Calcium Builds Strong Bones, and More Is Better—Correct? Well, Maybe Not

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Summary
Calcium supplementation has been considered the gold standard therapy for osteoporosis in the general population. It is given in both the placebo and treatment groups of trials evaluating antifracture efficacy of new therapies. Similarly, calcium-based phosphate binders have been considered the gold standard comparator for all new phosphate binders. However, large randomized trials demonstrate conflicting data on the antifracture efficacy of calcium supplementation, particularly in high doses, in patients with osteoporosis without CKD. In addition, recent data suggest an increased risk for cardiovascular events. These new studies raise safety concerns for the general approach with calcium supplementation and binders. This review describes recent data on the adverse effects of calcium supplementation for osteoporosis and how these new data should affect the strategy for phosphate binder use in CKD.


Ninety-nine percent of total body calcium is in bone. Thus, it would make sense that all calcium via supplement or calcium binder that is absorbed from the intestine would preferentially go into bone. This assumption is supported by balance studies that demonstrate positive calcium balance and bone calcium accumulation during linear growth in childhood and adolescence. Through unclear mechanisms, the intestinal absorption of calcium is increased during this growth period, implying some signaling between bone and intestine. After linear growth stops, some mineral still accumulates in bone. More importantly, however, homeostatic mechanisms that maintain a neutral calcium balance are activated. Ultimately, peak bone mass is achieved between ages 25 and 35 years, and for the remainder of adult life, there is a slow gradual decline in bone mineral content; this decline accelerates in the perimenopausal period (1–3). Note that even during pregnancy and lactation, homeostatic mechanisms maintain normal ionized calcium levels. The needs of the growing infant during pregnancy are primarily met by enhanced gastrointestinal absorption; during lactation, the needs are met by increased bone resorption. The addition of oral calcium supplements appear to have no effect on these adaptations, and according to bone density testing there are no long-term sequelae from the bone resorption during lactation (4,5). The mechanisms for this intricate and tightly controlled system are not completely understood but highlight the fact that attempting to override this system by providing more calcium supplementation are not physiologic and not always good for the bones. Put simply, more is not always better.

What data show that calcium supplements should be prescribed for bone health? The rationale for the use of calcium supplements to manage osteoporosis in patients without CKD is based on the following reasoning: First, 70% of bone consists of hydroxyapatite, of which calcium is an integral component. Second, decreases in bone quantity can lead to fractures. Third, increasing calcium intake will increase bone quantity and thus reduce fractures. The latter is also the basis for use of calcium supplements as the “gold standard” in clinical trials. Randomized, controlled trials of anti-resorptive agents (alendronate, risedronate, zoledronic acid, raloxifene, and denosumab), as well as the anabolic agent parathyroid hormone, for treatment of post-menopausal osteoporosis have all reported on the antifracture efficacy of these agents together with calcium supplements (at least 500 mg, with or without vitamin D) compared with the antifracture efficacy of calcium alone or with vitamin D (6–10) to demonstrate superior efficacy of their drug. This approach is similar to the use of calcium-containing phosphate binders as the gold standard to which all new binders are compared (11,12). In both scenarios, however, there are actually few data that calcium supplements or binders have “golden” effects on bone, and concerning data indicate that this approach may not be without risk. In this review, we review the benefit-to-risk ratio for calcium supplements and binders in both osteoporosis and renal osteodystrophy.

Efficacy of Calcium Supplements for Bone Health in the General Population
Overall, studies in the general population have not demonstrated an association between dietary calcium intake and either bone mineral density or fracture rate (13–16). For example, data from a meta-analysis that included four studies of dietary calcium supplements on fracture risk found no association between calcium...
use and risk for hip fracture (pooled relative risk [RR] per additional 300 mg dietary calcium per day, 1.01; 95% confidence interval [CI], 0.96–1.06) (15). A more recent meta-analysis found no association between the risk for hip fracture and milk intake based on data from seven prospective cohort studies (16). Potential explanations for these findings include the following: The intake of calcium supplements may have been suboptimal for fracture prevention; effects of calcium intake should be considered in the context of vitamin D (adequate levels of vitamin D may be a prerequisite for the efficacy of calcium supplements in fracture prevention); and dietary calcium may not reduce the risk for osteoporotic fractures, hip fractures in particular.

Data on the effects of calcium supplementation on bone mineral density and fracture rates in the general population are conflicting. One trial included 3270 women living in long-term care institutions (mean age, 84 years) randomly assigned to placebo or 1200 mg calcium supplement plus vitamin D. In a second trial, 389 men and women older than age 65 living in the community were randomly assigned to placebo or 500 mg calcium plus vitamin D. These studies found that the treatments modestly reduced bone loss and reduced the incidence of vertebral and nonvertebral fractures (17,18). However, larger multicenter trials, such as the Women’s Health Initiative (36,282 patients randomly assigned to 1000 mg calcium with 400 IU vitamin D3 or placebo) and the Randomized Evaluation of Calcium Or vitamin D [RECORD] trial (5292 patients randomly assigned in a 2×2 design to 1000 mg calcium, 800 IU vitamin D3, both, or placebo), have not confirmed these findings (19,20). Thus, findings from large randomized trials are inconsistent.

A meta-analysis of 29 randomized trials reported on the effects of calcium supplements alone or calcium together with vitamin D to prevent fractures and bone loss in men and women older than age 50 years who were followed for an average of 3.5 years (21). In the 17 trials that reported on fracture outcomes, calcium supplements or calcium with vitamin D was associated with a 12% risk reduction in fractures of all types (RR, 0.88; 95% CI, 0.83–0.95; P=0.0004). In the 23 trials that reported bone mineral density as an outcome, treatment was associated with a reduced rate of bone loss: 0.54% (95% CI, 0.35%–0.73%; P<0.001) at the hip and 1.19% (95% CI, 0.76%–1.61%; P<0.001) in the spine. The authors of this meta-analysis performed several subgroup analyses and showed that the fracture risk reduction was significantly greater (24%) in trials with a high adherence rate; in fact, if adherence was poor, fracture risk was not reduced (RR, 0.96; 95% CI, 0.91–1.01). Further, these authors found that the treatment effect was better with calcium supplement dosages of 1200 mg/d or more than with dosages <1200 mg/d (RR, 0.80 versus 0.94; P=0.006). Although the treatment effect was similar whether a person used calcium supplements alone or with vitamin D, the authors found a modest decrease in fracture risk by vitamin D dose. The authors suggest that if vitamin D is used, the dose should be 800 IU.

Other studies have suggested that calcium supplements may even increase the risk for fractures. A study in 2006 demonstrated a significant increase in hip fractures in women randomly assigned to calcium compared with those randomly assigned to placebo (22), but because the number of fractures was small the authors dismissed the finding. Most studies that have directly tested the effect of calcium supplements alone on hip fracture prevention reported no overall effect. However, when the concomitant use of vitamin D was evaluated, hip fracture increased among those randomly assigned to calcium alone and decreased among those assigned to calcium and vitamin D (15,23,24). These findings are clinically relevant because hip fractures account for the majority of morbidity, mortality, and health care costs associated with osteoporosis.

The differences in the outcomes of these meta-analyses of smaller trials compared with those of the larger randomized trials may be explained by differences in doses of calcium supplements, in use of vitamin D, in study duration and follow-up, and in patient age. The effects may be better in older persons and those taking vitamin D. Overall, these data have been interpreted to suggest that calcium may have some benefit for bone health in the general population. Furthermore, the use of calcium supplements was thought to be safe, justifying widespread use. As a result, the use of calcium supplementation to protect against fracture has become widespread in nearly all women older than age 50 years. What also has also become widespread is the notion that if some calcium supplementation is good for the bones, then more must be better. But is this really the case?

**Potential Adverse Effects of Calcium in the General Population**

Early studies with calcium supplements demonstrated modest decreases in systolic and diastolic BP and a reduction in total cholesterol or the HDL-to-LDL ratio (25,26). These potential vascular benefits led to the development of the Auckland Calcium Study. This randomized, controlled trial of 1500 postmenopausal women was designed to assess the effect of calcium supplements on cardiovascular events (death; sudden death; myocardial infarction; angina; other chest pain; stroke; transient ischemic attack; and a composite end point of myocardial infarction, stroke, or sudden death). The study randomly assigned 732 women to calcium supplementation (1000 mg daily in divided doses) and 739 to placebo. Of note, women in both groups were allowed to take dietary calcium, and the estimated dietary intake for both groups was approximately 800 mg. The investigators found that myocardial infarction was more commonly reported in the calcium group (average of 1800 mg of calcium per day) than in the placebo group (average of 800 mg of calcium per day). In total, 45 events occurred in 31 women in the calcium group compared with 19 events in 14 women in the placebo group (P=0.01). The composite end point of myocardial infarction, stroke, or sudden death was also more common in the calcium group (101 events in 69 women versus 54 events in 42 women, respectively; P=0.008). No other statistically significant differences were seen between the groups. The authors concluded that “calcium supplementation in healthy postmenopausal women is associated with upward trends in cardiovascular event rates and that potentially detrimental effect should be balanced against the likely benefits of calcium on bone” (27).
The findings from the Auckland Calcium Study generated much controversy and debate in the medical literature. It also prompted at least three published systematic reviews or meta-analyses, although none of the studies included in the reviews were designed specifically to assess effect of supplements on cardiovascular risk. The first (28) included prospective studies and randomized trials that examined vitamin D supplementation, calcium supplementation, or both, as well as subsequent cardiovascular events. The review included four prospective studies of healthy men and women and reported no differences in the incidence of cardiovascular disease (CVD) with the use of calcium supplementation. In contrast, some evidence suggested that vitamin D supplementation led to a slight but statistically nonsignificant reduction in CVD. The authors of this review concluded that calcium supplementation had minimal cardiovascular effects, whereas vitamin D supplements in moderate to high doses might reduce the risk for CVD (28).

The second publication was a meta-analysis designed to determine whether calcium supplements increase the risk for cardiovascular events; it included 15 trials (29). In 5 of these 15 studies that contributed patient-level data, 143 people allocated to calcium supplements had a myocardial infarction, compared with 111 allocated to placebo (hazard ratio, 1.31; 95% CI, 1.02–1.67; P=0.04). The meta-analysis of trial-level data showed similar results: A total of 296 people had a myocardial infarction (166 allocated to calcium and 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (pooled RR, 1.27; 95% CI, 1.01–1.59; P=0.04). The authors concluded that calcium supplements (without concomitant vitamin D) are associated with an increased risk for myocardial infarction (29).

The third, more recent publication included a reanalysis of the Women’s Health Initiative data set and an update of the meta-analysis discussed above (30). The authors used data from the Women’s Health Initiative Calcium and D study (WHI), a 7-year randomized, placebo-controlled trial of daily calcium supplements (1000 mg) and vitamin D (400 IU) in 36,282 healthy postmenopausal women. It is noteworthy that as a result of the design of the Women’s Health Initiative, 54% of the cohort, or 19,564 women, were using personal calcium supplements at baseline. The authors excluded these patients from the reanalysis and found that among the 16,718 women not taking personal calcium supplement at baseline there was increased risk for myocardial infarction (RR, 1.22; 95% CI, 1.0–1.5) in women randomly assigned to calcium and vitamin D. The updated meta-analysis in this publication reported that calcium supplements, or calcium with vitamin D, increased the risk for myocardial infarction (RR, 1.24; 95% CI, 1.07–1.45) and the risk for the composite end point of myocardial infarction or stroke (RR, 1.15; 95% CI, 1.03–1.27).

It is important to point out that these studies primarily evaluated calcium supplements and that results with dietary calcium may be different. A recent reanalysis of the European Prospective Investigation into Cancer and Nutrition study (EPIC) found a decreased risk for myocardial infarction with higher total dietary calcium and dairy calcium compared with the lowest quartile of intake. However, users of calcium supplements, compared with those who did not take calcium supplements, had an increased risk for myocardial infarction (hazard ratio, 1.86; 95% CI, 1.17–2.96) (31). Thus, it may be that only supplemental calcium pills increase the risk for cardiovascular events. This risk is not trivial. According to the patient-level data from the most updated meta-analyses using the WHI study (30), treating 1,000 people with calcium or calcium plus vitamin D for 5 years causes four myocardial infarctions, four strokes, and two deaths and prevents three fractures (30). These authors therefore concluded that a reassessment of the role of calcium supplements in the management of osteoporosis is needed, given the potential for these agents to cause harm.

It is important to note that some clinical practice guidelines have been modified on the basis of this new literature suggesting potential risk. For example, in its recently published evidence-based guidelines, Osteoporosis Canada recommended a total intake of calcium (from diet and supplements) of 1200 mg per day, a decrease from the previous recommendation of 1500 mg in supplements (32). The American Society for Bone and Mineral Research issued a statement regarding the potential risks of calcium supplements and suggested, among other points, that “the beneficial effects of calcium are found with relatively low doses. More is not necessarily better. Individuals should discuss the amount of their calcium intake with their healthcare provider” (33). The Institute of Medicine now recommends a daily dietary reference allowance of calcium of 1000–1200 mg per day in the form of diet and supplements (34,35). Finally, the draft United States Preventive Services Task Force statement, pending public comment (http://www.uspreventiveservicestaskforce.org/draftrec3.htm), currently states “the current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men.” Thus, these authorities acknowledge that although some calcium supplements may be beneficial for bone health, too much calcium may be harmful.

Efficacy of Calcium Binders for Bone Health in the CKD Population

In CKD, bones are not normal. Histologic analyses of bone biopsy specimens show abnormal bone remodeling in 95% of patients (reviewed in reference 36). Patients undergoing dialysis have a very high rate of hip fractures, exceeding that of the general population (2-fold to >100-fold greater, depending on age) (37,38). In addition, the mortality rate after hip fracture is double that in the general population (39). The prevalence of fractures in patients with CKD stage 3–4 is higher than that in persons without CKD (40,41). Most studies also demonstrate an overall decline in calcium content of bone by dual-energy x-ray absorptiometry (DXA) with progression of CKD (42–45). DXA is as predictive of fractures in CKD patients with estimated GFR < 60 ml/min per 1.73 m² as it is in persons without CKD (46). Finally, studies that look at bone architecture by micro-computed tomography; high-resolution peripheral quantitative computed tomography; or other,
more novel techniques also have found abnormal architecture to support observations in animal models of CKD (47,48). Thus, there is increased risk for fracture with CKD, and, as is seen in the general population, the risk for fracture is increased with low peak bone mass, low bone mass or volume (or calcium content) shown on DXA or CT, and abnormal bone architecture. Patients with CKD unfortunately suffer from major abnormalities in the latter two components, and thus it is no surprise that fractures are more prevalent. Therefore, if we knew that calcium in the form of supplements or binders helped bones, it would be an important therapy. Unfortunately, we have no evidence to demonstrate efficacy.

In the 1970s, studies using total-body isotope methods demonstrated positive calcium balance in patients with advanced CKD despite a relative decrease in intestinal calcium absorption, thought to be secondary to impaired conversion of vitamin D to 1,25(OH)2-vitamin D (49,50). In 1973, Jack Coburn commented (51) that the contribution of reduced Ca absorption as a pathogenic mechanism leading to deranged Ca homeostasis and osteodystrophy in uremia is uncertain. Since the total amount of calcium lost in urine is generally low in patients with chronic renal failure, it has been suggested that the reduction in (intestinal) calcium absorption merely represents a compensatory adjustment preventing excess accumulation of calcium in the body. However, the absorption remains low despite low dietary calcium content and despite the presence of skeletal demineralization, osteomalacia and reduction in total body calcium.

Thus, the findings of reduced intestinal absorption of calcium and abnormal bone led to the thought that increases in calcium intake would improve bone. However, the cause of abnormal bone in CKD is not calcium deficiency but rather is far more complex (52,53). Furthermore, a recent formal balance study demonstrated that patients with CKD stage 4 who were not receiving calcitriol or vitamin D analogues had a neutral calcium balance at 800 mg calcium intake but a significant positive calcium balance at 2000 mg (diet plus supplement) (54). This net balance is greater in patients with CKD than in healthy controls.

There are no randomized clinical trials with calcium binders or any other agent in CKD patients that use fracture as a primary end point. Secondary analyses of postmenopausal patients with osteoporosis and undiagnosed CKD in randomized, controlled trials of antiresorptive or anabolic agents show efficacy (55–58) compared with placebo (both the treatment and the placebo groups received calcium supplementation). Calcium-based phosphate binders (at doses generally greater than those used in placebo groups of osteoporosis trials) compared with non-calcium-containing phosphate binders did not show improvement in bone histology; some studies demonstrated the development of adynamic bone disease with calcium-based binders (12,59–63; further reviewed in 36). No studies have shown that calcium supplement or binder intake improves bone mineral density. Thus, no data indicate that calcium is good for bones in patients with CKD.

Potential Adverse Effects of Calcium Supplements and Binders in CKD

Similar to the data in the general population, some data from randomized trials suggest that calcium intake in the form of calcium-based phosphate binders may lead to adverse cardiovascular manifestations. In the Treat to Goal (TTG [64]) and the Renagel in New Dialysis (RIND [65]) studies, which included prevalent and incident dialysis patients, respectively, coronary artery calcification progressively increased with the use of calcium-containing phosphate binders. This increase was ameliorated with the use of non–calcium-containing phosphate binders. In a study of patients with CKD who were not undergoing dialysis (66), a similar difference was observed.

In contrast, in another randomized trial in hemodialysis patients, the Calcium Acetate Renagel Evaluation-2 (CARE-2) study (67) did not find a difference between calcium-based binders and sevelamer. However, in both groups, calcification of coronary arteries increased in both treatment groups in this study (67). Thus, the difference between the CARE-2 study and the TTG and RIND studies was not that the calcium binder had no harm; rather, it was that sevelamer showed no benefit in CARE-2. Finally, in the Phosphate Binder Impact on Bone Remodeling and Coronary Calcification (BRIC) study, calcium binders were more likely to lead to low-turnover disease seen on bone biopsy than was sevelamer, and low-turnover bone disease was more likely to be associated with increased coronary artery calcification (60,68).

Thus, although the benefit of sevelamer over calcium-based binders in slowing coronary artery calcification is controversial, in each study, the patients who received calcium as a phosphate binder had increased coronary artery calcification. Furthermore, there is a reciprocal relationship between the amount of calcium in bone and the amount of calcium in coronary arteries. This is best exemplified in the TTG study, in which a secondary analyses of bone mineral calcium content by computed tomography demonstrated that patients in the calcium binder group had reduced calcification of the lumbar vertebrae and increase coronary artery calcification (69). Thus, in patients with CKD there is no evidence of benefit of calcium for bones in CKD and some evidence of harm.

Conclusions

Calcium supplements or binders do not appear to improve bone in CKD. Multiple studies show that calcium supplements and binders, particularly in higher doses, might be associated with harm. So why was it assumed that calcium might be good for bones in CKD? Similar to the treatment approach for many medical problems in patients with CKD, data were extrapolated from the general population under the assumption that something good for osteoporosis would be good for renal osteodystrophy. The thought was that calcium could be used as a phosphate binder and either help the bones or not cause harm. However, this rationale has at least two limitations. First, calcium supplementation has, at best, only modest effects at increasing bone quantity and decreasing fractures in men and women with osteoporosis without advanced CKD, and more calcium is not better for these outcomes.
Indeed, recent data suggest that excess calcium supplementation may even be harmful in the general population, and health agencies have similarly questioned the evidence supporting widespread and indiscriminate use of calcium supplements for fracture prevention. Second, the pathophysiology of the homeostatic pathways for bone disease and mineral metabolism differs. Thus, we may need to rethink whether calcium supplements and binders should indeed be the gold standard for bone health in CKD.

Disclosures
S.A.J. is a consultant for Genzyme, Novartis, Shire, and Warner Chilcott and is on the speakers bureaus with Amgen, Genzyme, Novartis, and Warner Chilcott. S.M.M. serves as a consultant for and receives honoraria from Genzyme, Amgen, KAI, Novartis, and Litholink. She has received grant support from the National Institutes of Health, Department of Veterans Affairs, Amgen, Genzyme, Novartis, and Shire.

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