The Determinants of Peak Bone Mass

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Osteoporosis poses a significant health burden for the elderly. Although the medical community recognizes the considerable impact of this disease in adulthood, many primary care providers do not realize that osteoporosis has its origins in childhood and disorders of bone accrual are often ignored. Various factors potentially interfere with gains in bone density and structure during growth and development and add to the risk of osteoporosis in adulthood. Therefore, it is critical to obtain a better understanding of the determinants of bone acquisition, from infancy to early adulthood, and strategies to optimize peak bone mass (PBM).

Over one-half of the skeleton is laid down during the teenage years, a period when lifestyle habits may impede optimal bone accrual. The pubertal years are a critical period for bone mass acquisition, but the process by which new tissue produced by the growth plate is turned into metaphyseal bone (endochondral ossification) and the relative roles of androgens, estrogens, and insulin-like growth factors in the adolescent growth spurt requires further investigation. Furthermore, our understanding of the process of modeling, leading to increased bone size and strength, is still lacking. Although there have been significant advances including generation of sex- and race-specific reference data for dual energy x-ray absorptiometry (DXA) bone mineral content (BMC) and areal bone mineral density (areal BMD [aBMD]), large gaps remain in our understanding of bone quality and strength, and in the prevention and treatment of abnormal bone accretion rates in childhood chronic disease. Scientific advances have led to a population of children with chronic illness who live well into their adulthood. Chronic illness poses threats to bone health by interfering with bone accrual and often leads to suboptimal PBM.

We recognized the need to account for major advances in the field of pediatric bone health over recent years and, more importantly, the need to identify critical research gaps in this area. To address these important issues, a workshop entitled "The Determinants of Peak Bone Mass" was held on November 17-18, 2015 at the National Institutes of Health in Bethesda, Maryland. The workshop was open to the public. This meeting brought together recognized leaders in the field of pediatric and adolescent bone health to discuss the current state of knowledge and identify research priorities. Herein, we summarize highlights of this meeting and discuss advances in our understanding of the development of PBM among children and adolescents. We provide an overview of key research opportunities envisioned to move this field forward.

PBM: When Is It Achieved?

Rates of bone mineral accrual follow predictable patterns through childhood and resemble percentile charts for height velocity. Differences in the timing of bone mass accrual are related to sex-specific patterns of pubertal maturation.[1] PBM is the amount of bone acquired when accrual ceases or plateaus at some point after completion of growth and development. The greatest gains in bone mass occur approximately 6 months after the adolescent growth spurt,[2] but increases in bone mass and density continue for years thereafter. Most estimates of the timing of PBM are based on cross-sectional population surveys from US adolescents and young adults using DXA such as the National Health and Examination Survey.[3,4] Estimates of the timing of PBM based on longitudinal changes in DXA-measured aBMD (or 2-dimensional BMD), as were obtained in the Canadian Multicenter Osteoporosis Study, are similar, except for total hip aBMD among females.[5] One of the primary aims of Canadian Multicenter Osteoporosis Study has been to identify factors associated with osteoporosis and fracture during adulthood. The study's longitudinal design adds significant value. Other recent studies identified lifestyle factors that affect PBM during the transition to young adulthood. An early study of college age women found substantial gains in

aBMD	Areal BMD
BAT	Brown adipose tissue
BMC	Bone mineral content
BMD	Bone mineral density
CSA	Cross-sectional area
CT	Computed tomography
DMPA	Depot medroxyprogesterone acetate
DXA	Dual energy x-ray absorptiometry
EE	Ethinyl estradiol
GCs	Glucocorticoids
OCs	Oral contraceptives
PBM	Peak bone mass
RCTs	Randomized controlled trials
vBMD	Volumetric BMD

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bone mass and density in the third decade of life (eg, 6.8% increase in lumbar spine aBMD). Gains were associated with dietary intake (calcium/protein ratio) and physical activity.[6] A more recent 5-year prospective longitudinal study of young Swedish men, ages 18-24 years, showed that gains in aBMD were related to the timing of adolescent growth spurt and changes in physical activity.[7,8] Later timing of the adolescent growth spurt was associated with lower cortical and trabecular volumetric BMD (vBMD) and cortical thickness of the radius and tibia, and lower DXA aBMD of the total body, spine, femoral neck, and radius. Moreover, in follow-up of this cohort, gains in tibial cortical cross-sectional area (CSA) were positively associated with changes in physical activity and adversely affected by initiation of smoking.[9] Quantitative computed tomography (CT) measures of cortical and trabecular bone show very different trajectories of PBM. Trabecular losses in the peripheral skeleton are already occurring among young adults in their early 20s, but cortical losses occur later, well after age 40.[10,11] In the axial skeleton, bone acquisition reaches peak values at the time of sexual and skeletal maturity and reported increases in DXA measures of bone are likely due to the influence of soft tissues, rather than to changes in bone acquisition within the vertebral body.[12] Thus, the timing of PBM is dependent upon the skeletal site and bone compartment under consideration, sex, maturational timing, and lifestyle factors.

Genetics of PBM

Osteoporosis has a strong heritable component,[13] as suggested by differences in aBMD for population ancestry groups,[1,14] and familial heritability estimates.[13,15] Earlier candidate gene and family studies identified the vitamin D receptor,[16] collagen 1 alpha 1,[17] and low-density lipoprotein receptor-related protein 5[18,19] as determinants of BMD. In adults, genome-wide association studies have identified 56 loci associated with BMD and 14 loci associated with osteoporotic fracture.[20] Many loci are also associated with BMD in childhood, some with sex- and puberty-specific effects,[21,22] and their mechanism of action warrants further study. The rare variant, EN1,[23,24] and a common variant near SOX6,[24] each associate with high bone density in both children and adults,[24] suggesting that the risk of osteoporosis may be established during childhood. Recent studies that used a "genetic risk score" based on loci identified in adult bone studies have shown that genetic risk for low BMD in adulthood was associated with decreased bone accretion from age 9 to 17 years.[25] Further studies are needed to determine the interaction of genetic predisposition with modifiable factors such as diet and physical activity in determining the timing and magnitude of PBM.

Sex Differences in Bone Accrual and Structure

An area of progress in osteoporosis research is the identification of the structural basis accounting for much of the variation in bone strength among humans. Progress in elucidating the structural basis for sex differences in the prevalence of osteoporosis has been considerably greater for the axial than appendicular skeleton. Accumulating evidence suggests that diminished bone accrual in girls is the basis for the lower PBM in young women, which, in turn, is a major determinant of their 2- to 4-fold higher incidence of vertebral fractures compared with men.

Available data also indicate that sex differences in PBM in the axial skeleton are the consequence of differences in vertebral growth, rather than in bone density.[26] The CSA of the lumbar vertebrae is 25% smaller in young women than men, even after accounting for body size. This disparity is also present in children and has most recently been found to be present as early as infancy; newborn girls across races/ethnicities have, on average, 10.6% smaller vertebral cross-sectional dimensions when compared with newborn boys.[26]

Because the CSA of the vertebral body is a major determinant of its compressive strength, the smaller vertebral CSA of females imparts a mechanical disadvantage that increases the stress within vertebrae for all physical activities, and if such stress persists, the susceptibility for fragility fractures later in life. The smaller female vertebral CSA also results in greater flexion/extension and lateral flexion. Because greater flexibility of the spine may facilitate the lordosis needed to maintain upright posture, it could be hypothesized that fetal load during pregnancy is a selection factor in the evolution of the discrepant spinal morphology between the sexes in humans.

Bone Strength Accrual, Tracking of Bone Mass, and Fracture Risk

Among healthy children, approximately one-half of boys and one-third of girls will sustain a fracture by age 18 years.[27] The skeleton is particularly vulnerable to fracture during early adolescence when linear bone growth may outpace bone mineralization, causing a transient increase in bone fragility.[28] Children of European vs African ancestry have a greater fracture risk. Although physical activity is critical to building bone, it is noteworthy that more active children have greater exposure to trauma that may cause fractures.[29]

Bone characteristics during childhood and adolescence are associated with childhood fracture risk. Children with forearm fractures tend to have lower bone mass, areal and vBMD, and cortical thickness, area, and density. A 1 SD decrease in bone mass or density has been associated with a substantial increase in fracture risk.[30] Forearm fractures reflect deficits in bone mineral throughout the skeleton, not just at the forearm.

Fractures occur when loading exceeds skeletal strength. Strength depends on both geometric properties (size, shape) and material properties (density). The properties contributing most significantly to fracture risk differ depending on the skeletal site. Optimizing bone strength accrual during growth is important for fracture prevention. During growth, vertebral cancellous density is stable in both boys and girls prior to puberty, increasing significantly between the ages of 12 and 17 years for boys and 10 and 15 years for girls.[31] Density is similar for black and white children through Tanner stage 3, but diverges with higher density in blacks at Tanner stages 4