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Calcium Use in the Management of Osteoporosis: Continuing Questions and Controversies

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Abstract Calcium is a vital element in the health and maintenance of growing and mature bone. The amount of calcium recommended for ingestion varies by age, and these requirements can be met by dietary sources or calcium supplementation. This article reviews the role of calcium in the body and the benefits and risks to calcium supplementation. The effects of calcium on fracture risk reduction, bone density, and bone turnover markers as well as the conflicting data on cardiovascular events and increased risk of nephrolithiasis associated with supplementation are discussed.

Keywords Calcium · Calcium supplement · Osteoporosis · Nephrolithiasis · Osteopenia · Fracture · Dietary vs supplement

Introduction

Calcium is an essential alkaline earth metal first discovered in 1808. Over a hundred years later, a supplement was manufactured for the treatment of indigestion. Even more recently, calcium supplementation has been identified as an important element in the management of osteoporosis. Osteoporosis is a disease affecting over 5 million postmenopausal women in the United States today [1]. There is current controversy over whether calcium supplementation should be recommended in the management of osteoporosis after the United States Preventative Task Force (USPTF) released recommendations in February 2013. The task force concluded there was insufficient evidence regarding the benefits or risks of calcium supplementation in the primary prevention of fractures. The USPTF also concluded that there was an increased risk of kidney stones but further stated that "the magnitude of this harm was small" [2•]. This has caused some concern among patients and clinicians and as a result, a decrease in supplement use has been seen [3].

This article will review the role of calcium in bone health, the data on fracture risk, bone mineral density (BMD), and bone turnover markers as well as specific concerns about cardiovascular events and kidney stones.

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Calcium in the Body

Nutritional Requirements

Calcium is a vital element, essential for many physiological processes and pathways in the human body. The amount of calcium a person needs to consume daily depends on age. For young premenopausal women, 1000 mg of calcium daily is recommended, which increases to 1200 mg daily over the age of 50 [4, 5]. In men, an increased requirement of 1200 mg daily is not recommended until 71 years of age. Though there are many elements involved in the production of a healthy bone matrix, calcium, and vitamin D are important because they tend to be the most commonly deficient in the US population. Replacement of these two nutrients is recommended at the first signs of decreased bone density, and supplementation can be suggested if dietary intake is found to be inadequate.

Calcium Handling by the Body

The majority (99 %) of calcium found in the body is in the skeletal system or teeth with a small amount of free (not bound to albumin) ionized calcium found in the blood. Ionized calcium is the form that is essential for physiological

processes and required in the conduction pathways in the cardiovascular system. Calcium balance in the body is tightly regulated. We absorb calcium from food and supplements in our intestines via active and passive processes. If there is excessive intake, urinary calcium excretion increases. In the setting of deficiency, parathyroid hormone secretion stimulates osteoclastic resorption to release calcium from the bones, and also decreases urinary calcium excretion. Chronic deficiency of calcium will almost always result in bone loss.

Dietary vs Supplemental Calcium: Is it Really the Same Thing?

Absorption of calcium can vary in healthy individuals by 15 %–58 % [6•]. Estrogen deficiency, vitamin D deficiency, decreased gastric acid production, and malabsorptive disorders have all been shown to be decrease absorption of calcium. In a review article by Booth and Camacho in 2013, the efficacy of absorption and benefits of dietary vs supplemental calcium intake favored the bioavailability of dietary sources. Only smaller studies were reviewed as a large study directly comparing dietary calcium to supplemental calcium is lacking. Another review concurred with the findings that the best way for the general population to get adequate calcium is from diet [7]. However, for a postmenopausal woman who requires 1200 mg of calcium diet, consuming four servings or more of dairy is often difficult, and supplementation may be necessary.

Supplementation Benefits

Fracture Risk Reduction and Improvement in BMD

Osteoporosis is a life threatening disease when you account for the 20 % mortality rate in an elderly person with a hip fracture. This is comparable with the mortality rate for the diagnosis of breast cancer (11 %–30 %) [8, 9]. Calcium supplementation has been shown to have a positive effect on BMD in several studies, with some reduction in hip fracture risk [8, 10–16]. In Cumming's and Nevitt's article there was a reduced fracture incidence in the group on calcium supplementation; however, dietary intake was not accounted for in this study [10]. A few studies did not show any benefit of supplementation fracture incidence, although these studies could not account for confounding variables like compliance or dietary intake [17, 18]. However, all nonrandomized studies did show a trend of reduced vertebral fracture incidence for individuals taking a calcium supplement, which ranged 16 %–38 % [15, 16, 19–24].

In a study by Riggs et al, there was also an increase in bone density of 0.3 %–2.0 % in women receiving calcium supplementation vs placebo [25]. One of the biggest studies to date is the Women's Health Initiative (WHI), a large-scale multicenter study costing over 600 million dollars that included both clinical trials and observational design. The WHI study investigated major health concerns in postmenopausal women, among them the effects of calcium and vitamin D supplementation. In this study postmenopausal women age 50–79 years old were randomized to either receive calcium and vitamin D (500 mg calcium tablet and 200 IU vitamin D) supplementation or placebo. Both groups were allowed up to 1000 mg of daily calcium use as well as 600 IU vitamin D. Therefore, women in the intervention group could be taking 500 mg–1500 mg daily calcium while women in the control group could be consuming 0–1000 mg. Nevertheless, in the intervention group, there was a significant improvement in bone density in the hip and nonsignificant 12 % reduction in hip fracture risk [26].

The effect of calcium in certain at risk populations has been studied. Sambrook et al looked at preventing glucocorticoid-induced osteoporosis with calcium and/or calcitriol supplementation, or calcitonin [27]. The study found that the combination of calcitriol and calcium reduced bone loss at the lumbar spine, while calcium alone did not and there was no difference in fracture data.

The USPTF recognizes in their statement that the evidence is only insufficient for noninstitutionalized postmenopausal women. The benefits from calcium supplementation on fracture risk are most consistently beneficial for those who are predisposed to low dietary intake and some chronic comorbidities [12, 27].

An important aspect to remember is the risk of rare but severe hypocalcemia with the use of antiresorptive agents. This side effect has been reported with multiple agents including pamidronate, alendronate, denosumab and zoledronic acid [28–31]. Bisphosphonate-induced hypocalcemia is most likely to occur in subjects with unrecognized vitamin D deficiency, low dietary calcium intake, impaired renal function, or hypoparathyroidism [28]. Hypocalcemia can be avoided most of the time by correction of vitamin D deficiency and increasing calcium stores prior to treatment with antiresorptive medication.

Compliance with Calcium Supplementation and Fracture Risk Outcomes

In recommending calcium supplementation vs increased dietary intake, compliance needs to be considered. Some patients have dietary preferences or restrictions that may prevent increased dairy intake, whereas side effects of calcium pills, such as constipation or gassiness, can be a barrier to supplementation. Out of 14 randomized clinical trials, there was significant reduction in hip and nonvertebral fractures in eight of the studies (risk reduction ranged 22 %–52 %) [32, 33•]. Mixed or nonsignificant outcomes were seen more often in

community settings, which have higher rates of noncompliance compared with institutionalized patients.

The 5-year follow-up to the WHI study allowed personal calcium and vitamin D intake (up to 1000 mg/day and 600 IU/day, respectively), after the initial WHI 7-year intervention trial. The postintervention follow-up showed that women who were adherent to supplementation had a 23 % reduction in hip fractures [34••].

Decrease in Bone Turnover Markers

With adequate intake of calcium, there has also been an observed reduction in bone turnover markers and parathyroid hormone levels [33•, 35]. In the study by Aloia, the decrease in bone turnover markers was significant in subjects taking calcium alone and calcium plus vitamin D. Parathyroid hormone decreased significantly, though this was evident only in the vitamin D treated groups. In this study subjects received 900 mg daily calcium intake. This supports the Institute of Medicine recommendations for at least 1000 mg to 1200 mg daily calcium intake for bone health.

The persistence of effect of calcium supplementation on bone turnover markers is not well known. There have been studies looking at the long term effects of supplementation on c-telopeptide (CTX), bone alkaline phosphatase (BAP), and parathyroid hormone (PTH) but the results generally showed that supplementation 1450–1600 mg/day of calcium and vitamin D reduced levels in the first year. However, there was a trend back to baseline levels within 3–4 years [35, 36].

Supplementation Risks

Hypercalciuria/Renal Calculi

In the WHI study the hazard ratio was 1.17 for increased chance of postmenopausal women taking calcium supplementation to have renal calculi [26]. There has also been a reported 17 % increased risk of kidney stone formation with calcium and vitamin D supplementation [37, 38]. Baseline urinary calcium measurements were not reported in the WHI study, so there is the possibility that those who developed kidney stones had idiopathic hypercalciuria. More recent studies have reported a decreased risk of only 1.9 % of asymptomatic lithiasis [39]. The reason for the decrease is not well known, but perhaps increasing use of calcium citrate may be playing a role. Increasing fluid intake to over two liters a day can help with avoid stone formation [38].

The recommendation to reduce dietary calcium intake has been reconsidered as well as given the ineffectiveness of a low calcium diet in preventing kidney stones. Calcium ions in the kidney will activate inhibitors against the crystallization of calcium oxalate. When calcium is low in the diet, and, therefore, insufficient concentrations in the gut where oxalate is typically bound, urinary oxalate increases. Recent studies comparing low with high calcium intake showed a reduction in kidney stone formation by at least 34 % in the highest dietary intake group [40, 41]. Supplementation was not evaluated in these two epidemiologic studies, but an analysis looking at calcium citrate vs potassium citrate and placebo there was no increased risk of stone formation [42]. The calcium supplement was found to increase urinary calcium and citrate but decrease urinary phosphate and oxalate.

Cardiovascular Events

In the past, calcium supplementation was thought to have some benefit on cardiovascular risk factors. Recently though, there have been conflicting reports of increased risk of cardiovascular events associated with calcium supplement use. In a meta-analysis by Bolland et al 11 randomized controlled studies were analyzed to look at the incidence of cardiovascular events. The results showed a 30 % increased incidence of myocardial infarction in subjects taking calcium supplements [43]. There was a nonsignificant increase in the incidence of stroke and overall mortality. The study populations had patients taking anywhere from 406 mg to 1240 mg per day of dietary calcium. No vitamin D supplementation was included in the meta-analysis. Presupplement cardiovascular risk factors including diabetes, smoking, hypertension, ischemic heart disease, and hyperlipidemia were found in a minority of subjects and may have affected the results.

Table 1 [20, 24, 43–50] references recent articles that have examined the relationship between calcium and CVD. The two big meta-analysis included in the studies by Bolland [43] and Rautienen [44] were conflicting over the significance of calcium supplementation and CVD risks. Looking at the patient population and study design, the most recent study by Rautianinen had a longer duration of follow-up, the sample size was over 100 times larger and, given the prospective study design, had the ability to account for confounding factors throughout the study period.

On the contrary, other randomized studies have found no significant risk of cardiovascular events on calcium supplementation [51, 52]. These studies included populations that were larger with similar or longer follow-up than the Bolland study. In addition, other prospective studies looking at dietary calcium intake in the US showed a decreased incidence in cardiovascular mortality for those with high calcium intake [53–56].

More recently, there have been two large scale studies that have shown safety of calcium supplementation related to cardiovascular disease [45, 50]. These studies were still not the ideal long-term randomized control trial but were focused on CVD as a primary endpoint. The new studies highlight the

Table 1 Summary of articles reviewing calcium supplementation and CVD risks. I. One study that showed decreased incidence of CVD in subjects taking calcium supplement vs placebo. II. Three studies that found in increased relative risk of CVD in supplement users vs nonusers. III. Five studies that found no significant CVD risk with supplement use

Study reference	Study design	Population	Subjects	Calcium supplementation type	Follow-up (mean)	Primary outcome CVD?	Findings
I. Calcium supplementation and CVD benefit							
Paik 2014 [45]	Prospective cohort study	74,245 women participating in Nurse's Health Study	Community-dwelling	5 groups: no supplement, 1–100 mg/d, 101–500 mg/d, 501–1000 mg/d, and >1000 mg/d	24 y	Yes	RR of CHD was 0.56 (95 % CI: 0.49, 0.64; *P* for trend <0.001) for women taking >1000 mg/d of calcium supplements compared with none.
Downing 2013 [50]	MTA – OBs and RCTs	13 OBs (n=n/a) and 11 RCTs (n=~12,000)	Varied	Varied amongst studies: oral calcium supplement vs placebo or vs dietary intake.	Varied	No	CV risks vary, was noted to be 30 % greater risk in RCTs but nonsignificant for mortality or CVA; overall the benefits of fracture reduction outweigh the risk.
Summary	2	82,245					
II. Calcium supplementation and CVD risk							
Bolland et al. 2008 [46]	RCT	1471 postmenopausal women in New Zealand, calcium (*n*=732) vs placebo (*n*=739)	Community- dwelling, healthy Mean age- 74 y	1 gm elemental calcium daily (citracal) vs placebo	5 y	Yes-MI, CVA, death.	RR 1.66 (CI: 95 % 1.15–2.40), *P*=0.0075
Bolland 2010 [43]	MTA of RCTs	15 studies, 4 excluded (no data on CVD) for 11 total calcium (*n*=5613) vs placebo (*n*=5386)	Variable Mean age 74 y	Varied, 406–1240 mg/dl in supplement, type was variable.	4 y	No-MI, CVA, death as secondary end point. [a]	Only significant for MI: relative risk 1.27, 95 % (CI: 1.01–1.59), *P*=0.038 but not stroke, (*P*=0.11) the composite end Point (*P*=0.57), or death (*P*=0.18)
Xiao 2013 [47]	Prospective	388 229 men and women divided into quintiles by gender and dietary (high) vs dietary (low) and supplement users and nonusers	Community dwelling Mean 61–62 y	Men: 289 mg/d Women: 554 mg/d	12 y	Yes	RR 1.20 (95 % CI: 1.05–1.36) increased risk in supplement user in men but not women.
Total number (mean)	3	400,699	(69.8 y)		7		
III. Calcium supplementation and no benefit or risk on CVD							
Rautianinen 2013 [44]	MTA of Prospective Studies	Varied, 7 RCT studies looking at CVD and supplementation. *n*=709,466	Varied; dietary and supplemental intake >17–79 y	Varied, focused on amount of daily intake, range <500–>1599 mg/d	8.2 y	No-MI, CVA, and death as secondary endpoint.[a]	No effect, need RCT designed with CVD as endpoint.
Van Hemelrijck 2013 [48]	Cross-sectional study	Men and Women in NHANES III (*n*=18,714)	Noninstitutionalized, mean age 68.5 y	Varied, used questionnaire to ascertain dosage 0–2000 mg/d	18 y	Yes	No association between dietary intake or supplement calcium; HR 0.84 (0.67–1.04).
Baron 1999 [49]	RCT	672 men and 258 women,	Hospitalized, mean age 60 y	Oral calcium carbonate 0-1200 mg/d	4 y	No	CV event rate 10 % in supplement group and 11 % in placebo group.
Prince 2006 [20]	RCT	1460 postmenopausal women,	Random, chosen from Western Australia electoral roll, mean age 75 y	Oral calcium carbonate 0–1200 mg/d	5 y	No	No significant difference, RR of 1.12 (95 % CI: 0.77–1.64) was observed for the diagnosis of CHD.
Reid 2006 [24]	RCT	323 men, mean age 55–57 y	Community dwelling, mean age 74 y	Oral calcium supplement 600 mg and 1200 mg vs placebo	2 y	No	Nonsignificant difference between CVD events, *P*=0.24.
Total number (mean)	5	730,893	Range >17–79 (69.4)		(7.44)		

CVD cardiovascular disease, *MTA* meta-analysis, *OBs* observational studies, *RCT* randomized controlled trial

[a] Primary endpoint was not CVD for individual studies analyzed in meta-analysis

limitations seen in Bolland's studies including use of published and unpublished data, difference in baseline characteristics between calcium supplement users and nonusers, compliance was questionable, and the number of CVD events was small. A re-analysis of the WHI study done by Prentice in 2013 showed an insignificant association with calcium supplementation and CVD with focus on confounding variables and adherence of users [19].

Thus far, no causal relationship has been established for calcium supplementation and CVD events. The results of the Bolland's study appear to be in the minority of these studies that have looked at cardiovascular events.

Societies' Recommendations

Two of the leading medical societies, the American Association of Clinical Endocrinologist (AACE) and the National Osteoporosis Foundation (NOF), still recommend calcium and vitamin D intake for treatment and prevention of osteoporosis [57, 58]. The American Society for Bone and Mineral Research (ASBMR) also supports the continued use of calcium and vitamin D, emphasizing the importance to bone health overall. The ASBMR follows the 2010 Institute of Medicine's (IOM) findings in support of continued calcium use [59]. All societies agree that if individuals are able to obtain adequate amounts of calcium from their diet, then supplementation is not required.

Conclusions

Calcium is a vital element for the synthesis and formation of bone. The dietary requirements for calcium increase in older age due to multiple factors. Osteoporosis is condition that occurs most commonly in postmenopausal women and there is plenty of evidence that low dietary calcium is detrimental to bone health. The risks associated with supplementation are less convincing in the case of renal stones and unclear in the case of cardiovascular events. Physicians should be aware of patients at risk for low dietary intake as well as the risks in treatment of osteoporosis in the setting of calcium deficiency. Education of patients on the benefits and risks of attaining calcium goals may improve compliance.

Compliance with Ethics Guidelines

Conflict of Interest C. Wilczynski and P. Camacho declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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