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Scaling and adjusting growth-related data and sex-differences in the muscle-bone relation: A perspective

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Lengths, areas, volumes, mass and how they grow

Children come in all sizes and we sometimes compare the size or shape of shorter ones with taller ones, or even with adults. Growth charts for height (cm, one-dimensional) and weight (mass in kg, three-dimensional) guide health professionals in these comparisons. To maintain optimal shape and biomechanical competence, the body must keep the relationship of growth in bone width, areas, mass and volume in proportion/isometry relative to growth in bone length. This is essential since, for example, growth in bone length and width have opposing effects on bone strength[1]. Little is known how the body co-ordinates these different growth processes. Pitfalls occur when we attempt to compare growth rates of variables with different geometric dimensions, as the majority of growth-related variables (cross-sectional areas, mass, volumes, etc.) are not one-dimensional but of greater geometric dimension.

Growth and percentages

The observation that only ~30% of adult bone mineral content (BMC=bone mass, kg) but ~70% of adult bone length (cm) is attained before puberty has led to speculation about a deficit in bone mass relative to length and resulting fracture susceptibility[2,3]. However, the use of percentages of unscaled variables with differing geometric dimensions may lead to erroneous conclusions about the timing of bone growth in length, diameter and mass. Using small and large cuboids (with similar relationship [isometry] between length and width) as examples for a growing human long bone, it is evident that increments in one-dimensional length or width result in much greater increments in cross-sectional areas and even greater increments in volume and mass, simply as a mathematical necessity (see Figure 1). Therefore, it is not surprising that the weight (mass, kg) and height (cm) of a normally growing 8-year-old child correspond to ~30% and ~70% of the respective adult values. Any percentage comparison of variables with different dimensions therefore requires dimensional/geometric scaling.

Growth and dimensional scaling

Mammalian limb bones scale close to geometrical similarity with body size[4]. Surprisingly, only a few studies have investigated the allometric relation of body measures in humans[5-8] and hardly any such studies were done in growing children[9,10]. To demonstrate dimensional scaling of growth-related data, we compared the percentage attainment of adult values for determinants of femoral strength in pre-pubertal children. Femur length, mid-shaft diameter, cortical thickness (*all one-dimensional*), total (TA), cortical (CA), medullary bone areas (MA) and muscle area (*all two-dimensional*), BMC (*three-dimensional*), and cross-sectional (I_{max}, I_{min}) and polar (I_p) moments of area as well as bone strength index (BSI) (*all four-dimensional*) were measured at the proximal (66%) mid-shaft using magnetic resonance imaging and densitometry combined, in 145 subjects (6-25 years, 94 females). Dimensional

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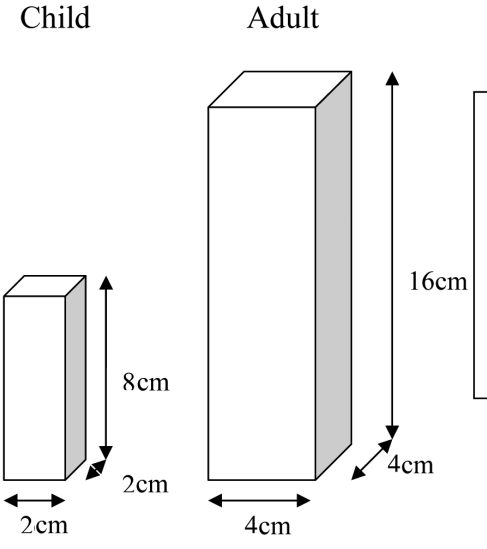

SCALING
% of Adult Value

	Unscaled	Scaled
Width (cm)	50	50
Length (cm)	50	50
Area (cm^2)	25	50
Volume (cm^3)	12.5	50
Mass (g)	12.5	50

Figure 1. Illustration of scaling effects. The cuboids are meant to represent two simplified long bones that have the same relationship between length and width, and are filled with the same material. Expressed as a percentage of the larger ('adult') bone, results in the smaller ('child') bone are lower for variables of higher dimension. Allometric, dimensional scaling eliminates these purely geometrical differences. Mass is regarded as a three-dimensional measure, as it is directly dependent on volume.

scaling was performed by raising two-, three- and four-dimensional variables to the power of 1/2, 1/3 and 1/4, respectively. While unscaled percentages of adult value were lowest for variables with highest dimensions (and highest for variables with lowest dimensions) before puberty, scaled percentages coalesced to 65-80% of adult values in both sexes.

Growth, functional adjustments and sex-differences

Not surprisingly, upper limb bones develop differently from lower limb bones between sexes in terms of bone elongation, and periosteal as well as endocortical expansion[11-13]. More specifically, in boys MA expands in both upper and lower extremities, but in girls MA does not expand at the radius[13] but does expand at the femur[11] and tibia[12]. To assess sex-differences in limb bone development, functional adjustments are necessary. One way is to adjust long bone measures purely geometrically, e.g., diameter/areas/mass/volumes etc. for bone length. However, such geometric adjustments must include dimensional scaling, e.g., bone length in the appropriate dimension[8], e.g., areas are adjusted for bone length^2, mass or volume for bone length^3. If variables grow in isometry, then such adjustments will create linear relationships on regression curves. Another way is to take the prevailing mechanical loads (e.g., mass and moment arm=bone length) into account, e.g., bone variables are usually adjusted for weight and bone length, following the beam theory. A third way of adjustment is to adjust for muscle force (or size as a surrogate for force), since during growth, bones constantly adapt to mechanical forces and the largest forces on the skeleton are due to muscle contraction[14,15], not weight. Apart from selecting an adjustment approach that suits the research question asked, there is still a good deal of preference or belief as to which of these, or other similar, adjustments are considered "optimal" or "correct". In general, applying any of these three adjustments approaches in pre-pubertal children results in usually no, or only marginal, sex-differences in bone or muscle variables. However, in young adults, results differ between sexes. We have applied all three adjustment approaches for our study at the mid-femur, which showed greater adjusted TA, CA, diameter, I_{max}, I_{min}, I_p and BSI (1-10%) in young adult men than women with the greatest sex-difference in muscle area (20%). Adult women attained less TA and CA in absolute terms and relative to femur length (as well as femur length and weight), but greater TA and CA for muscle area. These results, as well as bone/muscle relations calculated from a study at the distal tibia[16], suggest that women have a greater total cross-sectional bone area per unit muscle area than men. In contrast, studies at the forearm have shown that outer bone circumference per unit muscle area is similar between postpubertal males and females[17]. Therefore, not only is the method of adjustment debatable, but also the unifying hypothesis that larger muscles lead to a proportional increase in bone mass or size[18].

Hormone-induced changes in biomechanics — Integrated bone development

Dimensional scaling and functional adjustments are necessities when it comes to sex-comparisons of growth-related data. But there is more to consider. Hormones are blind to structure and X and/or Y chromosome presence may alter bone growth

not only due to resulting hormonal differences. In addition, hormones do not act on bone tissue in isolation. Rather, bone tissue must integrate a variety of signals that result from mechanical loads, hormones, and a multitude of other sources. For example, female puberty results in a widening of the transverse pelvic diameter[19]. A wider pelvis corresponds to a larger distance between femur and body mass centre, thus increasing the bending forces on the femur shaft during the single stance phase of a gait cycle. Greater forces are expected to lead to more periosteal apposition. Indeed, it is well documented that females have a relatively larger mediolateral diameter of the femoral diaphysis than men, which would compensate for the higher bending forces that act in the same direction[20]. Thus, it is possible that the sex- and site-specificity of the muscle-bone relationship, particularly in the lower limbs, is at least partly due to the anthropometric changes that come with puberty. Young adult women have attained narrower femora, less bone strength and muscle size than men in absolute terms as well as relative to femur length and weight, but they have wider femora and also a higher bone mass relative to muscle size[21-23]. These seemingly discrepant sex differences are likely to result from a combination of direct and indirect effects of the hormonal changes occurring during puberty.

On the timing of bone and muscle development and fracture risk

There is no obvious deficit in growth in femoral length and diameter relative to mass and strength before puberty once variables are dimensionally scaled. The assumption that bone fragility may originate during growth cannot be based on percentage comparisons of unscaled variables with different dimensions. During puberty, maximal BMC accrual rate lags behind peak muscle accretion rate and peak growth velocity[9,24-26]. Thus, bone elongation and muscle enlargement precede strain-induced periosteal expansion and modeling to some extent. This may be another possible explanation for the high pubertal fracture rate[27], in addition to the puberty/hormone-induced increase in risk-taking behavior.

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