Journal of Gerontology: MEDICAL SCIENCES
1999, Vol. 54A, No. 6, M275–M280

Efficacy of Calcium Supplements on Bone Mass in Postmenopausal Women

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THE consistent loss of bone with age is due to inadequate calcium intake, inadequate calcium absorption or excessive excretory loss, or a combination of these problems. The Institute of Medicine recommends that postmenopausal women should ingest 1,200 mg of calcium daily (1). However, the usual daily intake of calcium for 50–70-year-old American women is about 600 mg/day (2). Fifty-five percent of these estrogen-deprived women have insufficient absorption to maintain calcium balance at an intake equal to 800 mg/day (3). Nearly one fourth would still be in negative balance at an intake of 1,500 mg/day (3). In spite of the poor absorption and bioavailability of calcium in postmenopausal women, taking calcium supplements seems to be the most convenient, easy, safe, and inexpensive way to achieve the requirement and to help prevent or treat osteoporosis. Calcium supplements are particularly important for women who do not consume a sufficient quantity of dairy products or calcium-rich foods to meet their daily calcium needs.

This review will summarize the recent clinical studies of the effects of calcium supplements on bone mass in postmenopausal women, discuss the factors that may influence the effectiveness of calcium supplements in preventing bone loss, and report the safety of calcium supplements.

Clinical Studies of the Effects of Calcium Supplements on Bone Mass

Although calcium supplementation is being widely studied in the prevention and treatment of postmenopausal osteoporosis, the results are inconsistent. Most studies fail to find a significant effect of calcium intake in preventing bone loss in early postmenopausal women. For example, Ettinger and colleagues (4) found that there was no relationship between bone loss and the level of calcium intake, even across a broad range of 300 to 3,000 mg daily, during 3 years of follow-up of women just beyond menopause. Similar negative results were obtained in a prospective, randomized 2-year study by Riis and coworkers (5). Giving 2,000 mg of supplemental calcium to estrogen-deficient women had no effect on bone loss in the spine or distal radius. Several other studies also demonstrated that high calcium intake is not beneficial in the early postmenopausal years (6–10); in fact, one study even found that the rate of cortical bone loss seemed to be inversely related to calcium intake in 154 perimenopausal women whose daily calcium intake ranged from 564 to 2,580 mg (11). However, there are two studies demonstrating that calcium supplementation is able to slow the rate of bone loss in perimenopausal women (12,13). During a 2-year period, calcium reduced the rate of spinal mineral loss: women given 2000 mg calcium lost 0.7% of bone mass and women given 1,000 mg lost 1.4%, whereas women without calcium supplements lost 3.5% of bone mass (12). A modest cumulative benefit of calcium supplementation was also seen at the radius in a controlled calcium trial in early menopausal women (13).

There may be a physiological basis for the reduced efficacy of calcium supplements observed among women in their early postmenopausal years compared with older women. In women who had undergone menopause 5 or fewer years earlier, bone loss was rapid and was not affected by supplementation with calcium (13). The very high bone resorption immediately after menopause might indirectly inhibit intestinal absorption of calcium, making it difficult or impossible for supplements to gain access to the body. Following the estrogen-dependent phase of increased bone resorption, intestinal absorption of calcium is less impeded and supplemental calcium can be beneficial.

Most studies show that enhancing calcium intake may benefit late postmenopausal (6 or more years after menopause) women in reducing the rate of bone loss (13–16). In a 3-year study of nursing home residents whose mean age was 81, Smith and colleagues (15) reported that mean radial bone mineral content increased 1.6% in women given 750 mg calcium daily, compared with a mean 3.3% loss of radial bone mineral content in women not given supplemental calcium. In a 2-year study, increasing calcium intake from less than 400 to 800 mg/day in healthy older postmenopausal women prevented bone loss at the femoral neck, radius, and spine (13). Reid and coworkers (17) also showed a sustained reduction in the rate of loss of total body bone mineral density (BMD) in a calcium-supplemented (1,000 mg/day) group of postmenopausal women throughout a 4-year study period. In that study, the benefit from calcium supplements tended to be greater in the first year in the lumbar spine and proximal femur. At most sites, calcium supplementation produced an increase in BMD of about 0.25% per year. With continued use over 30 years of postmenopausal life, a cumulative benefit of 7.5% might be expected and, together with the larger gain in BMD during the first year of supplementation, would result in an approximately 10% advantage to calcium users. Such an increase in BMD would predict a reduction in fracture risk by 50%.

A number of studies have documented a beneficial effect of calcium on bone loss from appendicular cortical sites (5,18), the spine (12,19), and the hip (19,20). A recent study from Dawson-Hughes (21) demonstrated that calcium supplementation is more effective on cortical than trabecular bone in postmenopausal women, and in women with the lowest dietary calcium intake. It seems that enhancing calcium intake may benefit late postmenopausal women with low calcium intake. Lau and colleagues (22) also reported that calcium supplemen-

tation (800 mg/day) was effective in reducing bone loss at the hip in elderly Chinese women (aged 62–92 years) with a calcium intake of less than 300 mg/day.

Despite those encouraging findings, it is important to point out that neither Riggs (23) nor Anderson (24) and colleagues found that habitually higher calcium intake (obtained by diet history) was associated with lower rates of bone loss in older women. The discrepancies between observational studies of the efficacy of calcium supplements and randomized clinical trials may be due to inaccuracies in estimating dietary calcium intake (25).

Factors Affecting the Efficacy of Calcium Supplements

Because calcium supplementation is not always effective in preventing bone loss in elderly women, attention must be paid to improving the efficacy of this approach. The following factors affect the efficacy of calcium supplementation:

Age.—Sufficient data are available to indicate that calcium absorption efficiency declines in the later years. Absorption efficiency decreases with age after 40 years at a rate of about 0.21% per year as determined longitudinally in 189 middle-aged women (26). An additional decrease in calcium absorption of 2.2% accompanies the menopause. For women, the combined effect of age and menopause leads to a 20% to 25% decrease in absorption efficiency from age 40 to 60 (26). This finding is consistent with other studies (27,28) indicating a decline in absorptive performance with age. Mechanisms responsible for decreased calcium absorption with aging are multifactorial. It may be related to increasing intestinal vitamin D receptor resistance to the action of $1,25(OH)_2D_3$ (29) and also a reduced $1,25(OH)_2D_3$ production (30).

Baseline dietary calcium intake.—Calcium supplements proved most effective in studies in which baseline calcium intake was low. Late postmenopausal women with very low calcium intakes generally gain more bone mass from calcium supplementation than do women with higher usual calcium intakes (13,31). It has been suggested that the relationship between calcium intake and bone mass displays a threshold effect, so that beyond a certain intake additional calcium has no effect (32).

Vitamin D.—Vitamin D is the most important factor in calcium absorption. The 1,25-dihydroxyvitamin D_3 level decreases with age, due to decline in kidney function (33). There is also a decline in synthesis of vitamin D in the skin due to reduced exposure to the sun. Moreover, MacLaughlin and Holick (34) showed that the capacity of the skin to produce vitamin D_3 was decreased by more than twofold with aging. Nevertheless, short-term sunlight exposure might still benefit the synthesization of vitamin D in elderly people. Vitamin D deficiency causes malabsorption of calcium from the intestine. Therefore, taking calcium supplements together with vitamin D could improve the efficacy of calcium in preventing bone loss. Calcium plus vitamin D has been shown to reduce the risk of hip fracture in frail elderly women (10) and to reduce nonvertebral fractures up to 40% (35) and the risk of hip fracture (36) over an 18-month period. The most recent study by Dawson-Hughes and colleagues (37) also showed that dietary supplementation with calcium (500 mg/d) and vitamin D (700 IU/d) moderately reduced bone loss measured at the femoral neck, spine, and total body over a 3-year study period and reduced the incidence of nonvertebral fractures in men and women 65 years of age or older. However, none of these studies determined whether it was the calcium supplements, the vitamin D, or their combination that contributed to these therapeutic results. Similar studies using a smaller dose of vitamin D alone showed no effect on hip fracture incidence despite having a small positive effect on bone density (38,39). This suggests that vitamin D alone does not account for the whole therapeutic effect of combined calcium–vitamin D regimens. In general, it is prudent to increase intake of calcium and vitamin D in most postmenopausal women, calcium to at least 1,000 mg and preferably to 1,500 mg/day, and vitamin D to 400 to 800 IU/day.

Estrogen.—Estrogen promotes the intestinal absorption of calcium and suppresses bone resorption. One year of estrogen treatment in postmenopausal women increased both calcium absorption and bone mineral content (40). The usual dosage of conjugated equine estrogen (Premarin) is 0.625 mg/day. Estrogen in combination with 1,500 mg/day calcium was effective in increasing vertebral bone density (41). Several studies indicated that calcium supplementation plus estrogen regimen is more effective than taking calcium or estrogen alone in increasing bone mass (20,42,43). This benefit appears to be more pronounced in cortical than in trabecular bone, and may therefore have a greater effect on the femoral neck than the lumbar spine (42). In a single study, addition of a low dose of Premarin (0.3 mg/day) to calcium supplements completely prevented spinal bone loss over 2 years (44).

Exercise.—Limited data from randomized controlled studies are available to compare the efficacy of calcium supplementation or exercise alone with a combination of calcium supplements and exercise in postmenopausal women. In a 2-year randomized placebo-controlled study, Prince and coworkers (45) showed that the calcium and exercise group had less bone loss at femoral neck site when compared with calcium supplementation alone (+0.28% and −0.18%/year, respectively) in postmenopausal women. Exercise alone had no effect on bone loss at any site in postmenopausal Chinese women in a 10-month randomized study (22). However, exercise plus dietary calcium supplements (800 mg/day) significantly increased BMD at the femoral neck, but not at the spine (22). Bone loss at the distal and mid-forearm of postmenopausal women was also lower in the exercise–calcium group in a 2-year double-blinded study (46).

Interaction of calcium with fiber.—Increased fiber consumption decreases absorption of calcium, magnesium, zinc, and phosphorus in humans; negative balances occur in each of these elements due to increased fecal excretion (47). The mechanism by which diets high in fiber decrease intestinal calcium absorption is unknown. Calcium may bind directly to uronic acid components of fiber and to phytic acid, a compound commonly found in high-fiber foods (48–50). These calcium–fiber and calcium–phytate complexes reduce the bioavailability of calcium for absorption by the small intestine. Absorption of calcium also occurs in the colon, and the fraction of total calcium absorbed in the colon is increased in subjects with reduced small-intestinal calcium absorption (51). Colonic absorption may be especially important when the diet is high in fiber because bacterial action in the colon breaks down calcium–fiber complexes and releases calcium for absorption (48,52,53).

Interaction of calcium with lactose.—Several groups have reported that lactose, in doses of 39 g to 50 g, enhances calcium absorption in subjects with normal lactase activity, but inhibits it in those with lactase deficiency (54,55). The smaller quantities of lactose present in physiological loads of dairy products (there are approximately 5 g of lactose in 100 ml of whole milk), however, may not have a detrimental effect on calcium absorption in lactase-deficient subjects (56). One study (55) showed that in the normal lactase group, lactose prolonged the duration of absorption at a maximum rate and therefore increased the total fractional calcium absorption. In lactase-deficient subjects, lactose decreased the total absorption. The effect of lactose on calcium absorption is dependent on intestinal lactase activity. However, Horowitz and coworkers (57) showed that there was no relationship between lactose and calcium malabsorption. Vertebral and forearm mineral densities were not significantly different between normal lactose absorbers and lactase-deficient subjects.

Interaction of calcium with sodium.—High dietary sodium chloride intake increases urinary calcium excretion in humans (58), which promotes negative calcium balance. Therefore, habitual excess sodium chloride intake could be a factor in promoting bone loss (59,60). Some studies (61,62), but not all (60,63), suggest that postmenopausal women are more sensitive to the calcium-losing effect of sodium than premenopausal women. Approximately 1,000 mg/day of dietary calcium would prevent bone loss at the hip in postmenopausal women ingesting 2,000 mg sodium chloride per day. However, if salt intake rose to 3,000 mg, then calcium intake should increase to 1,500 mg to prevent loss of bone (64).

Interaction of calcium with caffeine.—Calcium and coffee intakes significantly influence calcium balance. A coffee intake in excess of 1,000 ml causes a calcium loss of 64 mg/day, whereas intakes of one to two cups of coffee per day had little impact on calcium balance in 85 patients, age 48 to 77, with postmenopausal crush fracture osteoporosis (65). However, Kiel and colleagues (66), studying 3,170 Framingham Study women (age 50–84) in 1971–1974, found that consumption of ≥2 units of caffeinated beverages (one unit = one cup of coffee or two cups of tea) increased risk of hip fracture by 53%. For younger adult women consuming adequate calcium, moderate caffeine intakes may have little or no deleterious effects. Increased urinary and intestinal losses may be compensated by increased intestinal calcium absorption. However, older women do not seem to compensate adequately to maintain calcium balance, especially when calcium intakes are below recommended levels (67). Caffeine-induced urinary loss of calcium is largely attributable to a reduction in renal reabsorption, because caffeine did not change creatinine clearance and filtered load significantly (68).

Interaction of calcium with protein.—High dietary protein intake increases urinary calcium excretion (69), possibly induced by the acidifying effect of sulfur-containing amino acids. However, another study (70) demonstrated that urinary calcium did not significantly increase during either a high protein–low calcium intake or an 800 mg calcium intake. The lack of a significant increase in urinary calcium was probably due to the high phosphorus content of the high protein intake. Calcium absorption does not change significantly during a high protein intake. In contrast to the high protein intake of a typical adult, protein intake in elderly people is often low. Low protein intake appears to play a distinctly detrimental role as a risk for hip fracture (71). In a recent survey in hospitalized elderly patients, a reduced protein intake was associated with lower femoral neck BMD (72). Protein supplementation in individuals admitted with femoral neck fractures reduced bad outcomes (e.g. death, institutionalization) by as much as 50% (73,74).

Interaction of calcium with phosphorus.—An increase in phosphorus intake from 800 mg/day (RDA) to 2,000 mg/day in adult men did not affect calcium balance regardless of the calcium intake (ranged from 200 to 2,000 mg/day) (75). Heaney and Recker (76) also showed that varying phosphorus intake had no effect on overall calcium balance in perimenopausal women. However, both studies observed low urinary calcium excretion, with high dietary phosphorus intake. It appears that high phosphorus intake decreases intestinal calcium absorption and renal calcium excretion but that these effects probably cancel one another so that calcium balance is not affected. Increased dietary phosphorus decreases the production of 1,25 dihydroxyvitamin D (77). This suggests that the ability to adapt to the changes in dietary phosphorus depends on the ability of the kidney to respond by changing its production of 1,25 dihydroxyvitamin D. No studies of the effect of dietary phosphorus on calcium and bone metabolism have been reported in postmenopausal women (78). High phosphorus intakes may contribute to age-related bone loss in this population because the ability to absorb and conserve calcium decreases with age.

Types of Calcium Supplements

Calcium carbonate is currently the most commonly purchased and cheapest form of supplemental calcium (79); however, it appears to be less effective than chelated forms of other calcium supplements such as calcium citrate, calcium gluconate, or calcium citrate-malate. Calcium carbonate is dependent on gastric acid secretion for dissolution and subsequent absorption of calcium from the intestinal tract. Gastric acid secretion may become impaired with advancing age or may be reduced by H_2 blockers and antacids (80). Elders and other people with achlorhydria may be unable to absorb calcium carbonate efficiently unless given with a meal (81). One study has also found that calcium carbonate is less effective than calcium citrate malate in reducing bone loss of postmenopausal women (13).

In contrast, calcium citrate is less dependent on acid for dissolution, because it has a modest solubility even in water. Calcium bioavailability from calcium citrate is greater than calcium carbonate as assessed by both urinary calcium post-oral calcium load or by radioisotopic measurement of intestinal calcium absorption in normal subjects (82). Calcium absorption from calcium citrate is higher than from calcium lactogluconate/carbonate in men aged 45 and 60 years (83). Calcium absorption from 500 mg of calcium citrate was greater than from 2,000 mg of calcium carbonate (82). The results from double-blinded, placebo-controlled, calcium supplementation studies in children and adolescents showed that calcium citrate malate has a greater fractional absorption than milk or calcium carbonate (84–86). Moreover, calcium citrate retarded bone loss in older postmenopausal women to a greater extent than calcium carbonate (13). The use of calcium citrate also

has the advantage of causing a citraturic response and could potentially reduce the risk of developing renal stones (87).

Timing.—There is evidence that suggests the benefit of calcium supplementation may be enhanced by administration at night to suppress the nocturnal rise in bone resorption (88). Evening calcium supplementation suppressed overall daily excretion of urinary bone resorption markers: deoxypyridinoline (DPD) by 20% and type I collagen cross-linked N-telopeptide (NTx) 18% and reversed the usual nocturnal increase in the level of serum parathyroid hormone (PTH). Morning calcium supplementation had no significant effect on overall daily excretion of either DPD or NTx.

Dosage.—In healthy women (above 35 years of age), the highest absorption fraction value is 0.5 when calcium intakes range from 465 to 582 mg/day. The normal absorption fraction value is 0.3 when calcium intakes range from 726 to 1,006 mg/day. If absorption fraction value is less than 0.15, it requires large calcium intakes to maintain the calcium balance (89). Intestinal calcium absorption and the ability to adapt to low calcium intakes are impaired in many postmenopausal women. This impairment can be overcome by increasing calcium intake.

Safety of Calcium Supplements

Three potential side effects of calcium supplements need to be considered: (a) hypercalcemia and hypercalciuria; (b) the development of calcium-containing kidney stones; and (c) lead contamination in fossil (oyster) shell calcium supplements.

Hypercalcemia and hypercalciuria.—Calcium intakes ranging from 1,000–2,500 mg/day do not result in hypercalcemia (90) in normal individuals. Daily calcium intakes of 1,500 to 2,400 mg, used to treat or prevent osteoporosis, did not result in hypercalcemia syndromes (1,91,92). The recommended upper limit of calcium intake is 2,500 mg/day (1). Extremely high intakes of calcium supplements (>2,500 mg/day) might produce hypercalciuria (93). Elemental calcium intakes in excess of 3,000–4,000 g/day should be avoided because they will cause hypercalcemia in most people (94).

Kidney stones.—Calcium restriction has been routinely recommended for patients who have kidney stones, because the majority of stones contain calcium (95,96) and because hypercalciuria has been associated with the formation of stones. However, several studies indicate that dietary calcium intake or supplementation was either inversely related or not associated with kidney stone formation. In a prospective study of patients with hypercalciuria, restriction of dietary calcium intake was associated with a 10% higher probability of stone formation, as determined on the basis of the urinary excretion of lithogenic factors (97). Giving calcium citrate supplements to a group of women who had previously formed kidney stones did not increase the lithogenicity of the urine as measured by the degree of calcium oxalate saturation (98). Norman and colleagues (99) also found that urinary calcium was only elevated for the first several weeks in healthy premenopausal women given calcium supplements. With more prolonged supplementation, there was a decrease in the fractional absorption of calcium, concurrent with a decrease in serum parathyroid hormone and $1,25(OH)_2D_3$. Thus, in a non-stone-forming population, intestinal adaptation to an increased calcium intake occurs, preventing hypercalciuria.

Oxalate is an important component of many kidney stones. Low-calcium diets can increase the degree of calcium oxalate saturation of the urine if oxalate hyperabsorption or changed dietary preferences cause hyperoxaluria (97). Therefore, women consuming low-calcium diets seem to be more at risk for stones than those with higher calcium intakes, perhaps because of reciprocal hyperoxaluria. The same inverse association between dietary calcium and risk for stone formation has also been reported among men (100). Some studies found that many stone formers have lower bone densities than age-matched control subjects (101–103). Stone formers often have a family history of osteoporosis in an earlier generation (98). Therefore, people who have been previously stone formers and have low bone density might be in need of extra calcium supplements.

Lead contamination.—High levels of lead have been reported in fossil shell calcium supplements as compared to calcium chelate supplements (104). Those supplements containing only low levels of lead were calcium chelates and refined calcium carbonate; supplements containing high levels of lead were dolomite, fossil shell calcium carbonate, and bone meal. The lead content of milk, normalized to 800 mg calcium by assuming a calcium concentration of 120 mg/100 g, was similar to that of chelate and refined calcium supplements (105). Lead can damage the nervous system, blood cell formation, renal function, and the reproductive system, especially in children younger than 6 years and in pregnant and nursing women.

Conclusions

Calcium supplementation is more effective in reducing bone loss and preventing osteoporosis in late postmenopausal women than in early postmenopausal women. Supplementation may be more effective in those with a low calcium intake or when combined with estrogen, vitamin D, or exercise regimens.

Calcium supplementation to 2,000 mg/day is considered safe in the absence of conditions causing hypercalcemia or nephrolithiasis (106). High calcium intake is not associated with kidney stones. Calcium restriction could actually be harmful and may lead to increased urine oxalate excretion and increased risk of kidney stone.

ACKNOWLEDGMENTS

This research was supported by grant AG-0012 from the National Institutes of Health.

The author thanks Dr. Claude D. Arnaud for reviewing the manuscript.

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Received February 20, 1998
Accepted July 1, 1998