

COMMENTARIES

Growth-Related Cortical Fragility at Metaphyseal Regions

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Commentary on: Kirmani S, Christen D, van Lenthe GH, Fischer PR, Bouxsein ML, McCready LK, Melton LJ 3rd, Riggs BL, Amin S, Müller R, Khosla S. Bone structure at the distal radius during adolescent growth. *J Bone Miner Res.* 2009 Jun;24(6):1033-42.

About one in three childhood fractures involve the distal radius (1). The incidence of these fractures is highest around the time of peak height velocity (2). Several investigators have reported that growth in the length of the radius reaches its peak velocity before mineral accrual reaches its peak and have suggested that this dissociation between longitudinal growth and mineral accrual contributes to bone fragility during growth (3). The structural consequences of this dissociation were explored recently by Kirmani *et al.* (4). These investigators report that there is a transitory increase in intracortical porosity and cortical thinning during the pubertal growth spurt, features likely to contribute to the transitory increase in skeletal fragility in peripubertal children. On the other hand, there were few differences in trabecular structure across the stages of pubertal maturation.

The tempo of growth of the axial and appendicular skeleton varies before and during puberty. Growth velocity in crown-heel length is most rapid shortly after birth and slows precipitously during the first year of life. During the prepubertal years appendicular growth in length is similar in boys and girls and proceeds at twice the velocity of axial growth (5). At puberty, appendicular growth decelerates while axial growth accelerates (6). This deceleration in appendicular growth occurs earlier in girls than boys because of their earlier puberty and accounts for the shorter appendicular (arm and leg) length in girls than boys (7). The sex differences in appendicular length

are thus largely the result of the longer duration of prepubertal growth rather than sex differences in the velocity of growth and reflect the differing regulation of growth of the axial and appendicular skeleton, a neglected area of research.

A fascinating aspect of growth is that lengthening of a long bone does not occur equally at each growth plate (8;9). At the radius, growth is more rapid at the distal than at the proximal growth plate. About 90% of the longitudinal growth of the radius occurs at the distal growth plate, while the remaining 10% occurs at the proximal growth plate. At the tibia, growth is more rapid at the proximal than at the distal epiphysis; the distal growth plate contributes only 30% of tibial elongation during puberty (8;9).

The apparent volumetric bone mineral density (vBMD) of a bone is determined by the external volume as defined by the periosteal envelope and the amount of bone mass within it (10). Both the absolute increase and relative increase in these two traits contribute to the apparent vBMD. If the external volume of a bone increases (by periosteal apposition) more rapidly than the net amount of bone deposited within the expanding periosteal diameter (by periosteal apposition and endocortical apposition or resorption), the apparent vBMD will decline. This occurs at the rapidly growing distal end of the radius (11).

Kirmani *et al.* report that total cross-sectional area of the radius increased rapidly with advancing age in both sexes but cortical

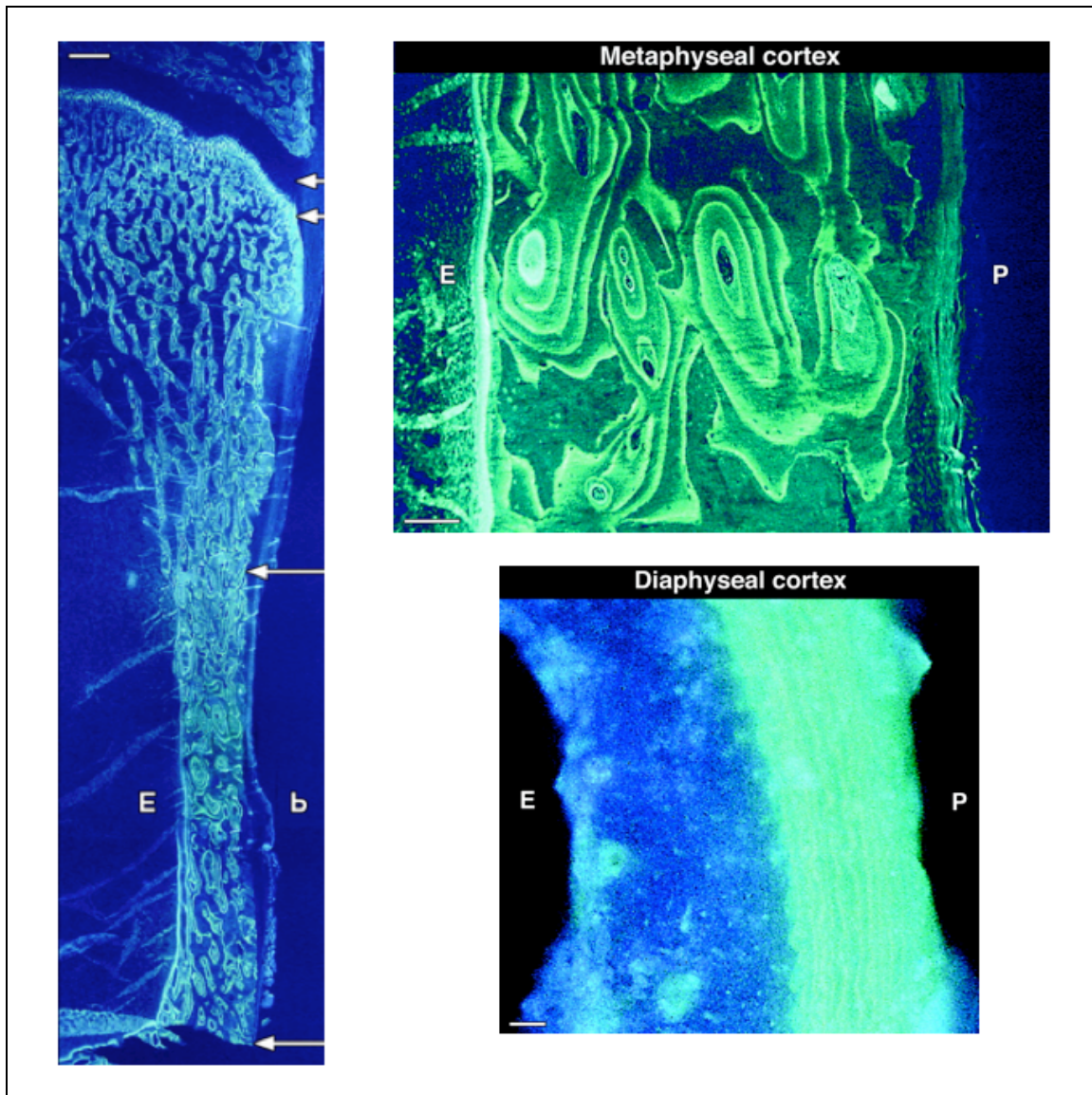


Fig. 1. Comparison of fluorescent histomorphometry, in the rabbit femur (left), between the cortices at the metaphyseal (top right) and diaphyseal (bottom right) regions. The cortices at the metaphyseal region are formed by trabecular coalescence leaving unfilled pores between trabeculae and increasing cortical porosity during rapid growth. In contrast, the cortices at the diaphyseal region are formed by periosteal apposition, with no pores left unfilled. From Cadet *et al.* Mechanisms responsible for longitudinal growth of the cortex: coalescence of trabecular bone into cortical bone. *J Bone Joint Surg Am.* 2003 Sep;85-A(9):1739-48, used with permission (12).

thickness decreased in girls and remained unchanged in boys from Tanner stage I to III and then increased in both sexes while trabecular thickness and number changed a little, if any, in both sexes during puberty (4). As a result, the total volume of the metaphysis of the distal radius occupied by cortex, and thus the proportion of load borne by the cortex decreased transiently during mid- to late puberty in both sexes. In addition, cortical porosity increased in mid-

puberty, more so in boys than girls, although not significantly so.

The mechanism responsible for the transitory increase in porosity has been examined by Cadet *et al.* (12). In this illuminating study of the longitudinal development of cortical bone in rabbits, the cortex at the metaphyseal region was shown to be formed by coalescence of trabeculae arising from the growth plate (Fig. 1). This

condensation of trabeculae occurs as bone formation on their surfaces causes them to coalesce to form cortex.

At sites of rapid longitudinal and radial growth, we suggest that apposition on trabecular surfaces does not 'keep up,' resulting in intracortical porosity (13). The porosity and fragility is transient because growth in length slows, allowing trabecular consolidation by bone formation to go to completion and thus to 'catch up'. Using micro-CT, Tanck *et al.* have reported higher cortical porosity in the metaphyseal region nearer the growth plate than what is observed more proximally adjacent to the diaphysis (14). As trabeculae adjacent to the endocortical surface coalesce, periosteal resorption produces cortical thinning and in-wasting to allow the metaphysis and diaphysis to 'fit' together. By contrast, cortical bone at the diaphyseal region is formed by periosteal apposition.

The pattern of growth of trabecular bone was different by sex. Trabecular vBMD remains unchanged from 5 years of age to young adulthood at the metaphyses of the distal radius and tibia in girls but increases in boys during puberty (15;16). The increase is the result of thickening of existing trabeculae in boys but not in girls. Trabecular number remained unchanged (4). The factors regulating trabecular thickness in boys and girls remain uncertain.

While transitory bone fragility is likely to be determined by this temporary dissociation in growth during puberty, the structural features present before puberty are likely to contribute as well. Children with upper limb fractures have reduced total vBMD of the distal radius before, during and after puberty, and this difference in vBMD in children with and without fractures is detected before the fracture as well as in young adulthood, suggesting the deficit in bone structure in children may be present before puberty and is exacerbated by the dissociation between longitudinal growth and mineral accrual during puberty (17).

Kirmani *et al.* also report that PINP and CTX correlated inversely with cortical vBMD and positively with cortical porosity, suggesting

that rapid bone turnover produced an unfavorable bone structure. Slemenda *et al.* have reported that high levels of tartrate-resistant acid phosphatase (TRAP) were associated with low aBMD of the spine, proximal femur and radius throughout puberty and explained the difference in aBMD between Caucasians and Blacks (18). Evidence from twin studies suggests that genetic factors influence the variance in rates of bone remodeling (19;20), the purpose of which is two-fold, one being to assemble a bone of appropriate size but the second to excavate that bone to minimize its mass from very early in life (21).

Region-specificity of growth and development of bone structure exists elsewhere. In the transiliac bone biopsy, cortical and trabecular thickness increases while trabecular number remains constant from 1.5 years of age to young adulthood. Lateral modeling drift of the iliac inner cortex (enlarging pelvis) is produced by the coalesced trabeculae at the endocortical surface, while the cortical trabeculization occurs at the endocortical surface of the outer cortex moving the medullary cavity outward (22).

Kirmani *et al.* now provide the structural basis of the transitory bone fragility accompanying growth and this partly explains the increased fracture incidence of the distal radius during puberty. Decreased cortical thickness and increased cortical porosity despite enlargement of bone size produce a transitory deficit in cortical bone strength at the metaphyseal region at a time when vigorous activity of youth predisposes to falls. The transitory cortical deficit is due to delayed coalescence of trabeculae at the endocortical surface at the metaphyseal region, especially at sites of rapid growth, which probably is the result of dissociated longitudinal growth and bone mass accrual adding to the early established bone deficit.

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