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PERSPECTIVES

Recommended Calcium Intakes in Children: Have We Set the Bar Too High?

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Abstract

Increasing peak bone mass in childhood has the potential to reduce the impact of age-related bone loss, so identifying ways to improve childhood bone acquisition is important. Research into nutritional factors influencing childhood bone acquisition to date has focused on the role of calcium. Evidence from calcium balance studies supports the setting of recommended calcium intakes up to 800 mg/day for children and up to 1300 mg/day for adolescents. However, recent evidence from a meta-analysis of randomized controlled trials of calcium supplements in children suggests that increasing calcium intake to levels approaching recommended levels has only limited benefits for improving bone acquisition. Focusing on achieving high levels of calcium intake risks neglecting other potential lifestyle factors that could have greater benefits and possibly less potential for long-term adverse effects. While calcium remains important for skeletal health, it may be that high levels of recommended calcium intake are both unnecessary and unrealistic targets. The resources used to encourage and enable otherwise healthy individuals to meet these high levels may be better used in promoting other aspects of a healthy lifestyle for bone development and in researching alternative nutritional interventions to improve bone health. IBMS BoneKEy. 2008 February;5(2):59-68.

Keywords: Bone; Calcium; Children; Diet; Nutrition

Introduction

Childhood is potentially an important time to intervene to prevent adult osteoporotic fractures as bone mineral density (BMD) in later life is a function of peak bone mass and the rate of subsequent bone loss (1;2). Modeling suggests that a 10% increase in peak bone mass will delay the onset of osteoporosis by 13 years (3). Low BMD in childhood is also a risk factor for childhood fractures (4-8), so optimizing age-appropriate bone mass may in addition have a more immediate preventive effect on fracture rates in children. Nutritional factors are important, potentially modifiable influences on peak bone mass acquisition. Much research has focused on the role of calcium in childhood bone development, possibly to the neglect of other potentially important nutritional factors (9). The aim of this article is to provide an overview of the literature pertaining to the role of calcium in peak bone mass acquisition, and to raise the question of whether an over-emphasis on calcium intake may lead to lost opportunities for improving children's bone health through other mechanisms.

The Role of Calcium

It is widely accepted that an adequate calcium intake in childhood is important for bone development. Calcium is a key component of bone mineral and there are very substantial increases in bone mineral throughout childhood and adolescence. The skeletal mass of the full-grown fetus at term is around 70-95 g (10). Based on a cross-sectional study of infants aged 1 to 391 days, whole body bone mineral content (BMC) increases by 389% during infancy (11). While bone mass continues to increase throughout childhood, puberty is a key stage for bone mass acquisition with skeletal mass approximately doubling between the onset of puberty and young adulthood (12), and at least 90% of peak bone mass is obtained by

18 years of age (13). It is therefore not surprising that increasing calcium intake is an approach to improving peak bone mass that has undergone intense investigation.

Observational Data

Despite the significant increases in bone mass needed in childhood, the results of cross-sectional and longitudinal observational studies examining the associations of dietary calcium intake and bone density outcomes are mixed, as has previously been noted in the qualitative review by Lanou *et al*. (14). Similarly, the results of studies with fracture outcomes are also inconsistent. In case-control studies, low calcium or dairy intake has been found to be associated with increased fracture risk in 11-13-year-old boys but this result has not been confirmed in other groups (4;5;15). Low calcium/dairy intake has also been found to be associated with recurrent fracture in both sexes (16;17). Avoidance of milk in childhood appears deleterious to children's bones. Prepubertal children who avoid milk have lower total body BMC and areal BMD (18) as well as an increased risk of childhood fracture (19). The effects of low milk consumption in childhood may extend into adult life, with low childhood milk consumption having been shown to be associated with lower BMD (20) and a higher risk of fracture in adult life in women (21). Nonetheless, the observational evidence does not provide clear evidence to specify an optimal level of calcium intake.

Calcium Requirements in Children

The nutritional reference values used to describe calcium requirements in children have been developed using different methodologies in different settings, such that there is some variation in the levels recommended, particularly in adolescents. US recommendations are based on assessments of adequate intake for all children *i.e*., the experimentally determined estimate of nutrient intake by a defined group of healthy people (22). This approach has been used for infants in other developed world settings (23;24) but alternative recommendations using recommended dietary intakes (RDIs) or recommended nutrient intakes (RNIs) have been proposed by FAO/WHO and taken up, for example, in Australia. These recommendations are based on an assessment of the estimated average requirement, *i.e*., the daily intake, which meets the nutrient requirements of almost all (97.5%) apparently healthy individuals in an age- and sex-specific population group, and is equivalent to US RDAs. High levels of calcium intake for children are recommended in many developed countries including the United Kingdom, the European Union, Australia, the United States, and Canada (350-800 mg/day for children and 800-1300 for adolescents) (23), but the exact level of intake required remains controversial.

Evidence that has led to increases in recommended calcium intake levels in some settings comes largely from calcium balance studies. Threshold behavior for calcium intake has been demonstrated in a growing rat model (25) in which skeletal calcium accumulation was related to intake below a given level of calcium intake, but skeletal accumulation remained constant above this level. Data from calcium balance studies in 348 children were examined to determine whether threshold behavior was apparent in humans (26), and if so, at what level of intake. In these studies, calcium balance was used as a proxy measure instead of direct measurement of bone accumulation. The resulting model suggested that calcium does exhibit threshold behavior, varying with age, at up to 1730 mg in 9-17-year-olds. The degree of variation in this estimate was not given. A similar threshold effect at about 1300 mg was described in a study in females aged 12-15 years (27). However, the relationship between achieving this threshold in short-term calcium balance studies and achieving bone outcome improvements from longer term calcium supplementation is unknown. In a meta-analysis of randomized controlled trials (RCTs) (28;29), bone outcomes were compared in studies where the total calcium intake in the intervention arms exceeded 1400 mg/day, *i.e*., approximated the proposed threshold, and in studies where calcium intake was below this threshold.

There was no difference in effect size between these 2 groups at any site. While this observation is not inconsistent with the concept of a calcium threshold, the data suggest that with long-term supplementation the threshold lies below the level of 1400 mg/day. Thus, the clinical data are suggestive that current recommended calcium intakes may be an overestimate of children's requirements.

The contrast between this clinical data and the evidence from calcium balance studies may be in part due to variability in calcium absorption both between individuals, *e.g.*, ranging from 17% to 58% in pre- and peri-menopausal women (30), and within individual children over time in response to changing calcium intakes (31;32) and with growth (33). Calcium absorption has been shown to more than double (from 26% to 58%) in girls after changing from a high to a low calcium diet (32). In addition, the estimated maximal calcium retention used to model the threshold in the study by Jackman *et al*. (27) has wide 95% confidence intervals (mean 473 mg/day, 95% CI 245, 701 mg/day). Varying this component of the model has large effects on estimates of calcium thresholds. For example, using a maximal calcium retention of 245 mg means that approximately 75% of children in the study would meet this level at an intake of 900 mg rather than 1500 mg of calcium per day. In an alternative approach, Bailey *et al*. (34) determined in a prospective longitudinal study that the peak of calcium accretion was 359 mg/day and occurred at age 14 years (SD 1.0, range 12.0-15.9 years) in boys and 284 mg/day occurring at 12.5 years (SD 0.9, range 10.5-14.6 years) in girls, which is lower than the mean maximal accretion derived from balance studies. Moreover, adolescents show decreased urinary calcium excretion compared to young adults (35) and so there may also be a capacity to adapt to lower calcium intakes by reducing urinary losses. In the study by Bailey *et al*. (34), the correlations of peak calcium accretion and calcium intake were low in both boys and girls and calcium intake accounted for less than 1% of the variance in peak calcium accretion, also suggesting that variations in absorption and excretion of calcium intakes play an important role in maintaining bone acquisition across a range of calcium intakes even with the increasing rates of calcium accretion needed to accomplish increasing growth rates in bone. The increase in accretion rates in these children was achieved in part by increased efficiency of dietary calcium retention.

What Effect Does Increasing Calcium Intake Have?

There are no prospective calcium intervention studies in children that have used fracture as an endpoint. However, both BMC and BMD have been shown to be predictors of fracture in both case-control (4-6) and prospective studies in children (7;36;37), indicating that they are both valid proxy measures (even given the confounding effect of size). Because of the inconsistency of individual RCT results with bone density outcomes (14), a systematic review with meta-analysis was needed to address the question of what effect, if any, calcium supplementation might have in childhood. We performed a meta-analysis of placebo-controlled RCTs of calcium supplementation (28;29) and found that calcium supplementation had no effect at the femoral neck or lumbar spine, two of the most important sites for osteoporotic fracture in later life (Table 1). While supplementation had a small effect on total body BMC, this did not persist once supplementation ceased, which suggests there is no long-term effect. There was a small persistent effect on upper limb BMD, estimated to be equivalent to a 1.7 percentage point greater increase in BMD in the supplemented compared to the control group, which was estimated to reduce the absolute risk of fracture in childhood by at most 0.2% per annum in boys and 0.1% per annum in girls. Furthermore, there was no evidence to suggest that increasing the duration of supplementation led to increasing effects, or that the effect size varied with baseline calcium intakes, down to levels < 600 mg/day. Thus, the small increase in bone density at the upper limb from increasing intake from an average of 700 mg/day to 1200 mg/day is unlikely to result in a clinically significant decrease in

Site	No. studies	N[a]	Effect size[b] at end trial	No. studies	N	Effect size after supplement ceased
Femoral neck BMD (g/cm^2)	10	1073	+0.07 (-0.05, +0.19)	5	617	+0.10 (-0.06, +0.26)
Lumbar spine BMD (g/cm^2)	11	1164	+0.08 (-0.04, +0.20)	5	617	-0.01 (-0.16, +0.17)
Total body BMC (g)	9	953	**+0.14 (+0.01, +0.27)**	1	96	0.00 (-0.40, +0.40)[c]
Upper limb BMD (g/cm^2)	12	1579	**+0.14 (+0.04, +0.24)**	6	840	**+0.14 (+0.01, 0.28)**

Table 1. Effects of calcium supplementation by site.
[a] N = number of participants
[b] bold denotes statistical significance at the 5% level; effect given as standardized mean difference (95% confidence interval (CI)); an SMD of 0.3 is regarded as small (65).
[c] single study only

fracture risk. These results do not support the use of calcium supplements in healthy children, but cannot be extrapolated to children with medical conditions affecting bone metabolism. There is also a paucity of trials during the time of peak calcium accretion in boys, when calcium requirements will increase (34), and some subgroup analyses were limited by the low number of studies measuring outcomes. For example, bone density outcomes after supplementation had ceased could not be analyzed by pubertal status, but one study showed a persisting effect of about a 4% femoral neck BMD gain by calcium supplementation of food in 8-year-old girls 3.5 years after supplementation had ceased (38), suggesting a biologically significant effect may be more likely to be achieved when calcium is added in the prepubertal period.

Because the meta-analysis only included placebo-controlled trials, some RCTs of calcium supplementation using dairy products were not included (39-45). However, qualitatively, the results of these studies were not dissimilar to those in the meta-analysis, demonstrating no effect (39) or only small to moderate short-term effects (41-44) that did not persist after supplementation ceased (42;45). In the only study with a substantial effect size (40), the intervention group had substantially higher levels of vitamin D intake (168 IU and 288 IU daily in the control and intervention groups, respectively), making it open to question how much of the effect was due to calcium and how much was due to vitamin D.

Risks of Setting Calcium Intakes Too High

Should we be concerned about setting the bar too high for calcium intake? We believe we should for a number of reasons. While calcium intakes in children are frequently below recommended levels (23) worldwide, including in the United States (46), it requires substantial effort and resources to increase calcium intake in children. For example, in children with pre-existing diseases affecting bone metabolism, an extensive behavioral training program delivered over 8 weeks, to both parents and children in motivated populations, was needed to enable children to meet calcium intake targets (47;48). Cost-effectiveness

data assessing the efficiency of such an approach is not available, to the authors' knowledge. In healthy children, mothers describe a variety of methods they used to try to increase their children's calcium intake (49), all of which require overcoming significant barriers and the cost and inconvenience to families as a whole. Even in RCTs of calcium supplementation, outside of those situations where supplements were administered by teachers or health care providers, compliance is generally poor (29). There is an opportunity cost involved in asking families, governments and other stakeholders in public health to pursue higher levels of calcium intake than may be needed to maximize bone health in children. This could extend to the patterns of research activity undertaken to improve peak bone mass in children. For example, from 1988 to 2003, there were 12 published RCTs of calcium supplements to improve bone health in children included in our systematic review, while over the same period there was to our knowledge only a single RCT of vitamin D supplementation that was published. Research into other potentially modifiable nutritional influences on bone in childhood, such as sodium intake and fruit and vegetable intake, are sparse and RCTs are lacking; these are neglected areas of research (9; 50).

An additional reason for concern is that there may be long-term safety issues with high levels of calcium intake. Evidence is emerging that there is a potential detrimental effect on cardiovascular disease outcomes in the elderly (especially myocardial infarction) from high levels of calcium intake (51). There was a lag time before an effect was seen, with curves for both myocardial infarction and stroke not starting to diverge until after approximately 2 years, underlining the need for a lengthy follow-up period to detect possible adverse cardiovascular effects. These results were somewhat unexpected, given other data suggesting that calcium supplements can substantially improve lipid profiles (52) and may have a small beneficial effect on blood pressure (53). The results also contrast with the absence of increased cardiovascular risk in the Women's Health Initiative study in younger postmenopausal women (54) though in view of the poor compliance seen in that study, a per protocol analysis of the data could be useful. Thus, while the recent RCT evidence is cause for concern, these findings need to be replicated in further studies or in posthoc analyses of existing data sets.

There is a biologically plausible mechanism for a detrimental effect of calcium on cardiovascular disease, mediated through vascular calcification. Coronary artery calcification predicts future cardiac events in asymptomatic individuals (55-57) even at a relatively young age. The possible mechanisms of vascular calcification are complex (58) but vascular smooth muscle cells can make a phenotypic switch to bone-like cells (58;59) and in the presence of high levels of calcium produce vascular calcification (60;61). Clinically, calcium intake is associated with vascular calcification in patients with end-stage renal disease even in young adult life (62). Furthermore, high levels of calcium intake from the use of calcium-based phosphate binders are associated with increased vascular calcification (63), and administration of calcium carbonate results in increased vascular calcification compared to administration of the non-calcium-containing phosphate binder, sevelamer (64), in pre-dialysis patients. While calcium intake is only one potential contributor to the pathogenesis of vascular calcification, these data do provide a possible biological explanation for the recent RCT findings of increased cardiovascular disease with calcium supplementation.

While calcium supplements do not appear to result in serious adverse events in childhood (28;29), the numbers of children in the calcium supplement studies were small and the length of follow-up mostly short, so potential adverse effects are difficult to rule out. For example, increases in renal calculi may not have been detectable given that in older women with a higher baseline risk than in childhood, over 36,000 women followed for 7 years revealed an absolute risk increase of less than 4 in 1000 women with calcium and vitamin D supplementation (54).

Detecting long-term cardiovascular adverse effects from calcium supplement use in childhood would require long-term follow-up of children in such large numbers that it is highly unlikely to be feasible. Thus, while reported short-term adverse events in childhood are infrequent and minor, the potential for long-term harm from prolonged exposure to excessively high levels of calcium intake cannot be excluded. Further research is needed to address this important issue.

Conclusion

While calcium intake remains an important nutritional influence on bone health, it may be that the high levels of calcium intake recommended in some countries for children (particularly levels approaching 1500 mg in adolescents) are both unnecessary and unrealistic targets. While calcium remains an important component of a balanced diet, the resources used to encourage and enable otherwise healthy individuals to meet high levels of intake may be better used to promote other aspects of a healthy lifestyle for bone development and to research alternative nutritional interventions to improve bone health.

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