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Adolescence

The Period of Dramatic Bone Growth

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Adolescence is a period of rapid skeletal growth during which nearly half of the adult skeletal mass is accrued. This life stage is a window of opportunity for influencing peak bone mass and reducing the risk of osteoporosis later in life. Endocrine factors that may influence peak bone mass include insulin-like growth factor-1, which regulates skeletal growth, and gonadotropic hormones, which stimulate epiphyseal maturation. Estrogen deficiency and amenorrhea can reduce skeletal mass. Weight-bearing exercise can increase bone mass. Appropriate mineralization of the skeleton requires adequate dietary intakes of minerals involved in the formation of hydroxyapatite; the most likely to be deficient is calcium.

Key Words: Adolescence; peak bone mass; calcium; physical activity; amenorrhea.

Introduction

Adolescence is a period of rapid skeletal development essential for the attainment of peak bone mass; insufficiency in peak bone mass contributes significantly to the risk of osteoporosis later in life. This review discusses the factors that influence development and attainment of peak bone mass. Some factors are programmed genetically. Others are under hormonal influence. Still others are predicated by lifestyle choices, which can be modified by education and behavioral change. Choices that limit peak bone mass may increase the risk of osteoporosis in vulnerable populations.

Bone density is similar in boys and girls, but the bones of boys are larger, giving them a distinct biomechanical advantage *(1)*. Figure 1, taken from Bailey et al. *(2)*, demonstrates how rapidly bone mineral content (BMC) accumulates during puberty in Caucasian Canadian children. Peak bone mineral velocity is higher in boys than in girls and occurs about 1.5 yr later in boys. The age of attainment of peak mass varies with the specific bone. For example, the hip matures first at age 16–18 yr *(3)*. In girls, approx 90% of total body mineral content is achieved by 16.9 ± 1.3 yr and 99% is achieved by 26.2 ± 3.7 yr *(4)*. The major determinant of bone mineral density (BMD) in girls appears to be Tanner stage, whereas in boys, weight is the major determinant *(5)*. In girls, calcium retention and bone formation rates decrease exponentially with postmenarcheal age after onset of menses *(6,7)*. Calcium retention was more strongly correlated with postmenarcheal age (–0.788, $p < 0.001$) and height (–0.650, $p < 0.001$) in white women ages 11–30 than with total body BMD (0.519, $p < 0.01$) or total body calcium (–0.595, $p < 0.01$) and remained unrelated to weight or body mass index *(8)*. In prepubertal boys and girls, bone formation rates do not correlate with body weight *(9)*. The relationships between calcium retention and bone formation rates have not been studied in pubertal boys.

How ethnic and racial differences may modulate the timing of peak bone mass is not known. At any given bone age, African Americans have greater bone mass than Caucasians. A study of 80 African American and 80 Caucasian children ages 8–18 using computed tomography showed that African American children had 10.75% greater cancellous bone density, but similar cross-sectional area of the vertebral bodies in the axial skeleton. While cortical bone area and cortical bone density were equivalent, femoral cross section was 5.7% greater in African American than in Caucasian children *(1)*.

Endocrine Factors That May Control Calcium Retention

Likely candidates that control pubertal age-related changes in calcium metabolism include gonadotropic hormones and insulin-like growth factor-1 (IGF-1). Recent studies have identified IGF-1 as an important intermediate phenotype for BMD *(10)*. Many of the physical changes in puberty, including active mineralization of bones, are mediated, at least in part, through the actions of sex steroids. Both testosterone and estrogen production increase gradually with puberty *(11)*. Their levels do not fall until later in life, whereas the peak rates of calcium accretion span <2 yr, as shown in Fig. 1. There may be two developmentally dependent threshold effects of testosterone *(12)*. In early puberty, low concentrations of testosterone may stimulate growth; in late puberty, higher testosterone levels may inhibit bone

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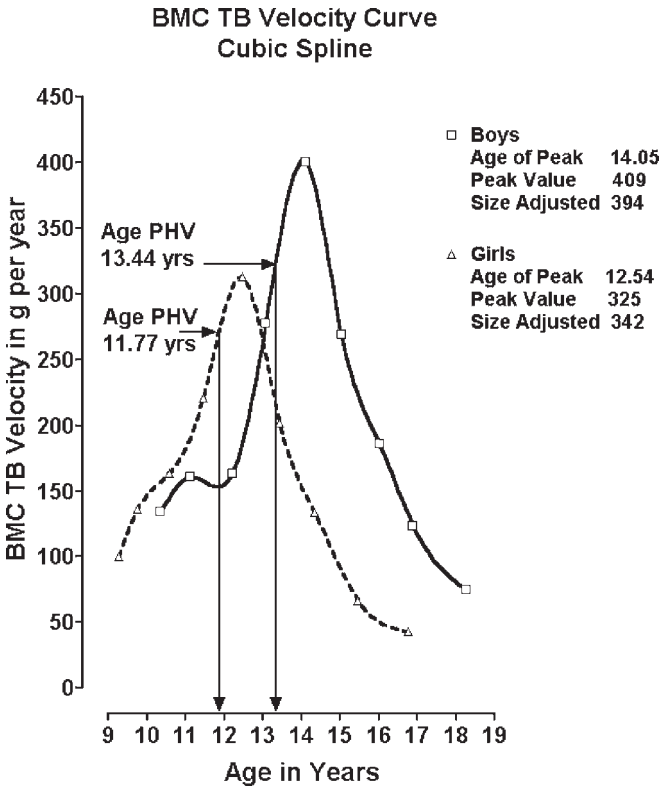

Fig. 1. Total body (TB) peak BMC velocity curve illustrating velocity at peak and ages at peak BMC and peak height velocities (PHV) by chronologic age for boys and girls. (Reproduced from ref. *2* with permission of the American Society of Bone and Mineral Research.)

growth by stimulating epiphyseal maturation. Evidence that testosterone mediates calcium accretion in boys comes from a report that 4–6 wk of testosterone administration in six healthy prepubertal boys significantly increased net calcium absorption and retention *(13)*. Induction of acute, severe testosterone deficiency with Lupron in healthy young men markedly decreased calcium balance and bone formation rates *(14)*. It has been speculated that the action of testosterone may be indirect, mediated by increased concentrations of IGF-1 *(13)*.

Estrogen appears to control the decrease in calcium retention and bone formation rates with advancing puberty and to regulate the mineralization and closure of epiphyses, indicative of a mature skeleton. A case report of a healthy male with a mutation in the estrogen receptor gene reported that epiphyses failed to fuse in the absence of estrogen and the skeleton continued to grow during mature adult life *(15)*. Supporting the hypothesis that estrogen decreases bone turnover in late puberty is the observation that biochemical markers of bone turnover correlate negatively with estradiol levels *(16)* and postmenarcheal age *(8)* in pubertal girls.

IGF-1 and its binding proteins, IGF-binding protein 3 (IGFBP3) and IGFBP5, are important regulators of bone growth and turnover. IGF-1 stimulates proliferation and differentiation of chondrocytes in the epiphyseal plate. In animals, administration of IGF-1 may increase the external diameter of long bone and bone mass *(17)*. Short-term (6 d) administration of rhIGF-1 to women with anorexia nervosa selectively increased markers of bone formation in a dose-dependent manner, with less effect on biomarkers of bone resorption, consistent with a direct effect on bone formation favoring accrual of bone mass *(18)*. By contrast, administration of estrogen for 1.5 yr did not prevent bone loss in anorexic women *(19)*. The profile of increasing IGF-1 levels to puberty closely matches peak calcium accretion and markers of bone turnover *(20,21)*, consistent with a regulation of the rate of skeletal growth.

The rapid rates of bone turnover and skeletal acquisition that occur during adolescence represent windows of opportunity to influence the size of peak bone mass, thereby influencing the magnitude of the lifelong risk of fracture. For a more in-depth review of factors influencing the development of peak bone mass, readers are referred to the report of experts convened by the National Osteoporosis Foundation *(22)*. Preadolescents and adolescents may adopt habits and lifestyles that impact bone health at a time when parents have decreasing influence over their choices. Education programs are needed in order for adolescents and their care providers to understand how adolescent lifestyle choices and behaviors (reviewed next) may provide benefits or risks to the skeleton.

Estrogen Deficiency and Amenorrhea

A number of lifestyle choices can lead to cessation of normal menses, amenorrhea, with adverse consequences for bone mass. The two most important risk factors associated with amenorrhea are energy intakes too low to sustain physiologic levels of estrogen and excessive exercise. Estrogen deficiency and amenorrhea, when accompanied by undernutrition, can reduce peak bone mass, so that osteopenia becomes irreversible. In adolescent girls with anorexia nervosa, the low levels of IGF-1, which have been correlated with reduced caloric intake, correlated strongly with low bone formation *(23)*. Amenorrhea for at least 6 mo owing to weight loss, in the absence of disordered eating or stress, resulted in vertebral bone density of 2 SDs or more below the mean *(24)*. Although radial density remained similar, amenorrheic athletes had 14% lower lumbar spine bone density compared with eumenorrheic athletes *(25)*. Osteoporosis associated with anorexia nervosa is more severe than with other causes of estrogen deficiency. Risk of nonspinal fractures in individuals with anorexia was sevenfold that of age-matched women *(26)*. Severity of the osteopenia was related to duration of amenorrhea; it was worse if the eating disorder was initiated in adolescence than during adulthood *(24)*. For more in-depth discussions of this problem, readers are referred to reviews of amenorrheic bone loss owing to excessive exercise, stress, or weight loss with and without eating disorders *(27,28)*.

Estrogen deficiency during puberty carries the risk of increased bone resorption and reduced peak bone mass. Although some of the lost bone density may be regained on weight gain and resumption of menses, significant osteopenia may persist *(26)*. Less severe hormonal disturbances, such as irregular cycles or anovulatory and short luteal phase cycles, can still increase vulnerability to stress fracture, despite the smaller magnitude of bone loss. How oral contraceptives, which regulate menstrual cycles, may modulate skeletal development and attainment of peak bone mass remains uncertain. Although cortical bone responds favorably to oral contraceptives *(22)*, 18- to 31-yr-old women who were given oral contraceptives and who participated in an exercise program developed bone loss at the spine and hip *(29,30)*. This effect was abrogated when women taking oral contraceptives and participating in the exercise program consumed approx 1200 mg of Ca/d.

Diet: Calcium, Phosphorus, and Vitamin D

Bone requires all essential nutrients, as does any other living tissue. Certain nutrients deserve discussion here because of their unique role in bone, and because of the high likelihood that they may be lacking in many adolescents diet, possibly increasing the risk of osteoporosis later in life. The importance of adolescent nutrition in preventing postmenopausal osteoporosis was reviewed in detail recently *(31)*.

Calcium comprises 39% of total body BMC. It is the dominant mineral in bone and the most likely nutrient to be deficient in the diet of an adolescent. Randomized controlled trials in children and adolescents have shown increased bone mass or BMD in one or more bones when dietary calcium is increased as supplements, fortified foods, or dairy products *(32–40)*. The greatest increase in bone mass occurred in children who originally had the lowest dietary calcium intakes. Bonjour et al. *(35)* were one of the first groups to observe that subjects consuming less than the average calcium intake of 1879 mg/d might bias the response of bone positively when supplemented. In nine randomized controlled trials, the most striking response occurred in African American children from Gambia, when their usual low intake of 342 mg/d was increased to 1056 mg/d *(39)*. When Wosje and Specker *(41)* compared trials by expressing the changes in BMD as the annualized percentage of changes in BMD, they concluded that increases in BMD occurred primarily in cortical bone sites and that spine BMD increased more in pubertal than in prepubertal children. Follow-up observations after calcium supplementation was withdrawn indicated that the increase in skeletal mass attributed to calcium supplementation was maintained in some studies *(42)* but not in others *(43,44)*. Failure to maintain dietary calcium-induced skeletal benefit is most likely the result of a lack of statistical power to detect small group differences in the study.

Another limitation of randomized controlled trials is that typically two extreme calcium intakes, rather than a range of intakes, are selected for study: the self-selected (lower) intake of the control group and the increased intake of the treatment group. This is an inadequate base on which to determine recommended calcium intakes to optimize skeletal accretion. In the absence of such data, short-term metabolic balance studies have been used to determine "optimal" calcium intakes. Since 99% of the body's calcium is contained within the skeleton, calcium accretion measured by metabolic balance protocols predicts bone accretion. Using this approach, the relationship between calcium intake and calcium retention was studied in adolescent girls *(45)*. Calcium retention increased over the entire range (800–2300 mg/d) of calcium intakes studied. A nonlinear regression model showed that calcium intakes >1300 mg/d did not confer an additional statistically different advantage. Currently, the recommended dietary reference intake to ensure adequate uptake of calcium in children ages 9–19 is 1300 mg/d *(46)*.

Phosphorus is a constituent of hydroxyapatite, the mineral accounting for 85% of adult BMC. The estimated average requirement for the intake of phosphorus by adolescents is 1055 mg/d, which lies close to the tenth percentile of intake in boys and below the fiftieth percentile in girls *(46)*. Inadequate phosphate consumption is rare in adolescents. Excess dietary phosphorus is viewed as a risk for the adolescent skeleton by some, since intakes of phosphorus increase with increasing consumption of soft drinks and processed foods *(47)*. It is commonly thought that dietary phosphorus should be maintained in a close to ideal ratio with calcium, based on their ratio in hydroxyapatite, since a suboptimal ratio may result in increased circulating parathyroid hormone (PTH). This dogma is based on outcomes seen with low-calcium, high-phosphorous diets *(48)*. After a critical review of published data, the Dietary Reference Intake Panel (which set the calcium requirement for North America) concluded that, with the exception of infants, the ratio of phosphorus to calcium in the diet was not important for setting requirements for either mineral *(46)*. The panel concluded that increased serum PTH was more likely with low calcium intake than with high intakes of phosphorus. The risk of excessive intake of phosphorus related to excessive consumption of soft drinks can be attributed to the current trend of substituting these for milk or other calcium-rich beverages. Healthy adolescents can adjust to a wide range in consumption of phosphorus, whereas their ability to adapt to low calcium intakes appears to be limited.

Vitamin D controls transcellular calcium transport, a saturable process, but not paracellular calcium diffusion. Transcellular transport is rate limited as calcium-binding proteins (e.g., calbindin) become saturated. Calbindin production requires activated vitamin D, 1,25 $(OH)_2$ vitamin D (calcitriol). Metabolism of 25(OH)D to 1,25$(OH)_2$D increases during puberty *(49)* and the increase in 1,25$(OH)_2$D may

explain the increased calcium absorption of adolescents compared with young women *(50)*. Transcellular transport dominates when calcium intake is low. By contrast, paracellular absorption of calcium does not require vitamin D and occurs linearly across calcium loads. If intakes of calcium are adequate, adolescents, except for those living in far northern or southern latitudes *(51)*, are not dependent on ingesting vitamin D, because most adolescents photosynthesize sufficient vitamin D on exposure to sunlight.

Whole Diet Considerations

Liberal consumption of dairy products will ensure an adequate supply of calcium, phosphorus, and vitamin D (only fortified products) to support optimal development of peak bone mass. Milk is also a good source of magnesium, another bone mineral that often is suboptimal in the diet. Girls on average consume close to required levels of magnesium until age 14, when dietary choices result in a fall in intake to about 60% of the recommended dietary intakes of 360 mg/d *(46)*.

Although children know that dairy products are a good source of calcium important for bone health, teenage girls often mistakenly think milk will add body fat. This myth is not supported by data from randomized controlled trials testing low-fat dairy products. Subjects assigned to the treatment group for which dairy products were provided and consumed daily for 12–18 mo showed that neither weight gain nor body fat gain were greater than in the control groups *(34,36)*. Dairy products provide equivalent contributions of calcium regardless of flavor or fat content. Often, the unavailability of calcium-rich foods is the major barrier to adequate calcium intake. A recent press release (Associated Press, May 2, 2001) described the success of a test market in Wisconsin in which soft drinks in school vending machines were replaced with milk. This gives practical evidence of the effectiveness of making calcium-rich products available.

Diets for adolescents should also include several servings of fruits and vegetables each day. These create an alkaline ash diet, thus reducing the risk of inducing bone resorption in order to supply anions to buffer acids, which are necessary to maintain pH balance when the diet is rich in muscle proteins. In addition to imbalances in pH, high protein and salt intakes may increase urinary calcium loss. Typical Western diets, which are very high in protein and salt, may exacerbate the consequences of inadequate calcium consumption. Vegetables supply necessary supplements; dark green vegetables are a source of magnesium, vitamin K (which is required for the carboxylation of osteocalcin), and trace elements, such as copper, a cofactor for lysyl oxidase required in forming collagen crosslinks.

In addition to individual nutrients, total calorie intake relative to energy expenditure influences body fat and body weight. Although body frame is influenced by genetics, overweight and underweight status can negatively influence bone mass and risk of fracture during adolescence. Overt thinness is a risk factor for osteoporosis, but obesity in children is also a risk factor for fracture of the forearm *(52)*.

Exercise

Weight-bearing exercise is now thought to play a large role in building peak bone mass. Accrued evidence indicates that exercise has the greatest impact on BMD before puberty *(53)*. In a retrospective study of 204 women ages 18–31, those reporting participation in high school sports exhibited a 7% increase in current femoral neck BMD. Energy expenditure associated with exercise after completion of high school gave no additional advantage at the femoral neck *(54)*. By contrast, BMD of other bone sites such as the spine, radius, and total body were influenced by post–high school energy expenditures. Sports participation before onset of menses will increase BMD more than when started after the onset of menses. For example, the effect of participating in tennis or squash on BMD was twice as great when initiated prior to the onset of menses *(55)*. A longitudinal study of Canadian children showed that physically active girls have 17% greater total body BMC, compared with their sedentary peers, 1 yr after achieving peak BMC velocity *(2)*.

There are few randomized controlled trials assessing the value of exercise on the skeleton of children. One recent randomized controlled trial of exercise involved children jumping 100 times from 61-cm-high boxes three times per week during the school year. This regimen resulted in a gain of 4.5% in femoral neck BMC and 3.1% in lumbar spine BMC, compared with a control group of 6- to 10-yr old children doing nonimpact stretching exercise *(56)*. Impressively, this simple, high-intensity (8.8 times body weight) impact exercise produced dramatic results within 7 mo. If physical activity modifies calcium requirement, it would be interesting to determine whether an exercise program of this level of intensity alters the optimal calcium requirements in this age group and in older children. It is important to emphasize the value of encouraging fitness for all youth, to replace the current trend of concentrating school resources on competition for a selected group of children. The only caveat to a more comprehensive fitness program remains that although weight-bearing exercises can improve bone, excessive training to the point of amenorrhea can be harmful to bone.

Smoking and Alcohol

Smoking is a risk factor for low bone density, because it reduces calcium absorption *(57)*. During the 1990s, teenage smoking increased to approx 36% in high school students *(58)*. Approximately 80% of those who use tobacco started before the age of 18 yr. Peak bone mass may be diminished by smoking, but the more detrimental effect of

smoking initiated in adolescence occurs later in life as more rapid bone loss *(22)*. The impact of alcohol on attainment of peak bone mass is unknown. In adults, excessive alcohol intake suppresses bone formation.

Recommendations

For bone health, the emphasis is on consuming adequate quantities of dairy products to achieve adequate intakes of calcium, vitamin D, magnesium, phosphorus, protein, riboflavin, and vitamin A. At least three daily servings of this food group are recommended for teenagers. If this recommendation cannot be followed, consumption of fortified foods or supplements will be necessary to meet calcium requirements. For most children, lactose maldigestion may be manageable by drinking milk in divided doses with meals to ensure that calcium requirements are met during adolescence. Symptoms of discomfort were negligible in African American adolescents who were able to ingest 1200 mg of calcium by consuming dairy products daily for 3 wk *(59)*.

Participating in sports through puberty greatly benefits bone. Especially dramatic increases in bone mass were observed after high-impact exercises, such as jumping off boxes or gymnastics. High-impact activity three times per week for approximately an hour is a good guideline. Developing lifelong habits of taking the stairs instead of the elevator, as well as other physical ways of increasing daily energy expenditure by challenging the skeleton, should be encouraged. Consequences of estrogen deficiency, such as amenorrhea, should be aggressively investigated to determine the cause. Intervention to restore regular menses and weight, if low, is essential to reduce the risk of osteoporosis later in life.

Several important questions are relevant to the development of recommendations to achieve acceptable bone health in adolescence. What is the impact of physical activity on calcium requirements? Do minorities have different requirements for optimal intake of calcium and other bone-related nutrients necessary to attain peak bone mass? What impact do lifestyle choices, which significantly alter diet or estrogen status for a prolonged time in adolescence, have on peak bone mass? It is hoped that future research will help us to identify those individuals with genotypes that will best respond to lifestyle interventions and lead to favorable peak bone mass.

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