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COMMENTARIES

Is Peripuberty the Most Opportune Time to Increase Calcium Intake in Healthy Girls?

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Commentary on: Cameron MA, Paton LM, Nowson CA, Margerison C, Frame M, Wark JD. The effect of calcium supplementation on bone density in premenarcheal females: a co-twin approach. *J Clin Endocrinol Metab*. 2004 Oct;89(10):4916-22.

The extent to which variations in calcium intake by healthy, apparently well-nourished children and adolescents affect bone mass accumulation has received increasing attention over the past 15 years. This particular interest essentially stems from the growing awareness of two usually accepted, related notions: 1) fragility fractures occurring during adult life are a major public health problem; and 2) the amount of bone acquired at the end of the growth phase is an important determinant of the risk of fragility fractures, the occurrence of which exponentially increases from the sixth decade of life onward.

International and national agencies have adopted recommendations for calcium intake from infancy to the last decades of life. Decisions from these recommending bodies can be based on either calcium balance, allowing one to estimate maximal retention, or factorial methods, which sums available data on calcium accretion and endogenous losses modified by fractional absorption. Recommendations vary widely among regional agencies (1). Thus, for children ages six to 10 years, recommended calcium intakes are set at 500, 700, 800, and up to 1200 mg/day in the United Kingdom, Nordic European countries, France, and the United States, respectively. For female adolescents ages 11-17 years, the intakes are set at 800, 900, 1200, and up to 1500 mg/day in the same geographical regions, respectively.

Variability in calcium intake recommendation can be explained partly by the discrepant results obtained from numerous published epidemiological reports on the relationship between dietary calcium and bone mineral mass in children and adolescents over the past 20 years. A literature survey indicates that some (but not all) observational studies have found a positive correlation between calcium intake and bone mineral mass accumulation during growth (2). Stage of pubertal maturation is one of several factors that can account for the discrepant findings. Longitudinal observation made in healthy female and male subjects ages nine to 19 years suggests that the positive impact of high calcium intake on bone mineral mass accrual (2-4) is more substantial before than during or after the period of pubertal maturation (Figure 1). This previous finding is particularly relevant to the results of the paper discussed in detail below (5).

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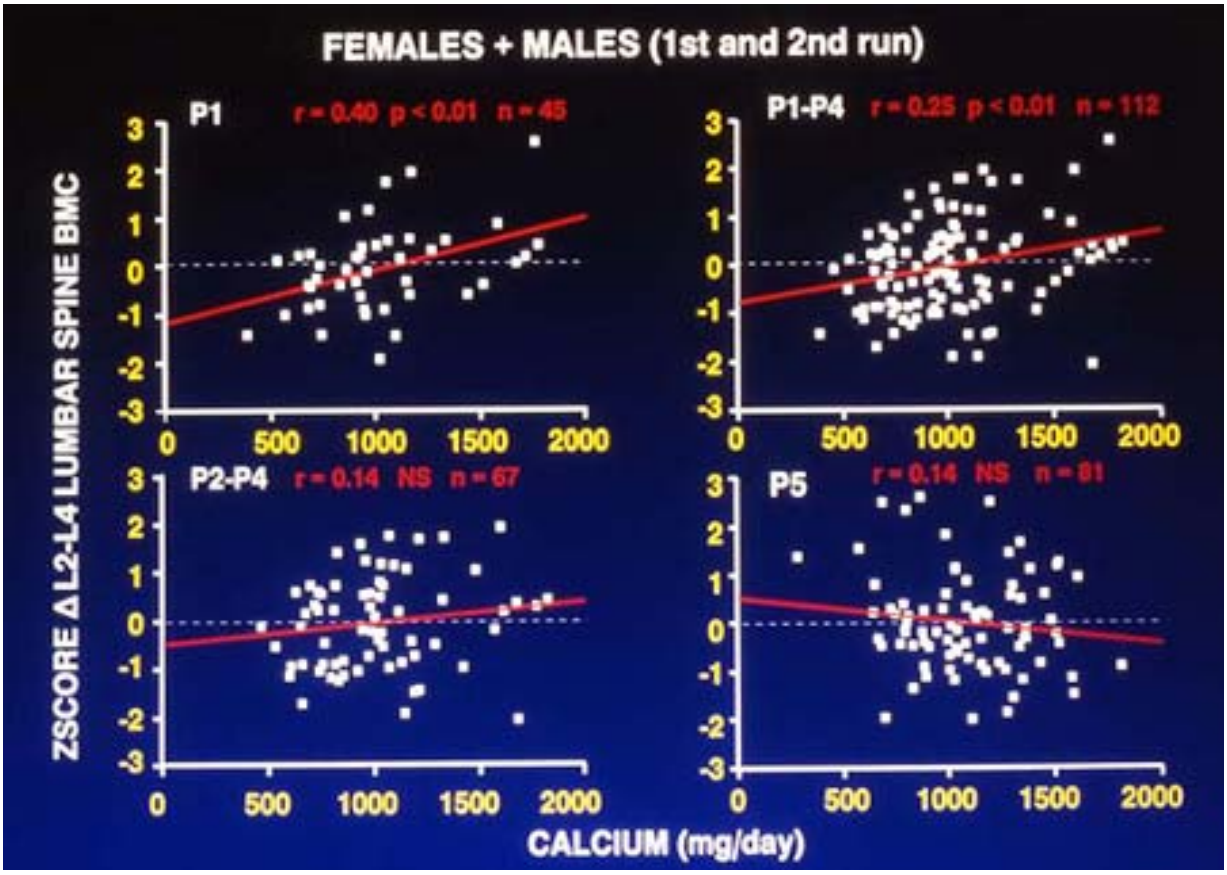

Figure: Relation between calcium intake and change in lumbar BMC in pre-, peri-, and postpubertal female and male adolescents. The mean calcium intake from dairy, vegetal, and mineral sources was recorded in two five-day diet diaries at one-year intervals. A positive correlation was found in prepubertal (P1), but not peripubertal (P2-P4) or postpubertal (P5) subjects. Each dot corresponds to the change in BMC adjusted for age and gender (Z-score) in 193 subjects ages from nine to 19 years. The BMC data are from Theintz *et al.*, *J Clin Endocrinol Metab.* 1992;75:1060-5 (3). The diet diary method is detailed in Clavien *et al.*, *J Adolesc Health.* 1996;19:68-75 (4). This figure is reprinted from Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis*. Vol 1. 2nd ed. 2001. p.631, with permission from Elsevier.

Several intervention studies have been carried out in children and adolescents (6-13). Overall, these studies indicate increased bone mineral mass gain in children and adolescents receiving calcium supplementation over periods varying from 12-36 months. However, the magnitude and characteristics of bone response to calcium supplementation, as observed at the end of intervention, seems to depend on various factors. These factors include spontaneous calcium and protein intake, pubertal maturation, and age at the time of intervention (14). Likewise, these factors may also determine whether the effect will last after discontinuation of calcium supplementation (14). The benefit of supplemental calcium was usually found to be greater in cortical appendicular than axial trabecular-rich bone (15). It may be particularly substantial in children with a relatively low calcium intake (11). Thus, in some conditions, calcium supplementation could modify bone growth trajectory and thereby potentially increase peak bone mass (16). Interventions limited to the first period of life and aimed at increasing the availability of bone mineral elements, as achieved for instance by physiological supplementation of vitamin D (17), may shift the trajectory of bone mass accrual upward. This kind of observation is in keeping with

the general "programming" concept in biology, indicating that exposure to environmental stimuli during critical periods of early development can provoke long-lasting modifications in structure and function (18, 19).

In a recent publication, Cameron *et al*. (5) described a well-designed intervention trial on the effects of calcium supplementation on areal bone mineral density (aBMD) in premenarcheal female twins (mean age, 10.3 ± 1.5 years at baseline). As indicated by the authors, the co-twin design conferred a substantial advantage in statistical power, compared with intervention studies in unrelated individuals. Daily supplementation was quite substantial, amounting to 1200 mg of calcium, given in tablet form as carbonate salt. Accordingly, total calcium intake increased from an average of 700-800 mg/day, the recorded spontaneous consumption, to 1900-2000 mg/day in the supplemented group. Despite this large supplementation and optimal design that allowed for greater control of both genetic and environmental factors, the within-pair percentage difference (calcium-placebo) was not statistically significant after two years of intervention (5). This lack of recording of any significant calcium effect was noticed even after analyzing the “active treatment” cohort exclusively (i.e., 24 of 51 enrolled twin pairs remained compliant until the end of intervention). Indeed, after two years of such large calcium supplementation, the within-pair percentage difference in bone mineral mass gain from baseline was not statistically significant at the level of lumbar spine aBMD (1.81%; 95% confidence interval [CI], -1.39-4.70); total hip aBMD (0.04%; CI, -2.76-2.27); femoral neck aBMD (–0.43%; CI, -4.44-2.24); and total body bone mineral content (BMC) (1.94%; CI, -2.71-6.18). Furthermore, no within-pair difference in forearm aBMD was observed (5).

The results were further analyzed after adjustment for age, height, and weight. It is important to note that such an adjustment might have been considered unnecessary, given the twin pair approach and the fact that there was no difference in height and weight, neither at baseline nor at 24 months, between the placebo and calcium-supplemented group. In any case, the additional mathematical analysis did not demonstrate a statistically significant calcium effect at the level of osteoporosis-relevant skeletal sites, such as the spine, proximal femur, or forearm, where the risk of fragility fracture in late adult life is particularly high. Thus, the results of this well-conducted study are negative, despite the optimal co-twin design, and even though the results were analyzed by an “adjusted” statistical evaluation limited to the compliant twin pairs (thus avoiding the more conservative “intention-to-treat” analysis that would have also taken into account the reexamination of noncompliant enrolled subjects at the end of the intervention).

Assuming that the power of the trial to demonstrate a calcium effect was sufficient, the bioavailability of the tested calcium form was adequate, and the compliant subjects of each twin pair adhered strictly to the assigned placebo or calcium tablets, the negative outcome deserves some comments, particularly because the observation is not unique. Indeed, the current study is in full agreement with a former intervention study that also used the powerful cotwin approach. In the previous study, the calcium effect, which increased the daily intake from about 900-1600 mg after 36 months of supplementation, was significant in prepubertal (but not peripubertal or postpubertal) subjects (6). Taken together, the data from these two cotwin trials (5, 6), could lead one to legitimately infer that the peripubertal period does not seem to be the most opportune time to achieve greater bone mineral mass gain by increasing calcium intake. This inference, based on robust recorded data, is in sharp contrast to the widespread intuitive belief that the period of pubertal maturation (between ages 10-11 and 13-14 years in girls) corresponds to the most attractive time for enhancing calcium intake to implement an early prevention strategy against adult osteoporosis. Indeed, this growth period is characterized by an acceleration of bone mineral mass accrual. It is estimated that the daily *net* calcium deposition into the skeleton amounts to 90-140 mg at age one to nine years. It increases to about 250 mg/day at

ages 10-14 years and then declines to approximately 100 mg/day at ages 15-19 years. Therefore, the period during which more calcium is required for responding to the demand of accelerated skeletal building has usually been considered one of the most favorable times to detect a difference in bone mineral mass gain between low and high calcium consumers. Accordingly, one would expect the peripubertal period to be quite an opportune time to document the benefit of calcium supplementation in randomized placebo-controlled trials. However, there is no scientific evidence supporting such an “intuitive” notion, at least to the knowledge of the author of these comments -- unless, obviously, “low” intake would be set at such a reduced level that bone growth would be impaired merely by lack of mineral substrate.

Additional evidence suggests that the period of pubertal maturation is associated with an array of adaptive mechanisms that are in a close relationship with skeletal development, which enhances the availability of bone mineral elements (2). The capacity to transfer calcium and inorganic phosphate (Pi) from the intestinal lumen to the extracellular compartment is stimulated. This response can be explained, at least in part, by an elevation of renal production and plasma level of 1,25-dihydroxycholecalciferol (1,25-$(OH)_2$D), the endocrine form of vitamin D. The renal tubular capacity to reabsorb Pi, as assessed by measuring the maximal tubular reabsorption of Pi/glomerular filtration rate (TmPi/GFR), is also enhanced. This dual renal physiological response leads to an augmentation of the extracellular Ca-Pi products, thus favoring the mineralization of bone organic matrix. The hepatic production and plasma level of insulin-like growth factor 1 (IGF-1) increase in parallel with the peripubertal acceleration and then deceleration of the bone growth rate. IGF-1 exerts a positive effect at the kidney level on both the production of 1,25-$(OH)_2$D and TmPi/GFR (2). In addition, IGF-1 is a factor favoring skeletal development by direct activity on osteogenic cells. The renal and skeletal effects of IGF-1 act in concert with sex hormones, the production of which increases at the onset of pubertal maturation, and have a gender-specific effect on the structural development of bone (20). Thus, thanks to these adaptive mechanisms, one can infer that the dependency on the environmental mineral supply to secure bone growth demand is not necessarily increased during the peripubertal years.

By analogy, it is interesting to mention pregnancy and lactation, two other periods of increased calcium demand. These two situations are also associated with physiological adaptive changes in mineral metabolism, probably similar to those that occur during pubertal maturation (21). These changes are independent of the dietary supply within the range of normal intakes. Unless the supply is marginal, these adaptative mechanisms provide the minerals required for fetal growth and breast milk production, without requiring an increase in maternal dietary intake or compromising maternal bone health in the long term (21, 22).

Thus, by taking into account the adaptive mechanisms described briefly above, it is possible that a daily spontaneous calcium intake of about 700-800 mg covered the needs of the majority of the peripubertal girls enrolled in this recent co-twin study (5). In any case, based on the strength of the current evidence, including the results of the two co-twin studies discussed here (5, 6), there is serious doubt that increasing daily calcium intake from 800-900 mg (and up to 1500 mg) in girls from the onset to the end of pubertal maturation, as recommended by some national agencies, will prove to be effective for substantially increasing peak bone mass in the general population.

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