

MEETING REPORTS

Bone Acquisition/Pediatric Bone: Meeting Report from the 32nd Annual Meeting of the American Society for Bone and Mineral Research

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A substantial number of papers dealing with bone growth in healthy individuals and in pediatric diseases were presented during the 2010 Annual Meeting of the ASBMR. These studies covered several aspects of bone mass and structure acquisition, including technical ways to assess it, its relation to other anthropometric variables, pubertal maturation stages, and environmental factors, particularly physical activity and nutrition. How bone mass and structure acquisition may explain the occurrence of fractures during childhood and adolescence was also the topic of several abstracts.

Technical Approaches to Assessing Bone Mass and Structure Acquisition

In the clinical setting, DXA scanning performed at relevant skeletal sites is still the technique of choice for assessing, in pathologic conditions, the degree of departure from normative values. It remains the standard for providing reliable reference data from infancy to post-puberty, taking into account age, sex, race, maturation and size effects on areal bone mineral density (aBMD) and bone mineral content (BMC). For infants and toddlers, new software has been developed that improves bone mineral detection, thus enabling the measurement of spine aBMD or BMC with good precision (1).

Regarding the measurement of trabecular density using QCT in children, appendicular or peripheral (p) sites are obviously preferred because of lower radiation exposure compared to spine scanning. The number of clinical research reports using

pQCT equipment, some endowed with high resolution (HR) detection, has increased substantially compared to previous ASBMR meetings. Like any other *in vivo* quantitative technique for bone, HR-pQCT can generate spurious images due to uncontrolled motions, especially at the radius level. Such motions compromise image quality, thus confounding the accuracy of cortical and trabecular densitometry and structure measurements. A basis for quantitative characterization of motion artifacts was developed that should avoid the use of subjective acceptance/rejection criteria (2).

Without access to pQCT technology, DXA-derived indices of radius bone geometry, density and theoretical strength appear to be relatively well-correlated to corresponding pQCT measurements as studied in one investigation of females aged 8.0 to 22.8 years (3).

Early Programming and Peak Bone Mass or Osteoporosis Risk in Adulthood

There is evidence indicating that environmental factors such as nutrition can modify the trajectory of bone acquisition during childhood and adolescence, and consequently peak bone mass (PBM) and the risk of fragility fracture in later life (4-6). Among nutritional factors, breastfeeding for more than 3 months has been reported to be positively associated with aBMD measured in 8-year-old prepubertal children (7). In agreement with this notion, breastfeeding duration was an independent predictor of trabecular vBMD, cortical BMC and cortical

thickness as measured at the tibia by pQCT in 21-year-old female subjects (8).

The last trimester of pregnancy is crucial for fetal bone acquisition, since during this period about 80% of body calcium of a term newborn is normally accrued, with the peak accretion rate occurring at about 35 weeks of gestation. Previous studies have shown that low birthweight individuals (< 2500 g) have decreased bone mass at some skeletal sites when assessed either in prepubertal girls at 8 years of age (9) or in young adulthood (10), compared to their normal birthweight peers. Two papers from this year's meeting corroborate this idea. In adolescents who were preterm born (< 37 weeks gestation) as compared to full term (> 37 weeks gestation) peer controls, BMC was low at both spine and hip levels (11). In 25-year-old women, total body BMC was predicted by their birth weight (12).

Bone Growth Characteristics: Timing and Magnitude According to Age and Pubertal Stage

Normative values of whole body, lumbar spine and femur BMC were established for breastfed infants longitudinally followed during the first year of life (13). Previous cross-sectional and longitudinal studies have shown that, at several sites of the skeleton, the greatest gain in aBMD or BMC occurs during pubertal maturation, and more precisely a few months after peak height velocity (PHV) in both genders, corresponding approximately to menarcheal age in girls (14-18). It is estimated that in healthy girls, bone mass accumulated between 11 and 14 years of age corresponds approximately to the amount lost during the 30 years following menopause. In a prospective study, lumbar DXA scans were performed in girls from 9-11 years of age (Tanner stage 1-2) for 8-10 years at 6-month intervals (19). Median menarcheal age was 12.8 years (range 10.1-16.7). From 9.6 to 17.9 years, spine BMC increased by about 2.5 fold, *i.e.*, from 22.6 to 57.3 g. The rapid BMC gain occurred over 4 years (\pm years around menarche), *i.e.*, from 10.8 to 14.8 years, in agreement with previous data obtained for spine aBMD or BMC gain in healthy girls (15).

The Relation Between Bone Growth and Anthropometric Variables (Fat and Muscle Mass)

The adjustment of skeletal traits, whether aBMD or BMC, by anthropometric variables, particularly standing height and body weight, has been advocated during growth although it can result in spurious interpretation. Note that once PBM is attained, it has been shown, in young healthy adults of either gender, that adjustment by standing height minimally reduces the variance of aBMD, BMC or bone size measured at the lumbar spine level (20). Body weight adjustment would rely on the theoretical notion that optimal bone mass should be adapted to body weight and/or to lean mass in relation to the impact of gravity and/or muscle strength on bone modeling and remodeling. However, as an example, by applying such body weight or lean mass adjustment in the case of young adult females who suffered from anorexia nervosa, the marked decrease in aBMD or BMC with increased fragility fracture risk (21) would appear erroneously normal or even as having a largely positive T-score. Likewise, whereas PBM is lower in females than in males, contributing to the gender difference in fracture risk in later life, a 10% greater total body BMC to lean mass ratio in young adult females compared to males was found (22). According to the authors this greater ratio would support the theory suggesting that in girls an excess of bone accrual during pubertal maturation would supply a bone mineral "reserve" for reproductive needs in adult females. However, the notion of a "reserve" should correspond to an absolute amount of bone mineral, and not to a ratio related to lean body mass.

In several other reports, standing height, body composition including fat and lean mass, and pubertal stages were analyzed in relation to bone mass and structure acquisition either in healthy female and male subjects (23-26) or in various pathologic conditions (27-29). There are two main objectives for undertaking this kind of analysis. One aim is to discover in healthy subjects some physiologic/biochemical link between fat tissue or skeletal muscle mass/strength and bone accrual, assuming

that bone is under the influence of either adipocyte-produced cytokines and/or skeletal muscle mechanical forces. In these kind of studies, purely statistical associations are sometimes considered as causal relations, and not merely as platforms for hypothesis-driven research.

The Influence of Physical Activity on Bone Mass and Structure Acquisition

Several reports also confirmed the positive impact of physical activity on bone mass and structure acquisition by using mainly DXA and/or pQCT technology. Intervention programs were tested in early childhood (30), prepubertal children (31-33), adolescents (34-36), in both children and adolescents (37), or in young men between 19 and 24 years of age (38). The impact of mechanical loading in relation to sexual maturity of female subjects was also evaluated, for both BMD and geometry at the radius (39) and lumbar spine levels. Interestingly, in females, gymnastics during growth was associated with greater lumbar vertebra width (40), a morphologic feature compatible with greater resistance to loading. Another report highlighted the importance of menstrual cycle history as compared to body fat or leptin for predicting lumbar spine and hip aBMD in exercising young (18-35 years of age) women (41).

The Influence of Nutrition on Bone Mass and Structure Acquisition

As compared to the marked interest in the impact of physical activity, there were very few reports on the influence of nutrition. Calcium balance studies represent one important approach to estimating calcium requirements in various categories of subjects (42). The calcium intake level at which body retention of calcium reaches a maximal value reflects the amount required to fulfill the calcium needs of the body. It was reported to be the major predictor of calcium retention both in girls and boys 10-15 years of age (43). Adequate building of the skeleton during growth is essential for bone health in adulthood (44). In keeping with this notion, adolescent calcium and vitamin D intakes were significantly

associated with hip and spine aBMD/BMC in young adult or middle-aged women (45).

A Positive Interaction Between Nutrition and Physical Activity

A significant positive interaction on bone mass acquisition between nutrients like calcium (46) or proteins (47) and physical activity has been documented previously. The period before the onset of pubertal maturation appears to be an opportune time to swing upward the bone growth trajectory and thereby increase PBM. In support of this notion, the positive influence of relatively high protein intake on the impact of physical activity observed before pubertal maturation in boys aged 7.4 years can be monitored unabated at the age of 15.2 years with regard to bone mass and structure measured by DXA at the femoral neck and by HR-pQCT at the distal tibia (48). Furthermore, this positive interaction of protein intake and physical activity was also expressed in terms of bone strength as a significant increase in stiffness and failure load as assessed by micro-finite element analysis (μ FEA) of the distal tibia (48).

The Influence of Vitamin D on Bone Acquisition

There is worldwide interest in how adult vitamin D status is related to fragility fracture risk (49). Several presentations indicated similar interest with regard to bone growth, in studies carried out in children and adolescents living in several regions of the world, including Argentina (Ushuaia, a city localized at 55° South) (50), Japan (51), Finland (52) and Saudi Arabia (53). A high prevalence of vitamin D deficiency with cases of rickets was found in Japan (51). Vitamin D insufficiency (defined as a serum 25(OH)D level below 50 nmol/L) was frequent in healthy Finnish children and adolescents (52). In Saudi Arabia, vitamin D insufficiency was more frequent in girls than in boys, probably because of the traditional female dress code (53). In subjects living in Ushuaia, prevention of vitamin D deficiency or insufficiency (mean 25(OH)D: 32.5 nmol/L) could be achieved by administration of 100,000 IU of vitamin D₂ or D₃, three times a year (50). None of these studies

related the level of circulating 25(OH)D to bone mass and structure.

Studies in adults have documented a positive relationship between circulating levels of 25(OH)D and intestinal calcium absorption (54). Such a relationship was not found in children with adequate calcium intake (55). Counter-intuitively, in Nigerian children with calcium-deficient rickets or in healthy children on a low calcium intake, there was no positive relationship between fractional calcium absorption and the concentration of serum 25(OH)D (56). The reason underlying this difference between children and adults remains to be elucidated.

The Relation Between Bone Mass and Structure and Fracture Risk During Childhood and Adolescence

Fractures during childhood and adolescence may reflect either a transient fragility phenomenon related in time to peak height velocity (PHV) during pubertal maturation, or an early expression of reduced mechanical resistance that will persist and thus increase the risk of osteoporosis in later life; these two possibilities are not mutually exclusive. This issue is still confounded by the non-negligible role that high impact trauma can play in childhood fractures. Similar to the 2009 Annual Meeting of the ASBMR, findings on this topic were discussed in several papers (57-60).

One report in young adult women with a mean age of 20.4 years supports the concept that fractures occurring during childhood and adolescence could be a hallmark of lifelong bone fragility (57). DXA-measured aBMD is decreased at the radius and to a lesser extent at the proximal femur in fracture as compared to non-fracture subjects. This was associated with lower trabecular and/or cortical thickness at the distal radius and tibia as assessed by HR-pQCT. In keeping with this deficit, decreased bone strength, as assessed by μ FEA with simulation of an axial compression, was documented at the distal radius and to a lower extent at the distal tibia (57).

In a large cohort of young men with a mean age of 24 years, trabecular BV/TV resulting from reduced trabecular number, as assessed by distal radius HR-pQCT, was more strongly associated with prevalent forearm fracture than DXA-measured forearm aBMD (58).

In growing girls aged 8-13 years (59) and adolescent males aged 15.2 years (60), other studies using pQCT also indicated an increase in relative fracture risk associated with reduced trabecular vBMD and/or trabecular number at the distal tibia (59;60). Furthermore, evidence was provided for an intrinsic component of skeletal fragility as assessed by distal tibia μ FEA (60). This biomechanical deficit assessment by μ FEA provides more direct evidence of reduced bone strength than that suggested from densitometry and structure measurements by DXA and HR-pQCT.

Thus, these 4 studies carried out in healthy female and male subjects strongly suggest that all fractures occurring during growth or in young adulthood are not merely due to transient fragility during puberty or to high-impact trauma. Some probably reflect an intrinsic structural deficit that may persist, thus increasing the risk of osteoporosis during adult life.

Finally, in relation to momentary bone fragility, circulating sclerostin, an osteocytic factor that inhibits bone formation, was found to be correlated to the transient increase in cortical porosity during pubertal maturation, and interestingly at the time of maximal forearm fracture (61).

The Timing of Pubertal Maturation

Several studies have shown that late menarche is associated with lower PBM with reduced femoral aBMD and tibial vBMD in young adult and middle-aged women (62) and increased risk of fragility fractures at several skeletal sites in later life (63-65). Later pubertal timing is predictive of low PBM and increased risk of fracture in young adult men (66). The importance of pubertal timing as a predictive factor of bone mass in young adulthood was confirmed in a

multicenter study in both genders (67), but only in females in another report (68).

Oral Contraceptives and Bone Acquisition

There is concern that use of oral contraceptives (OC) in adolescents, *i.e.*, before PBM attainment, could reduce bone mass accrual at skeletal sites relevant to adult osteoporosis. A 24-month prospective study aimed at testing the dose effect of ethinyl estradiol (EE) used as an OC suggests that 30-35 mcg but not < 30 mcg is associated with reduced bone accrual at the spine level in 14-18-year-old adolescents. In this age category, total hip accrual was minimal and was not affected by EE, regardless of dose (69). Furthermore, in young women aged 19-30 years, when PBM is attained, spine and hip aBMD values remained unchanged over the 24-month observation period in EE users as well as in non-users.

Pediatric Diseases

Regarding treatment of pediatric bone disorders, a very innovative approach was taken regarding the treatment of hypophosphatasia (HPP), a disease characterized by low serum alkaline phosphatase with accumulation of inhibitors of mineralization such as pyrophosphate (70). In a phase II study carried out in 13 HPP patients aged 5-12 years, a quite promising beneficial effect of enzyme replacement therapy was obtained for radiological and clinical signs of rickets, by using bone-targeted tissue-non-specific alkaline phosphatase. In anorexia nervosa, a combination of gonadal (HRT) and adrenal (dehydroepiandrosterone, DHEA) steroid replacement therapy may have a beneficial effect on femoral shaft but not femoral neck cross-sectional geometry (71).

Other reports provide new insight into the characteristics of pediatric bone disorders, particularly in patients with primary osteoporosis (72), cancer (73), or treated with glucocorticoids for chronic illnesses (74), or still suffering from Legg-Perthes disease taken, interestingly, as a model of unilateral reduced mechanical loading (75).

Finally, in infants presenting with multiple unexplained fractures, a study considered the risk of an erroneous diagnosis of child abuse when rather a defect of bone mineralization could explain the condition (76).

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