See corresponding article on page 274.

Does poor zinc nutriture retard skeletal growth and mineralization in adolescents?[1,2]

Janet C King

A good diet and an active lifestyle during the peripubertal and late adolescent years are essential for normal skeletal growth and development. About half of the peak adult bone mass is accumulated during the adolescent growth spurt (1). Nutrient intake, particularly that of calcium, is thought to influence peak bone mass and may be instrumental in preventing subsequent postmenopausal and senile osteoporosis (2). Regular weight-bearing exercise and a normal age-related body weight in adolescence and young adulthood are also necessary to achieve peak bone mass (3). It has been recommended that a national program for prevention of osteoporosis be established that focuses on the calcium intakes and physical activity of young girls before puberty (4).

Although there is no doubt that dietary calcium is a factor influencing skeletal development, focus on that nutrient alone may be too simplistic. Most, if not all, of the essential nutrients are required for normal bone metabolism. The study by Golub et al (5) in this issue shows that moderate deprivation of dietary zinc (2 μg Zn/g diet) in a group of rhesus monkeys from the beginning of puberty through the postmenarcheal period retarded skeletal growth, maturation, and mineralization. This is the first demonstration in a nonhuman primate that moderate zinc deficiency, in the presence of an adequate intake of all other nutrients, limited skeletal growth and mineralization during adolescence. Other common indicators of poor zinc nutriture were not evident in these animals. Plasma zinc concentrations did not fall outside the normal range and food intake did not decline. Puberty was not prevented. It is doubtful, therefore, that a potentially growth-retarding zinc deficiency could be detected in a human population of adolescents.

The important role of zinc for skeletal growth and development has been observed previously in severe zinc depletion. Congenital malformations and abnormalities of skeletal growth have been shown in several species fed diets virtually free of zinc (6). Severe postnatal zinc deficiency also caused bone abnormalities in experimental animals. In the first demonstration of human zinc deficiency among adolescent boys (7), bone age was markedly depressed. The effect of marginal zinc depletion on skeletal maturation was investigated by enrolling infants and young children < 5 y of age in double-blind randomized clinical trials of zinc supplementation (8). Studies done in the United States and Canada showed that zinc supplementation of short, but generally well-nourished infants and young children improved linear growth but did not affect weight gain. The results of studies done in developing countries were inconclusive, suggesting that other dietary and environmental conditions, such as the presence of infections and diarrhea, modulated the response to supplemental zinc. Very few zinc supplementation trials of peripubertal or adolescent children have been done. There was a recent report, however, of 21 short prepubertal Japanese children who were considered to have marginal zinc status as defined by an elevated rate of zinc kinetics (9). Supplementation of 10 of the 21 children with 5 mg Zn/kg as zinc sulfate for 6 mo improved growth velocity as well as energy intake, serum zinc, serum alkaline phosphatase activity, and serum osteocalcin concentrations. Taken together, all of these supplementation trials suggest that marginal zinc nutriture may limit skeletal growth in some infants, children, and adolescents.

It is interesting that skeletal growth retardation was not evident in the zinc-deprived monkeys studied by Golub et al (5) until the end of the rapid growth spurt that occurred between 27 and 36 mo of age. The monkeys were fed a normal amount of zinc until 18 mo of age. Possibly, tissue zinc reserves were utilized to support normal skeletal maturation until 33–36 mo of age when the reserves were depleted. Although zinc cannot be stored, it appears that high zinc intakes may cause modest increases in tissue zinc concentrations. For example, a group of chickens fed a high-zinc diet accumulated zinc in bone, liver, and intestine and maintained growth when switched to a zinc-free diet significantly longer than chicks fed normal amounts of zinc before depletion (10). In a previous study of rhesus monkeys fed a marginally zinc-deficient diet (4 μg/g diet) from conception through 36 mo of age (11), defective skeletal mineralization was most evident at 6 mo of age. Thereafter, bone mineralization improved so that values were only slightly below those for control monkeys at 36 mo. Thus, it appears that the timing of skeletal growth retardation is influenced by the onset of a low intake of zinc. Also, retardation in skeletal maturation is most likely to occur immediately after a period of rapid growth.

[1] From the USDA/ARS Western Human Nutrition Research Center, San Francisco, and the Department of Nutritional Sciences, University of California, Berkeley.

[2] Address reprint requests to JC King, USDA/ARS Western Human Nutrition Research Center, PO Box 29997, Presidio of San Francisco, CA 95129. E-mail: jking@nature.berkeley.edu.

The mechanisms underlying zinc deprivation–induced skeletal growth and mineralization have not been defined. Zinc is highly concentrated in the hypertrophic zone of epiphyseal cartilage. In vitro, zinc enhanced the ATP-dependent calcium uptake of matrix vesicles in a dose-dependent manner (12). Zinc also modulated the effect of insulin-like growth factor in osteoblastic MC353-E1 cells (13) and influenced the activity of osteoblast alkaline phosphatase (14). The effect of zinc deficiency on bone metabolism has not been studied extensively, and further studies are needed to define the mechanism whereby zinc deprivation inhibits skeletal growth and mineralization in vivo.

In addition to enhancing bone formation, zinc also appears to inhibit bone loss. A recent 2-y intervention trial of 59 women with a mean age of 66 y, showed that zinc, along with calcium, copper and manganese, prevented bone loss whereas a calcium supplement permitted bone loss (15). The potential role of zinc in maintaining the bone of these postmenopausal women is confirmed by studies of ovariectomized rats showing that prolonged oral administration of a zinc-histidine compound completely prevented femural bone loss (16). In vitro studies also support a role for zinc in inhibiting bone resorption. Zinc inhibited rat-isolated osteoclasts at concentrations as low as 1×10^{-14} mol/L (17). Zinc, therefore, appears to be a potent inhibitor of bone resorption as well as a promoter of bone formation.

Osteoporosis is a major public health problem in the United States affecting 25 million people and costing society an estimated $10 billion annually (18). Because the disorder is easier to prevent than to treat, the goal should be to ensure that each individual reaches their potential peak bone mass through regular exercise and good dietary habits. The study reported by Golub et al (5) in this issue, as well as other research, showed that intake of zinc should be considered along with calcium, vitamin D, protein, magnesium, fluoride, and other trace elements. Nutritional surveys show that the zinc intake of adolescents is frequently below recommended standards (19), and that intakes in 1976–1980 tended to be higher than those observed in more recent surveys (20). Future efforts to achieve peak bone mass in adolescence and, thereby, reduce the risk of osteoporosis later in life, should promote the intake of foods rich in zinc as well as other nutrients.

REFERENCES

1. Parfitt AM. The two faces of growth: benefits and risk to bone integrity. Osteoporos Int 1994;4:382–98.
2. Matkovic V. Calcium and peak bone mass. J Intern Med 1992;231:151–60.
3. Welten DC, Kemper HC, Post GB, et al. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. J Bone Miner Res 1996;9:1089–96.
4. Anderson JJ, Metz JA. Contributions of dietary calcium and physical activity to primary prevention of osteoporosis in females. J Am Coll Nutr 1993;12:378–83.
5. Golub MS, Keen CL, Gershwin ME, et al. Adolescent growth and maturation in zinc-deprived rhesus monkeys. Am J Clin Nutr 1996; 64:274–82.
6. Hambidge KM, Casey CE, Krebs NF. Zinc. In: Mertz W, ed. Trace elements in human and animal nutrition. 5th ed. Orlando, FL: Academic Press, Inc, 1986:1–137.
7. Prasad AS, Miale A Jr, Farid A, Sandstead HH, Schubert AR. Zinc metabolism in patients with a syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism and hypogonadism. J Lab Clin Med 1963;61:537–49.
8. Allen LH. Nutritional influences on linear growth: a general review. Eur J Clin Nutr 1994;48:875–89.
9. Nakamura T, Nishiyama S, Futagoishi-Suginohara Y, Matsuda I, Higashi A. Mild to moderate zinc deficiency in short children: effect of zinc supplementation on linear growth velocity. J Pediatr 1993;123:65–9.
10. Emmert JL, Baker DH. Zinc stores in chickens delay the onset of zinc deficiency symptoms. Poult Sci 1995;74:1011–21.
11. Leek JC, Keen CL, Vogler JB, et al. Long-term marginal zinc deprivation in rhesus monkeys. IV Effects on skeletal growth and mineralization. Am J Clin Nutr 1988;47:889–95.
12. Hsu HH, Anderson HC. Effects of zinc and divalent cation chelators on ATP hydrolysis and Ca deposition by rachitic rat matrix vesicles. Bone 1995;17:473–7.
13. Matsui T, Yamaguchi M. Zinc modulation of insulin-like growth factor's effect in osteoblastic MC3T3–E1 cells. Peptides 1995;16:1063–8.
14. Togari A, Arakawa S, Arai M, Matsumoto S. Alterations of in vitro bone metabolism and tooth formation by zinc. Gen Pharmacol 1993;24:1133–40.
15. Strause L, Saltman P, Smith KT, Bracker M, Andon MB. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. J Nutr 1994;124:1060–4.
16. Yamaguchi M. beta-Alanyl-L-histidinato zinc and bone resorption. Gen Pharmacol 1995;26:1179–83.
17. Moonga BS, Dempster DW. Zinc is a potent inhibitor of osteoclastic bone resorption in vitro. J Bone Miner Res 1995;10:453–57.
18. Riggs BL, Peck WA, Bell NA. Physicians resource manual on osteoporosis: a decision-making guide. 2nd ed. Washington, DC: National Osteoporosis Foundation, 1991.
19. Johnson RK, Johnson DG, Wang MQ, Smiciklas-Wright H, Guthrie HA. Characterizing nutrient intakes of adolescents by sociodemographic factors. J Adolesc Health 1994;15:149–54.
20. Mares-Perlman JA, Subar AF, Block G, Greger JL, Luby MH. Zinc intake and sources in the US adult population: 1976–1980. J Am Coll Nutr 1995;14:349–57.