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MEETING REPORT

Meeting Report from the 29th Annual Meeting of the American Society for Bone and Mineral Research

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BONE ACQUISITION AND PEDIATRIC BONE

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Childhood and Adolescence – Critical Periods for Bone Development

A continual struggle in pediatric bone research is how best to control for individual variability in growth and maturation. In prospective studies spanning the adolescent growth spurt, multi-level modeling techniques can be applied to compare children according to biological age (years from age at peak height velocity). At this year's ASBMR meeting, results from the longest follow-up study of bone mineral accrual, which were generated using such modeling techniques, provide further evidence that the adolescent growth period is crucial for skeletal development, as more than 98% of bone mineral is accrued by 4 years beyond the age of peak height velocity (PHV) (1). Although up to 40% of total body bone mineral is accrued in the 2 years before and 2 years after PHV, the post-adolescent period also influences skeletal development as a further 18% of adult bone mineral is laid down during this time.

It is a common assertion that sex differences in fracture risk are determined, in part, by sex differences in bone mass and strength that emerge during growth. However, questions remain as to when this sexual dimorphism emerges and what factors influence the magnitude of the difference in bone parameters between boys and girls. Data from Australian twins suggest that boys have greater bone mass and periosteal width (by DXA) than girls in prepuberty (2). Similarly, at the tibia, pQCT outcomes are greater in boys at both the metaphysis and diaphysis in prepuberty (3), although greater muscle cross-sectional area in boys may explain this difference at the tibial shaft. Together with previously published pQCT findings at the tibia in prepubertal children (4), these findings challenge the traditionally held belief that sexual dimorphism is driven only by differences in sex hormones that become more apparent in early puberty.

Another common notion, based on the early work of Stanley Garn and colleagues (5), is that increasing levels of estrogen in girls leads to greater endosteal apposition compared with boys. Prospective pQCT data for the tibial shaft (6) challenge this theory, as do previously published pQCT results on the same cohort (7). However, pQCT data for Finnish girls suggest a negative relationship between time relative to menarche and area of the marrow cavity, suggesting increasing endosteal apposition with advancing maturity (8). Thus, it appears this theory is still up for debate.

Is Dietary Protein a Friend or Foe of Bone Mineral Accrual?

Calcium took a back seat to dietary protein intake at this year's meeting. Two abstracts reported associations between dietary protein and bone mass by DXA. In Chinese girls, there is a negative relationship between BMC accrual over 5 years and protein intake (9). In contrast, cross-sectional data on Swiss boys (mean age 7 years) indicated a positive relationship between BMC and protein intake (10). Further, high levels of protein intake in combination with high levels of physical activity were associated with greater BMC

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than that observed in boys with high physical activity but low levels of protein intake. The discrepancy in these findings is likely related to dietary calcium intake, which was low among the Chinese girls (~440 mg/day) compared with the Swiss boys (~750 mg/day). Thus, the calcium-protein ratio was lower among Chinese girls, and this may have a negative effect on bone accrual (due to higher levels of calcium excretion). Further investigation of these relationships is required in prospective cohort studies and randomized controlled trials.

Moving Beyond Standard pQCT Analyses

As researchers become more knowledgeable in the assessment of bone geometry with pQCT, it is not surprising that this modality is being used to address more specific questions relating to skeletal development. However, often additional software is needed (other than the standard Stratec software) to answer these questions. One abstract (11) presented pQCT results that were obtained with the free NIH software ImageJ in combination with customized macros. Bone bending strength (Imax) at the tibial shaft increased significantly more in boys who participated in a school-based physical activity intervention (11). Two abstracts presented pQCT data analyzed with Bonalyse software that described changes in the distribution of bone material at the tibial midshaft during growth and how these changes influence bone bending strength (Imax, Imin) (12;13). Although an individual's skeletal structure is largely genetically predetermined and is thus established before puberty (13), adaptation to loading occurs throughout growth and appears to differ between sexes such that boys demonstrate greater increases in bone bending strength compared with girls.

Although standard pQCT offers many advantages over DXA technology, it lacks the resolution to evaluate trabecular microstructure and to obtain accurate measures of cortical thickness at metaphyseal sites. At this year's meeting, the first high-resolution pQCT data for children and adolescents were presented (14). Across puberty in girls there were minimal changes in trabecular microstructure (i.e., bone volume/total volume, trabecular thickness) at the distal radius. In contrast, a transient decrease in cortical thickness was apparent during puberty, and this decrease mirrored the temporary increase in forearm fractures that was previously reported in this population (15).

Physical Activity During Growth – Do the Benefits Persist?

The age-old question in studies of physical activity and pediatric bone is whether the benefits of intervention persist once the stimulus is removed. At this year's meeting, the longest follow-up data from a school-based trial were presented (16). The BUGSY study (Building Growing Skeletons in Youth) found that almost 8 years after completion of the jumping program, children who were in the intervention group maintained a 1.4% advantage in total hip bone mineral accrual compared with the control group. The question is now whether this skeletal advantage will be maintained into adulthood.

There also appears to be some debate on whether general physical activity has a sustained effect on bone mineral accrual. Data from the Finnish Calex Study (17) indicate that over almost 7 years of follow-up, the significantly higher BMC in high-active compared with low-active girls observed after 2 years was no longer apparent, suggesting that the benefits of physical activity during puberty may be temporary. In contrast, when multi-level modeling techniques were applied to data from the UBC Healthy Bones Study (18) to account for variability in growth and maturation, leisure-time physical activity was found to be a significant predictor of bone mineral gain over 7 years at the femoral neck and total proximal femur in girls and boys, respectively.

The Muscle-Bone Relationship

At the last several ASBMR meetings, a focus within the pediatric abstracts has been the muscle-bone relationship and how this relationship changes during growth and

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differs between sexes. This theme continued at the 2007 meeting. In cross-sectional and longitudinal studies, muscle cross-sectional area (MCSA, by pQCT) and lean mass (by DXA) were consistently identified as predictors of bone geometry, strength and bone mass (3;8;13;19-21). Interestingly, growth in bone width (total cross-sectional area) precedes growth in MCSA in Finnish girls. This finding does not agree with previous longitudinal data showing that the peak in lean mass precedes the peak in bone mineral accrual (22). Further, it appears that lean mass by DXA may not fully account for skeletal loading associated with physical activity. Even after adjusting for differences in arm lean mass, gymnasts have greater pQCT-estimated bone strength at the radius compared with non-gymnasts (23). What is not clear is whether similar results would be obtained with pQCT-derived measures of MCSA or more functional measures of muscle force and power.

Muscle-bone indices are also useful indicators of bone development in clinical populations (24). In adolescent girls with Type I diabetes, the ratio of tibia BMC to MCSA is lower than that of healthy girls, suggesting a possible "bone-muscle disconnect" in this clinical group due to compromised bone mineral acquisition (25). In contrast, muscle-bone indices (by MRI) in children with cerebral palsy were not significantly different from healthy controls, suggesting that bone strength is adapted to muscle force in this group despite an inability to ambulate independently (26).

Bisphosphonate Therapy for Pediatric Patients with Low Bone Mass

Evidence-based recommendations for bisphosphonate therapy in pediatric groups with low bone mass, other than those with osteogenesis imperfecta, are not well-established (27). Two abstracts presented results demonstrating the efficacy and safety of intravenous pamidronate (28) and oral alendronate (29) in pediatric patients with glucocorticoid-induced osteoporosis. A concern of bisphosphonate use in the treatment of bone disorders is the reported relationship between bisphosphonate therapy and osteonecrosis of the jaw (ONJ) in adults (30). The question is whether bisphosphonates have similar effects on the jaw in pediatric patients. The answer appears to be no, as long-term pamidronate exposure was not associated with any cases of ONJ in a large cohort of pediatric patients (31). It may be that oral hygiene is better in pediatric patients as this is highlighted as the primary preventive strategy for ONJ (30).

In summary, the pediatric abstracts at this year's meeting highlight both how far the field has come in a short time and also how much we have still to learn. The expanding use of pQCT and other imaging modalities and software applications to investigate bone geometry and strength indices is encouraging and helps to further our understanding of skeletal development in both healthy children and in clinical groups.

Conflict of Interest: None reported.

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