

COMMENTARIES

Calcium and Peak Bone Mass: How Much Is Needed and When?

Laura K. Bachrach

Stanford Medical School, Palo Alto, CA, USA

Commentary on: Matkovic V, Goel PK, Badenhop-Steven NE, Landoll JD, Li B, Illich JZ, Skugor M, Nagode LA, Mobley SL, Ha E-J, Hangartner TN, Clairmont A. Calcium supplementation and bone mineral density in females from childhood to young adulthood: a randomized controlled trial. *Am J Clin Nutr.* 2005;81:175-88.

Calcium is accepted as an essential nutrient for bone health (1). Between infancy and adulthood, more than 1000 g of calcium are incorporated into the skeleton. For optimal bone health, calcium intake must be sufficient to meet the demands of bone mineral accrual and to compensate for losses in feces, urine, and sweat. Experts in the United States, Europe, and Australia have developed age-adjusted recommendations for calcium intake based on the best available calcium balance, bone mineral accrual, and fracture data (2). For individuals aged nine to 18 years, calcium intakes of 800–1300 mg/day have been advised. Despite these guidelines, the “threshold amount” of calcium required for maximal calcium retention and bone mineral accrual remains a contentious issue (2;3).

Data from myriad observation studies have been used to support the link between calcium and bone, but the protective “threshold” is difficult to discern (1;3). In retrospective studies of premenopausal and postmenopausal women, measures of adult bone mass and/or fracture rate have been linked to reported calcium consumption during childhood or adolescence. For example, Kalkwarf *et al.* (4) found that postmenopausal women who recalled drinking less than one serving of milk daily as youth had more fractures than did women who consumed more dairy products. Some studies of children and teens have found similar associations between calcium intake and bone mass or fracture, whereas other studies have not (3). The limitations of these

observational studies are obvious. Recall of dietary intake from weeks to years earlier may be inaccurate. Food questionnaires may not capture all of the calcium consumed. The range of habitual calcium intake in some studies was limited; if most subjects consumed close to the putative “threshold,” the beneficial effects of this nutrient on bone would be masked. Skeletal effects of calcium are likely to be modified by other factors, such as pubertal stage, activity level, or genetic variables, for which often there were no control subjects. It is plausible that dietary habits are linked to other lifestyle patterns that also affect the skeleton, thus confounding the analysis. For example, an individual who consumes more dietary calcium may have a different activity level than one who consumes less.

Prospective observational studies that avoid the pitfalls of recall have also shown inconsistent associations between habitual calcium intake and bone mineral accrual. Some (but not all) longitudinal studies show that gains in bone mass are linked to calcium consumption (3). As in retrospective studies, the discrepant findings may reflect a limited range of reported calcium intakes, variability in the maturity of the subjects, or the influence of confounding variables. The “threshold” for bone health cannot be established based on these data. Furthermore, several studies, in which both activity and calcium were tracked, found a stronger association between activity than diet and rate of bone mineral accrual (3).

Recognizing the methodologic uncertainties of observational research, several investigators have designed double-blind randomized controlled trials of calcium supplementation. Unfortunately, even this "gold standard" study design has failed to resolve the issue of optimal calcium intake. Although these studies found greater gains in bone mass in the supplemented youth (*i.e.*, in those given calcium carbonate or citrate, fortified foods, or dairy products), responses varied by maturity and skeletal site. For example, Johnston *et al.* (5) observed a benefit with calcium only in prepubertal subjects, whereas Nowson *et al.* (6) documented gains with supplemental calcium only after menarche. Added calcium increased bone mass most consistently at cortical sites, such as mid-radius and femoral diaphyses, and less often at the spine. The variable findings may reflect differences in baseline calcium intake, the type and amount of added calcium, duration of the intervention, and genetic factors. For example, Ferrari *et al.* (7) observed gains in bone mass with calcium supplementation only in subjects whose baseline dietary calcium intakes were less than 880 mg/day. Vitamin D receptor genotyping also affected the response to calcium supplementation, with significantly greater BMD gains in subjects with Bb polymorphisms and a trend toward gains in those with BB (but not bb) genotypes (7).

The skeletal benefits of one to three years of calcium supplementation seem to be short-lived. Most (but not all) follow-up studies have found that the differences in bone mass between supplemented and control subjects disappear within one to two years of stopping the supplements (3;8). Two hypotheses have been proposed to explain the transient benefit of calcium supplementation for the young skeleton. One possibility is that calcium supplementation merely reduces bone remodeling, rather than increasing modeling (9). Alternatively, supplementation might need to be sustained through adolescence to achieve any increase in peak bone mass.

Matkovic *et al.* (10) recently completed a seven-year study to determine whether continuing calcium supplementation through

adolescence could augment young adult bone mass. Dietary calcium intake in all female subjects at baseline averaged 830 mg/day of calcium; supplemented subjects received an additional 670 mg/day (on average) as calcium citrate-maleate from ages 10-18 years. Skeletal effects were assessed by dual energy x-ray absorptiometry (DXA) of the total body and radiogrammetry of the metacarpals. At the end of the study, no differences were observed between the groups in height, bone area, or markers of bone turnover. The greater gains in bone mass seen in the supplemented group after the first four years had diminished at seven years; the supplemented subjects exhibited greater gains only in metacarpal cortical area and cortical area/total area. Supplemented subjects who were taller than the mean height and more compliant with medications also had greater gains in proximal radial bone mass.

Why did the supplemental calcium contribute so little to young adult bone mass? We would have hoped for greater gains at clinically relevant skeletal sites. It seems that calcium supplementation accelerated gains in bone mineral during periods of bone modeling (*e.g.*, perimenarche), but that unsupplemented subjects had "catch-up" gains during late adolescence and achieved similar young adult bone mass. Possibly, higher calcium consumption reduced bone remodeling more than it increased modeling, although there were no group differences in bone turnover markers. Alternatively, the influence of calcium might have been masked by effects of other lifestyle or genetic variables, although the groups were matched for maturity, energy expenditure, urinary sodium, and dietary intake. Finally, it is possible that the baseline calcium intake of 830 mg/day in all subjects approximated the threshold for optimal bone mineral accrual, at least for the half of the cohort below the mean for height. The findings of Matkovic *et al.* (10) contrast those of Chevalley *et al.* (8), who followed girls 7.5 years after the end of a supplementation trial (8). The latter investigators found that added calcium (provided as a protein extract) was associated with an earlier onset of menses

in some supplemented subjects and that those with earlier menarche had sustained gains in both the axial and appendicular skeleton. These findings suggest a mechanism for potential sustained benefits of added calcium.

Despite this long and ambitious supplementation study, we remain uncertain about the "threshold" and optimal form of calcium that will translate to optimal bone health. Pediatric studies have been powered to examine changes in bone mass, not lifetime fracture risk. It is possible that calcium protects against fracture by influencing bone quality in ways not captured by DXA. For example, Nevitt *et al.* (11) found that low calcium intake during pregnancy (or adolescence, for women who had never borne children) was associated with an increase in incidental vertebral fracture that was independent of BMD. This observation is consistent with retrospective fracture study data suggesting that as little as one daily serving of dairy in youth provides prolonged protection against bone fragility (4).

To best define the true "threshold" of calcium intake for lifetime bone health would be a Herculean task. This would entail a randomized controlled trial of several doses and forms of supplementation tested in an ethnically diverse cohort of youth matched for activity patterns, growth, pubertal development, and other key modifiers of response. Given the evidence for synergism between skeletal loading and calcium, it would also be worthwhile to include activity intervention arms (12;13). Associations between polymorphisms of candidate genes linked to bone and the response to calcium would be relevant. Finally, subjects would need to be followed beyond peak bone mass to assess the influence of early calcium intake on lifetime fracture risk. This ideal study will never be initiated and completed, but less ambitious short-term research is needed. The importance of dietary calcium and dairy intake has come under attack (2). Even if optimal intake were established unequivocally, calcium consumption by today's youth is likely to fall far short. As we exhort children and teens to increase their calcium intake, we need to

build an even stronger evidence-based "case" for the benefits of lifestyle for bone health.

References

1. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver C. Peak bone mass. *Osteoporosis Int.* 2000;11(12):985-1009.
2. Lanou AJ, Berkow SE, Barnard ND. Calcium, dairy products, and bone health in children and young adults: A re-evaluation of the evidence. *Pediatrics.* 2005 Mar;115(3):736-43.
3. Wosje KS, Specker BL. Role of calcium in bone health during childhood. *Nutr Rev.* 2000 Sep;58(9):253-68.
4. Kalkwarf HJ, Khoury JC, Lamphear BP. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. *Am J Clin Nutr.* 2003 Jan;77(1):257-65.
5. Johnston CC Jr, Miller JZ, Slemenda CW, Reister TK, Hui S, Christian JC, Peacock M. Calcium supplementation and increases in bone mineral density in children. *N Engl J Med.* 1992 Jul 9;327(2):82-7.
6. Nowson CA, Green RM, Hopper JL, Sherwin AJ, Young D, Kaymakci B, Guest CS, Smid M, Larkins RG, Wark JD. A co-twin study of the effect of calcium supplementation on bone density during adolescence. *Osteoporos Int.* 1997;7(3):219-25.
7. Ferrari SL, Rizzoli R, Slosman DO, Bonjour JP. Do dietary calcium and age explain the controversy surrounding the relationship between bone mineral density and vitamin D receptor gene polymorphisms? *J Bone Miner Res.* 1998 Mar;13(3):363-70.
8. Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour JP. Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. *J Clin Endocrinol Metab.* 2005 Jan;90(1):44-51.

9. Dibba B, Prentice A, Ceesay M, Stirling DM, Cole TJ, Poskitt EM. Effect of calcium supplementation on bone mineral accretion in gambian children accustomed to a low-calcium diet. *Am J Clin Nutr.* 2000 Feb;71(2):544-9.

10. Matkovic V, Goel PK, Badenhop-Stevens NE, Landoll JD, Li B, Ilich JZ, Skugor M, Nagode LA, Mobley SL, Ha EJ, Hangartner TN, Clairmont A. Calcium supplementation and bone mineral density in females from childhood to young adulthood: a randomized controlled trial. *Am J Clin Nutr.* 2005 Jan;81(1):175-88.

11. Nevitt MC, Cummings SR, Stone KL, Palermo L, Black DM, Bauer DC, Genant HK, Hochberg MC, Ensrud KE, Hillier TA, Cauley JA. Risk factors for a first-incident radiographic vertebral fracture in women > or = 65 years of age: the study of osteoporotic fractures. *J Bone Miner Res.* 2005 Jan;20(1):131-40.

12. Specker BL. Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. *J Bone Miner Res.* 1996 Oct;11(10):1539-44.

13. Iuliano-Burns S, Saxon L, Naughton G, Gibbons K, Bass SL. Regional specificity of exercise and calcium during skeletal growth in girls: a randomized controlled trial. *J Bone Miner Res.* 2003 Jan;18(1):156-62.