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Title:
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Date:
2016-12-01

Citation:
Seeman, E. & Ghasem-Zadeh, A. (2016). Challenges in the Acquisition and Analysis of Bone Microstructure During Growth. Journal of Bone and Mineral Research, 31 (12), pp.2239-2241. https://doi.org/10.1002/jbmr.3015.

Persistent Link:
https://hdl.handle.net/11343/291904

LETTER TO THE EDITOR

Challenges in the Acquisition and Analysis of Bone Microstructure During Growth

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Journal of Bone and Mineral Research, Vol. XX, No. X, Month 2016, pp XXXX–XXXX

DOI: 10.1002/jbmr.3015

To The Editor

Gabel and colleagues[(1)] report sex and racial differences in distal tibial and distal radial microstructure. This was a mixed longitudinal study of white and Asian males and females aged from 9 to 20 years. The authors confirm that males grow larger bones than females. Cortical porosity was higher in males but there was no sex difference in cortical volumetric bone mineral density (vBMD), leading the authors to suggest, but not show, that cortical matrix mineral density may be higher in males. The findings are questionable given several methodological challenges we face studying growth.

First, assessment of bone microstructure is based on positioning a region of interest (ROI) of only 9.02 mm in length at the distal metaphysis of the radius and tibia.[(2,3)] In a longitudinal study, it is difficult to relocate the identical anatomical location in the same individual. In cross-sectional or longitudinal studies, it is difficult to know whether the same anatomical region has been chosen when individuals differ by sex or race and so differ in forearm and tibial lengths. In adults, a fixed distance from the joint line is chosen as beginning the 9.02 mm ROI (9.5 mm for radius and 22.5 mm for tibia).

This approach positions the ROI more distally in taller persons. Because cortical porosity is higher more distally, finding a higher porosity in males than females may be the result of positioning, not biology. Hence, taking a percentage of the length of a long bone is recommended in adults.[4]

Whether taking a percentage of the length of the radius and tibia is the correct approach when bone length is increasing rapidly during growth and at different rates at each growth plate is not known.[5,6] Growth of the radius occurs mainly at the distal growth plate so that the ROI first measured moves proximally. As the radius lengthens, using 7% of the lengthening bone moves that ROI proximally. However, if growth is nonlinear, it is unlikely that a fixed percentage of the lengthening bone will relocate the first ROI measured. The tibia initially grows equally at each growth plate so the first ROI at the distal metaphysis measured moves proximally. Later, most tibial growth occurs at the proximal growth plate so the ROI measured earlier moves distally but the subsequent ROI chosen using 8% percent of the increasing length moves proximally.

Differences in positioning of the ROI by even 1 to 2 mm may exaggerate or obscure microstructural differences between sexes and races, particularly at the distal radial metaphysis, a heterogeneous irregular rhomboidal structure. Cortical porosity and trabecular density are high distally and decrease in nonlinear fashion, often by over 50% within a few millimeters.[7] Positioning errors produce differences in microstructure that are the same order of magnitude as sex and racial differences reported when the positioning errors are corrected.

Second, males and whites enter puberty ~12 months later than their respective female and Asian counterparts so they have had more growth of the legs and trunk at the time of entering puberty. It is difficult to understand how an estimated measure of peak growth velocity of height controls for the longer prepubertal growth and so controls for "maturation."[8] Growth velocity of total height is highest at birth, it decreases precipitously then accelerates at 1 year of age because growth velocity of the legs, not trunk, increases and remains twice that of truncal growth until puberty when leg length decelerates and trunk length accelerates (Fig. 1, left panel). Peak height velocity is therefore driven by truncal growth but measurements of the appendicular skeleton at being taken. A later age at puberty in males and whites produces longer legs than in their

female and Asian counterparts, respectively.[9,10] A longer intrapubertal growth in males produces a longer trunk. Pooling whites and Asian (almost one-half the cohort) when comparing males and females adds to the difficulties. It remains plausible that sex and racial differences in height are the result of differences in the *duration* of prepubertal and intrapubertal growth in males and whites than females and Asians respectively, the rapidity of growth may not differ by sex or race.[11,13]

<Insert Figure 1>

Third, the authors report boys had higher porosity than girls but cortical vBMD was no different. They suggest, but do not show, that males may have higher matrix mineral density. Available evidence suggests the reverse is the case. The higher the porosity, the lower the matrix mineral density.[14] This inverse association is likely to be the result of the rapidity of remodeling; excavation of cavities increases porosity, refilling with under mineralized matrix reduces matrix mineral density. This inconsistency signals the likelihood that there are errors in segmenting cortical and trabecular bone using thresholding and then calculating porosity in a cortex that is probably erroneously estimated.[15,16]

During growth of the distal radial metaphysis, trabeculae arising from the periphery of the growth plate coalesce ("corticalize"), forming the cortex by endochondral apposition (Fig. 1, middle panel).[17,18] Longitudinal growth of the distal radius is rapid and transiently out paces osteoid apposition upon trabeculae so coalescence is delayed producing a transiently porous cortex. At a pixel size of 82 µm and a spatial resolution of about 100 µm, pixels containing incompletely coalesced trabeculae abutting against cortex may be registered as "cortical" bone and so overestimate "cortical" thickness (Fig. 1, right panel). When porosity is calculated, the intertrabecular void may be erroneously included, leading to an overestimate of "cortical" porosity. Alternatively, porosity may be underestimated if mineralized matrix in a voxel containing part of a pore increases photon attenuation above the threshold designated to identify porosity.

Measurement of bone density using bone densitometry was a good beginning. Young investigators growing up under the shadow of the two-dimensional "areal" projection of a three-dimensional structure are unlikely to think about the morphological

basis of bone fragility. Measurement of bone microstructure using high-resolution image analysis is changing the cerebral silence. However, this technology is not trouble-free press-button motoring. Understanding the microstructural changes that accompany growth, aging, and drug therapy requires attention to the challenges we face in image acquisition and analysis.[19]

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Figure caption

Fig. **1**. (Left panel) Growth velocity of the total body length decelerates after birth then accelerates at 1 year of age due to acceleration of the growth of the legs. Truncal growth accelerates at puberty. Males have a longer prepubertal and intrapubertal growth period than females. (Middle panel) Metaphyseal trabeculae coalesce to form the metaphyseal cortex.[17] (Right panel) Incorrect segmentation of trabecular from cortical bone may result in this being “seen” as cortical bone.