stroke and recommended that the use of such supplements in older people should be reassessed (Bolland et al. 2011).

However, the conclusions and recommendations of Bolland, Reid, and colleagues, based on their own data and interpretations, have been questioned by a number of experts who have raised concerns and unanswered questions about the methodology employed and the potential for bias and confounding (Letters to the Editor 2008, 2010, 2011; Bockman et al. 2011; Nordin et al. 2011). These concerns remain unanswered.

More recently, Li and colleagues reported that, in a large epidemiological study, higher intakes of total dietary and dairy calcium significantly reduced the risk of myocardial infarction but users of calcium supplements had significantly increased risk (Li et al. 2012).

Given the widespread use of calcium supplements and the potential of harm from inadequate calcium intake, the Council for Responsible Nutrition (CRN) concluded that a thorough examination of the evidence for harm and for benefit from calcium supplementation was warranted. To accomplish this goal, CRN convened a group of academic and industry experts to develop a consensus on the available evidence, with emphasis on five of the Bradford-Hill criteria for causal inference from data: strength, consistency, dose-response, biological plausibility, and results from experimentation.

Heaney and colleagues summarized data not only from the papers by Bolland et al. and Li et al. but also results from other pertinent long-term prospective cohort studies and clinical trials (Heaney et al. 2012). A review and meta-analysis by Wang et al. (2010), funded by the American Heart Association and the National Heart, Lung, and Blood Institute, showed that the relative risk for cardiovascular disease events was 1.14 (95 percent confidence interval, 0.92 to 1.41) in studies involving calcium supplementation without vitamin D. An additional meta-analysis

including clinical trials with both calcium and vitamin D showed a relative risk of 1.04. The authors concluded that vitamin D at moderate to high intakes may reduce cardiovascular disease risk, whereas supplementation with calcium alone seems to have minimal cardiovascular effects.

Although there was no overall indication of a connection between calcium intake and atherosclerotic heart disease or stroke, a few of the cited studies showed a weak but statistically significant positive association of calcium intake and cardiovascular disease, whereas a similar number show the opposite (protective) effects. Because of these mixed results, Heaney and colleagues determined that the findings from available clinical trials and prospective cohort studies indicate that there is no significant effect of calcium supplements on cardiovascular disease (Heaney et al. 2012).

CRN Recommendations

A wide range of clinical and epidemiological studies discussed by the IOM, the EC SCF, the EVM and several published reviews and meta-analyses have shown no adverse effects with calcium intakes of 2,000 mg or less in adults ages 51 years or older. Based on the judgment of the IOM, the calcium UL for persons aged 19 through 50 years should be 2,500 mg, which is the midpoint between the value for individuals ages 51 years and older and the 3,000 mg UL for adolescents. Considering the quite variable calcium intake from foods, dairy products, and fortified foods, CRN agrees with the EVM that a maximum supplement level for adults should be 1,500 mg. Thus, the CRN UL for supplemental for calcium is set at 1,500 mg per day for adults.

Quantitative Summary for Calcium

CRN UL, supplemental intake	1,500 mg/day for most adults
IOM UL, total intake	3,000 mg/day for adolescents; 2,500 mg/day for adults ages 19–50; and 2,000 mg/day for adults ages 50 and older
EFSA UL, total intake	2,500 mg/day
EC supplement maximum	Not determined
EVM, guidance level, supplemental intake	1,500 mg/day

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