Abstract
Bone mineral accretion during childhood and adolescence is subject to a number of influences, including body composition changes, sexual maturation and growth. Bone mass and density increase with age and vary by sex, so bone health must be evaluated like other growth outcomes, i.e. in relation to age- and sex-specific reference ranges. Peak bone mass, the amount of bone acquired at the end of skeletal development is an important determinant of lifelong skeletal health. The timing of puberty is inversely related to peak bone mass, such that individuals who experience puberty at older ages have lower bone mass in young adulthood. Height, an indicator of skeletal size, is correlated with bone mineral content and density. Even more importantly, children who are tall for their age have greater bone mass and density than children of average or short stature. Body composition, particularly lean body mass, has a positive effect on bone accretion because of the mechanical strains of muscle mass on bone accretion. The effect of height growth is positively associated with bone accretion, but the magnitude of the effect is not the same at all pubertal stages; in Tanner stage 5, height growth has a more pronounced effect on bone accretion than at the beginning of puberty. Understanding these complex relationships is essential to understanding bone metabolism during this part of the life cycle and the challenges of assessing bone health in children with medical conditions that threaten bone health.

Skeletal growth is a component of somatic growth characterized by increasing bone dimensions and bone strength. It is subject to a number of influences, including body composition changes, sexual maturation, physical activity, nutrition, genetics and overall health [1]. Children with complex medical conditions are at-risk for poor mineral acquisition because of disease processes or medical therapies, accompanied by poor growth, altered body composition and delayed maturational timing. For this
reason, potential effects of growth in body size and body composition, and maturation on bone mineral acquisition are of particular concern. Addressing these concerns will: (1) improve our understanding of underlying mechanisms of bone acquisition, (2) are needed to distinguish direct effects of diseases on bone metabolism as opposed to effects mediated through altered growth and maturation, and (3) are important for monitoring the effects of diseases and their treatment over time.

**Importance of Peak Bone Mass**

During the first two decades of life, bone mineral accretion is rapid. Peak bone mass (PBM) is the amount of bone mineral accrued by young adulthood when gains in bone mass cease. The timing of PBM differs for men and women, and depends on the skeletal site evaluated. The largest prospective study to evaluate the timing of PBM is the Canadian Multicentre Osteoporosis Study that evaluated 615 women and 527 men aged 16–40 years in a mixed longitudinal study design [2]. They estimated the timing of PBM occurs at ages 33–40 years in women and at 19–33 years in men for the lumbar spine, ages 16–19 years in women and 19–21 years in men for the total hip.

The PBM attained [3] and the rate of bone loss in later adulthood [4] are likely the chief determinants of bone fragility in older age. Thus, maximizing PBM during the period of bone acquisition is thought to have lifelong consequences. Environmental factors, such as suboptimal nutrition, reduced physical activity, and complex medical conditions can threaten the attainment of optimal PBM. Increasing attention is now directed to pediatric bone health assessment in children with complex medical conditions, and public health measures to optimize PBM in all children.

**Association of Height Status and Peak Height Velocity on Bone Accretion**

The pattern of bone mineral accretion is similar to that of growth in stature (fig. 1). Key features are (1) the nonlinear age related increase in bone mass, with the most rapid changes occurring during adolescence, (2) increasing variability in bone mass with age, and (3) greater bone mass in males than females at most ages. In addition, females begin to plateau in bone mineral mass at an earlier age than males; reference values from the multi-center Bone Mineral Density in Childhood Study show that between ages 18 and 20 the median total body bone mineral mass increased by 3% (from 2,288 to 2,359 g) in African-American and 1% (from 2,091 to 2,119 g) in non-African American females, and by 3% (from 2,850 to 2,943 g) and 4% (from 2,586 to 2,694 g) in African American and non-African-American males, respectively [5].

Height is one of the primary determinants of bone mineral content (BMC) and density (BMD) during childhood [6–8]. However, because height increases with age, as does BMC and BMD, it is difficult to separate the effects of stature from the
expected age related increase in BMC and BMD, especially in studies that encompass a large age range. Moreover, children who are tall for age have greater BMC and BMD z-scores than children who are average or short for age. Zemel et al. [7] reported that the correlation between height z-score and BMC z-score was 0.60 for the lumbar spine and 0.64 for the total body in 1,546 subjects, 7–17 years of age. The association was somewhat lower for spine BMD z-score \((r = 0.36)\), as BMD adjusts in part for bone size.

Gains in bone mineral mass occur throughout childhood but are particularly profound during adolescence. It is estimated that 25–40% of adult bone mineral is acquired in the 2 years surrounding the adolescent growth spurt [9, 10]. Peak bone acquisition occurs approximately 6 months after the age when PHV is attained for both males and females; the Saskatchewan Pediatric Bone Mineral Accrual Study estimated that the age at peak bone accretion was 14.1 years in males and 12.5 years in females [10].

Several studies have shown that the timing of peak height velocity (PHV) is inversely associated with PBM. A study of male military recruits in Sweden reviewed medical records to determine age at PHV. They found that young men with an earlier age at PHV had greater BMD of the total body and radius in young adulthood, as well as fewer fractures [11]. The Saskatchewan Pediatric Bone Mineral Accrual Study performed a similar analysis of their longitudinal data, but also controlled for

**Fig. 1.** Total body bone mineral content, g. Adapted from Zemel et al. [5].
age, body size, and body composition. They found that by age 20 years, girls who had undergone an earlier age at PHV had $62.2 \pm 16.8$ g more total body BMC, and those with a later age at PHV $50.7 \pm 15.6$ g less total body BMC than girls with an average age of PHV. However, maturational effects were not found at other skeletal sites, and no effects were observed for males using this approach that controlled for important covariates (body size and composition) that may also be affected by timing of the adolescent growth spurt.

**Effects of Puberty on Bone Accretion**

Pubertal maturation has distinct effects on bone accretion and strength beyond the changes associated with growth. Over two decades ago, Bonjour et al. [12] showed the effect of pubertal stage of maturation on spinal and femoral bone mass accumulation in a cross-sectional sample. They showed the pronounced increase in bone mass accumulation at the later stages of puberty, and that the delayed increase in lumbar spine BMC in males was related to the later timing of pubertal onset compared to girls. Similarly, Gilsanz et al. [13] found a significant increase in trabecular volumetric BMD assessed by QCT of the spine in girls during pubertal stages 4 and 5.

The tempo of puberty also affects bone accretion and PBM. A study of young adult men with a history of constitutionally delayed puberty showed decreased BMD at the spine and radius [14]. Since then, longitudinal studies have demonstrated the inverse effects of pubertal timing on PBM. In the multicenter Bone Mineral Density in Childhood Study consisting of a large cohort of children followed for 7 years, Gilsanz et al. [15] showed that the age at which girls and boys transition from Tanner stage 1 to stage 2 was inversely associated with BMC and BMD attained by Tanner Stage 5 at all skeletal sites. Interestingly, Chevalley et al. [16] showed that girls who attained menarche at an earlier age had greater BMD z-scores at all assessment ages both before and after menarche, from age 7.9 to 20.4 years.

**Effects of Body Composition on Bone Accretion**

The onset and progression through puberty is accompanied by sex specific alterations in body composition. The effects of muscle mass on bone accretion are of particular interest because of the beneficial effects of weight-loading on bone accretion. Muscle contractions generate forces which stimulate bones to adapt their shape and density to such loads [17]. The contribution of lean tissue to bone accretion has been a topic of numerous investigations. In a study of 363 healthy schoolchildren, aged 10–17 years, the contribution of lean body mass (LBM) to BMC varied by skeletal site,
and was greater in boys (5.7–12.3%) than girls (4.3–10.5%). LBM was most strongly associated to BMC of the femoral neck in both sexes, whereas fat mass was associated to BMC of the total body and lumbar spine [18]. Fat mass accounted for only a small percentage of explained variance in BMC, although it had a higher contribution in females than males (up to 6.5 vs. 1.9% explained variance). In obese children and adolescents, Petit et al. [19] showed that the greater femoral bone strength in obese children was attributed to their greater LBM; fat mass did not contribute to measures of femoral strength.

Prospective studies have shown that LBM accretion peaks before the peak bone mass accretion, further suggesting a causal association between these measures. Rauch et al. [20] showed that peak in LBM accretion occurred, on average, 0.51 years before peak BMC accretion in girls and by 0.36 years in boys. Further, peak LBM accretion was the primary determinant of total body peak BMC accretion, explaining 50% of the variability in peak BMC accretion. Using peripheral quantitative computed tomography of the tibia, Xu et al. [21] examined multiple indicators of bone density and strength of the tibia in relation to changes in muscle mass of the lower leg in a prospective longitudinal study. They showed that the peak gains in cross-sectional muscle area, a measure of muscle mass, occurred 1 year after the peak gains in tibia length and total cross-sectional area, and earlier than cortical cross-sectional area, total BMC and cortical volumetric BMD. Thus, there are dynamic changes in the distribution and density of bone that occur in late puberty, not all of which are directly responding to changes in muscle mass.

**Combined Effects of Growth and Puberty on Bone Mineral Accretion during Childhood**

To date, there are no studies that have fully considered the effects of growth on bone mineral accretion across the spectrum of pubertal development. The multicenter Bone Mineral Density in Childhood Study measured bone mass and density annually in 2,000 children and adolescents in the US for up to 7 years. As in previous reports, they showed that BMC accretion was similar for Tanner stages 1 and 2, and increased significantly in subsequent Tanner stages in both males and females [22]. They showed that annual height increments were significantly associated with BMC accretion at all stages of pubertal development, but most strongly predicted bone accretion in Tanner stages 4 and 5 for both the total body (less head) and the lumbar spine. The level of explained variance (R2) in Tanner stages 1 and 2 combined was 0.09–0.38, and for Tanner 4 and 5 was 0.46–0.65. These findings suggest that expected gains in BMC are only modestly growth dependent in pre- and early pubertal children, but growth measures are important predictors later in puberty, particularly in Tanner stage 5, a developmental stage which generally occurs after PHV.
Conclusion

Bone mineral accretion during childhood is a complex process influenced by a variety of factors. The effects of growth, developmental tempo, pubertal maturation and body composition on the growing skeleton underscore the complexities of understanding bone metabolism during this part of the life cycle and the challenges of assessing bone health in children with complex medical conditions. For these children, we must ultimately be able to answer questions such as: does this child with moderately delayed puberty have a normal rate of bone accretion? Will bone density recover in this child who is responding to treatment and experiencing catch-up growth in height?

To address these questions, it is necessary to address the combined effects of sexual maturation, growth and body composition on bone accretion from childhood to young adulthood. Studies to date have demonstrated that the age, size, body composition and puberty status of a child influence the amount of bone mineral accretion in the following year. Furthermore, the effect of growth in height on bone accretion varies as a function of sexual maturity; height growth has a much bigger impact on bone accretion in late puberty. The rapid and extended accretion of bone mass in mid-to-late puberty may provide an opportunity to maximize PBM. Future research is needed to determine if there are different genes involved in regulation of bone accretion at different stages of puberty, whether puberty modifies the impact on bone accretion of behavioral factors such as diet and physical activity, and whether the latter stages of puberty are critical period for optimizing bone accretion and risk of osteoporosis later in life.

References


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