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Histomorphometric evaluation of skeletal development

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During skeletal development, external bone shape undergoes marked changes through growth in length and in width. Whereas the former process has received a great deal of scientific attention, much less is known about bone growth in width. However, bone growth in width determines cross-sectional bone size, which is a major determinant of bone strength throughout life[1].

At a typical mid-diaphyseal site, a bone's cross-sectional size increases through the action of osteoblasts that add mineralized tissue on the outer (periosteal) bone surface, a process called periosteal apposition[1]. On the microscopic level, the periosteum consists of two readily distinguishable layers. The outer layer is mainly composed of fibrous tissue, the inner layer, called cambium layer, harbors osteogenic cells. These cells produce primary periosteal bone, which is later converted into secondary bone through a process called intracortical remodeling. At the same time, the endocortical bone surface may undergo resorption or formation, depending on skeletal location and developmental stage.

Fetal development

Only a few studies have examined the histology of human fetal bone development. However, it is well-established that by the start of fetal life (9th week post-conception), skeletal patterning is complete and the basic shapes of all bones are established. The skeletal soft tissue templates undergo ossification and growth, resulting in a dramatic increase in size, but only small changes in shape. For example, the femur increases 2.3-fold in length and 2.1-fold in mid-diaphyseal width during the second half of pregnancy, indicating that dimensional relationships change little[2,3]. Concomitant with the increase in bone size, the internal structure is modified. The average thickness of trabeculae in the proximal femoral metaphysis increases by about a third during the second half of gestation[4]. Cortical thickness at the femoral midshaft approximately doubles during the same period[2].

Postnatal development

Cortical bone

Histomorphometric studies of rib and iliac bone have yielded the expected result that periosteal bone formation is much more active in children than in adults[5-7]. However, there may be a more fundamental difference between periosteal bone metabolism in children and in adults. In children, bone formation is continuous, which is the hallmark of modeling[7]. In adults, periosteal bone may undergo cyclical resorption and formation, which is characteristic of remodeling[8].

It is clear that wider bones must have higher mid-shaft periosteal apposition rates, because this is how they become wider. For example, during male puberty the estimated peak periosteal apposition rate of the metacarpal is about 0.5 μm/day, but it is close to 2 μm/day at the mid-shaft humerus[1]. What is less widely appreciated is that periosteal growth is not necessarily synchronized between bones. For example, in 3-month-old babies, the humerus grows in width by a third faster than the femur[1]. At the age of one year, the two bones expand at about the same rate, whereas at 33 months of age periosteal apposition is almost four times as fast at the femur as it is at the humerus. At 5 years of age, this difference in periosteal apposition rate between the two bones has shrunk to 25% in favor of the femur. These differences in bone growth in width between the humerus and femur mirror the mechanical usage of these extremities during development between 1 and 4 years of age[1]. When infants start to walk, the femur is exposed to much higher forces and gets stronger quickly. At the same time, the humerus is used less and less for locomotive purposes and, accordingly, humerus strength increase is slow.

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The situation at the usual site of bone biopsy, the ilium, is complicated by the fact that this bone undergoes a modeling drift in an external direction during growth[7]. This means that bone formation predominates on the periosteal surface of the outer cortex and the endocortical surface of the inner cortex, whereas resorption is more active on the endocortical surface of the outer cortex and the periosteal surface of the inner cortex[9]. As the modeling drift comes to a standstill after 14 years of age, the metabolic activity on the endocortical and periosteal surfaces of the two cortices become more similar.

Regarding intracortical remodeling, very little is known about this process during human bone development. We examined transiliac bone samples from 56 individuals between 1.5 and 22.9 years of age who did not have evidence of metabolic bone disease[10]. Parameters of osteonal structure (osteon diameter, wall thickness, diameter of osteonal canals) and dynamic measures of intracortical remodeling were determined separately for the external and internal cortex. We found that measures of osteonal structure were independent of age. However, the percentage of osteons showing metabolic activity was lower in the older study subjects, corresponding to a slowdown in the turnover of cortical bone. Most dynamic parameters of bone metabolism were higher in the internal cortex than in the external cortex. Cortical porosity was negatively associated with age on the external, but not on the internal cortex. The bone-forming activity that refills the remodeling cavities seemed to favor the side of the osteonal canal that faced towards the periosteum. These results suggested that intracortical remodeling activity varies markedly during bone development, and is slightly asymmetric between the two cortices of an iliac bone specimen. Remodeling during development is thus an age-dependent process that varies with location even within the same bone.

Trabecular bone

Studies using quantitative computed tomography at the lumbar spine have shown that volumetric bone mineral density (BMD) increases by about 25% during puberty[11]. What structural changes underlie this increase? Schematically, there are three ways to increase trabecular BMD. First, material density might increase. Second, there might be a rise in trabecular number, i.e., the trabeculae could be packed more closely together. And third, it is possible that trabeculae become thicker.

Roschger et al. found that material trabecular bone density in the L4 vertebral body increased by only 3% from 1 to 80 years of age[12]. Thus, material density does not appear to be a major contributor to changes in trabecular BMD during bone development.

Trabecular number, in histomorphometric terminology, reflects the number of trabeculae that a line through the bone would hit per mm of its length[13]. Trabecular number in the L4 vertebral body does not seem to increase between 10 and 20 years of age, which is similar to our results in the ilium[7,14]. Thus, both trabecular number and material density cannot account for the increase in trabecular BMD during puberty. By default, then, trabecular thickening must be the explanation.

Studies in the ilium indeed revealed an increase in trabecular thickness during bone development[7]. Similar to vertebral bodies, no change in trabecular number was found throughout the growing period. Dynamic histomorphometric measurements suggested that the increase in trabecular thickness was due to remodeling with a positive balance[7]. This means that during each remodeling cycle osteoblasts add more bone than was previously resorbed by osteoclasts. The difference is small, however, and only leads to a gain of a few μm of trabecular thickness per remodeling cycle. As in growing children, each location on the iliac trabecular surface undergoes a remodeling cycle every 9 to 10 months on average, remodeling with a positive balance results in a very slow and gradual increase in trabecular BMD.

Thus, in growing subjects, bone cell activity changes rapidly with age and differs markedly between bone surfaces.

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