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Review Article

Hylonome

Examining the developing bone: What do we measure and how do we do it?

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Abstract

The clinical tools available to evaluate bone development in children are often ambiguous, and difficult to interpret. Unfortunately bone densitometry methods (i.e., dual energy X-ray absorptiometry, DXA) which have a relatively straightforward application in adult osteoporosis, are far more difficult to evaluate in the growing skeleton. Even with adequate "adjustment" for bone size or maturity, bone "density" (areal or volumetric) alone often gives an inaccurate assessment of bone strength – especially in children. Ideally, we would like to measure both material and geometric properties of bone to accurately estimate "strength". Mechanically meaningful measures of bone geometry (bone cross-sectional area, cortical thickness) and estimates of bending strength (section modulus, or SSI) are available with non-invasive techniques such as (p)QCT and some DXA software. With new technology it might be possible to also measure bone material properties, which will be especially important in some pediatric disorders. In children, we also need to know something about the loads imposed on a child's bone and consider not only absolute bone strength, but also the strength of bone relative to the physiologic loads. Interpreting bone strength in light of the loads imposed (particularly muscle force) is critical for an accurate diagnosis of the developing bone.

Keywords: Bone Strength, Bone Geometry, pQCT, DXA, Pediatric

Introduction

Pediatricians are frequently presented with a child in whom there is a suspicion of a subtle anomaly of skeletal development or in whom skeletal treatment is to be evaluated. The available tools for clinical evaluation of bone in children are often qualitative, ambiguous, and difficult to interpret. Dual energy X-ray absorptiometry (DXA) has a growing acceptance for such purposes due to its broad availability, low radiation dose and quantitative nature. Unfortunately, bone densitometry methods which have relatively straightforward application in adult osteoporosis, are far more difficult to evaluate in the growing skeleton[1-3]. In an attempt to address this problem, several large DXA studies in children provide a reference for normative bone mineral density (BMD, g/cm^2) values[4-6], although few of these studies were designed specifically for that purpose. There are also some new, ongoing studies designed specifically to provide better normative DXA data for pediatrics. Given the considerable heterogeneity in the growing skeleton, it is not clear that better density reference standards will meet the clinical need nor is it certain that densitometry is the most appropriate way to assess the pediatric skeleton.

The fundamental clinical question relates to the mechanical strength of the child's bones, i.e., whether bone strength is low enough to make fractures more likely in typical childhood traumas and whether strength is improving in response to treatment. Despite the plethora of studies and insightful perspectives, there remains some confusion about what, and how, to measure bone "strength" in pediatric populations, both in clinical and research settings. We are limited partially by the technology available, but also by how we view and interpret measurement outcomes. The purpose of this review is not to provide another technical discussion of the various techniques available, but rather to stimulate a dis-

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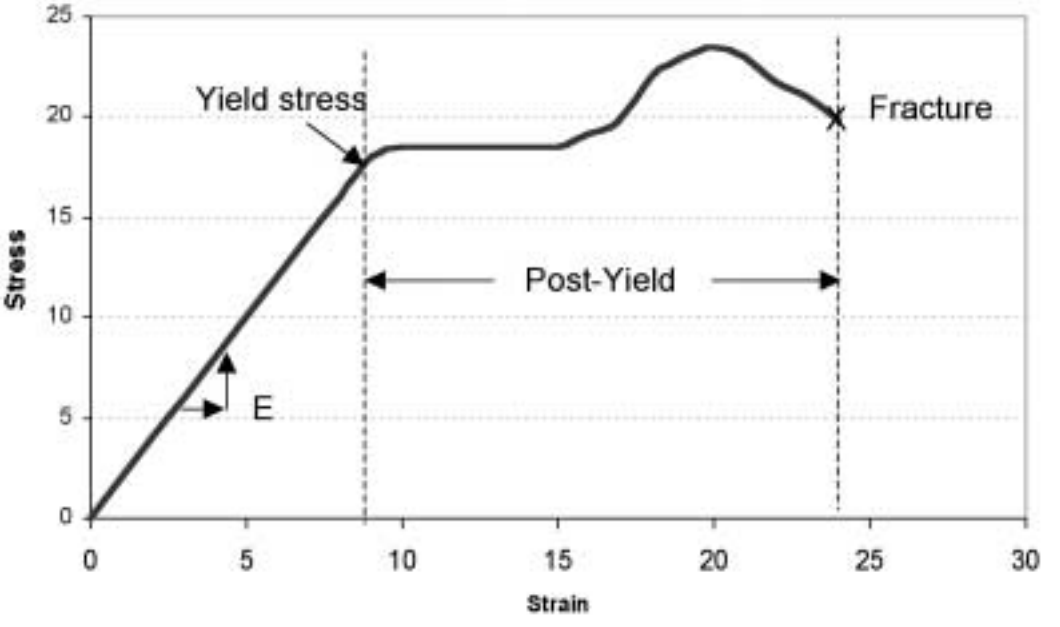

Figure 1. Stress-strain curve. E = Elastic modulus (also called "material stiffness") which is the slope of the stress-strain curve and describes pre-yield material behavior. Post-yield behavior is difficult to characterize and not measurable non-invasively, thus we defined "material strength" as the stress necessary to cause material yield, i.e., the yield stress. If the x-axis is changed to deformation (change in length) and the y-axis to load, a similar curve can be used to characterize bone structural (whole bone) strength. The difference is that the material properties characterized by the stress-strain curve are not size dependent, while bone structural strength characterized by the load-deformation curve is influenced by bone dimensions (geometric properties).

cussion about which bone properties we would *like to* measure, what we *are*, and *are not* measuring with non-invasive techniques and how we can interpret bone outcomes in a mechanically meaningful way. We will focus most of our discussion on two commonly used non-invasive techniques for assessment of bone in pediatric populations, peripheral quantitative computed tomography (pQCT) and DXA.

Bone strength: What is it?

"*Bone development is usually seen as a process of bone mineral accretion or increase in bone mass... However, from a functional perspective, bones should not be as heavy as possible, but rather as stable as necessary*" – Rauch and Schönau[7].

Bone strength is conventionally defined as the amount of loading force required to cause the material to fail under a certain loading condition[8,9], but – for reasons that will become apparent – we are going to use a slightly different definition. Consider how a test of bone material strength is done with a small rod-shaped piece of bone that is gradually pulled on its ends causing it to stretch in length. If the stress (force per area) produced by the pulling force is plotted as a function of the deformation (strain) caused, a curve similar to that in Figure 1 is produced. As loading begins, there is a linear relationship between the stress and strain. The slope of this portion of the curve is an important material property called the elastic or Young's modulus (also referred to as "material stiffness"). If the force is released within the linear range, the rod elastically returns to its original length. But beyond that point, some damage occurs and the material begins to yield, so that when released it does not return completely to its original length. Further loading causes the material to deform plastically until it ultimately fails (or in the case of bone, fractures), but the amount of plastic deformation is extremely variable. Some material fails right away after yielding begins while others, like most growing bone[10], will deform considerably before fracturing.

It may not be possible to reliably measure the properties that govern post-yield behavior, especially in real three-dimensional bones. However, it may ultimately be possible to assess the elastic modulus of the material in a non-invasive way. Since there is a linear relationship between elastic modulus and yield stress[11] (the point where yielding begins) the empirical relation could be used to predict material yield. Properties that influence stress (i.e., bone geometry) can be measured with available non-invasive techniques. To avoid the uncertainties of post-yield behavior, we hereafter describe strength as *the load necessary to cause material yield*, rather than material failure (fracture in the case of bone).

In order to gain a complete picture of the strength of bone then, we would need to know not only something about the properties of the material itself, but also about the stresses

within bone. If strength of a whole bone is diminished, then 1) higher stresses are produced within the bone for a given load, 2) the *material* yield stress is reduced or 3) both have occurred. Under a given loading condition, stresses within the bone are only determined by bone dimensions. Those dimensions include the lengths of bending moment arms and the surface dimensions of cross-sections at likely fracture sites. The surface dimensions are collectively called bone cross-sectional *geometry* and quantify the amount of bone surface and its distribution about bending and torsion axes.

Engineers use knowledge of geometry and material properties to predict the strength of a structure under a specified loading condition. The same principles can be applied to human bones[12-16] but the value of the estimate depends on how well the geometry and material strength are specified. Geometry of bone cross-sections can be measured, although doing so with accuracy and precision can be problematic. We shall discuss methods for measuring cross-sectional geometry by commonly used 2-D and 3-D imaging techniques (especially DXA and pQCT) as well as their problems and pitfalls.

Measurements: What and how

"*An engineer would laugh if asked to predict the behavior (of whatever kind) of a very complex structure like the proximal femur, given only the information available to the clinician*" – JD Currey[13].

Until recently, most non-invasive methods for clinical assessment of bone strength have focused on measuring bone mineral mass or its density – whether or not that is what we are, or should be, measuring. To adequately evaluate bone strength in children, we would ideally want to incorporate components of bone strength from the material level, the tissue* level, and the whole bone level.

Evaluating bone strength under traumatic conditions likely to cause fracture has some relevance, but bones continually adapt to the physiologic loading conditions encountered in normal physical activities. Those conditions may be very different in character and magnitude. In an absolute sense, bone strength should increase during growth and adapt to changing mechanical loads. Strains on bone increase with growth in bone length and muscle mass, and adapt up or down with changing physical activity (Figure 2)[17]. So we not only would like to know how strong a child's bones are in an absolute sense but also whether the strength is appropriate for the physiologic loads that it normally experiences.

* The term bone "tissue" has been used to refer to bone at both the material level or tissue level. Here we will differentiate the mechanical properties of bone as a *material*, which is the solid bone making up the trabeculae or cortex, from the *tissue* level which is the behavior of the whole trabecular or cortical structure, spaces included[14]. At the organ level, we refer to the geometry and dimensions of the whole structure at any given cross-section.

Below we first discuss properties that reflect yield stress (material level) and relevant geometric properties (tissue and organ level), followed by suggestions on how to incorporate load and address the relevant clinical questions. Many of the underlying concepts have been discussed in greater detail elsewhere[1,3,9,12,16,18].

Bone material properties: The yield stress

"*The bone material of a young child is very different in its mechanical properties from those of a young adult, yet at all intermediate times the bone must remain functional*" – JD Currey[19].

What to measure. At the material level, the yield stress of bone depends primarily on the properties and orientation of collagen fibers constituting the organic matrix and on the mineralization, i.e., the degree to which the matrix spaces are filled with inorganic mineral (calcium hydroxyapatite). At a more macroscopic level, yield stress is also influenced by the orientation and arrangement of osteons. In adults, the existence of accumulated microdamage also influences the yield stress, but this is likely not important in children. The relative importance of each of these factors depends on the loading condition[11,20], but generally there is a reasonably linear relationship between mineralization (or mineral volume fraction) and elastic modulus which can in turn be used to estimate yield stress[21]. Still, a large component of bone material strength depends on collagen properties. Material properties are probably not of high importance in adult osteoporosis, but may nevertheless be important in children. Certain collagen anomalies reduce the material strength of bone tissue[22] and rapid changes in normal growth produce deficits in mineralization, since the secondary mineralization process that fills the matrix occurs more slowly than growth in skeletal size[23].

How to measure. Currently, material properties can only reliably be assessed by invasive means, for example by nano- or micro-indentation analysis of bone biopsies or – more traditionally – by machining a piece of cadaver bone to a specific geometry so that it can be tested to failure[9]. The degree of bone mineralization on the material level (Figure 3) can be assessed in the laboratory by measuring the relative mineral (or ash) weight of dried bone samples, defined as ash weight divided by total dry bone weight. It can also be assessed in bone biopsy specimens using backscattered electron microscopy[24,25].

It might be possible to obtain an *estimate* of material mineral density using pQCT by measuring a small region of interest in a thick cortex region free of partial volume effects. One can then use empirical relationships between mineralization and material properties to estimate them. This is unlikely to be completely satisfactory since a large component of the material properties are determined by the unmeasured collagen (X-ray based techniques can only measure the mineral portion of bone). It is also not a true measurement of mineralization, since the resolution is typi-

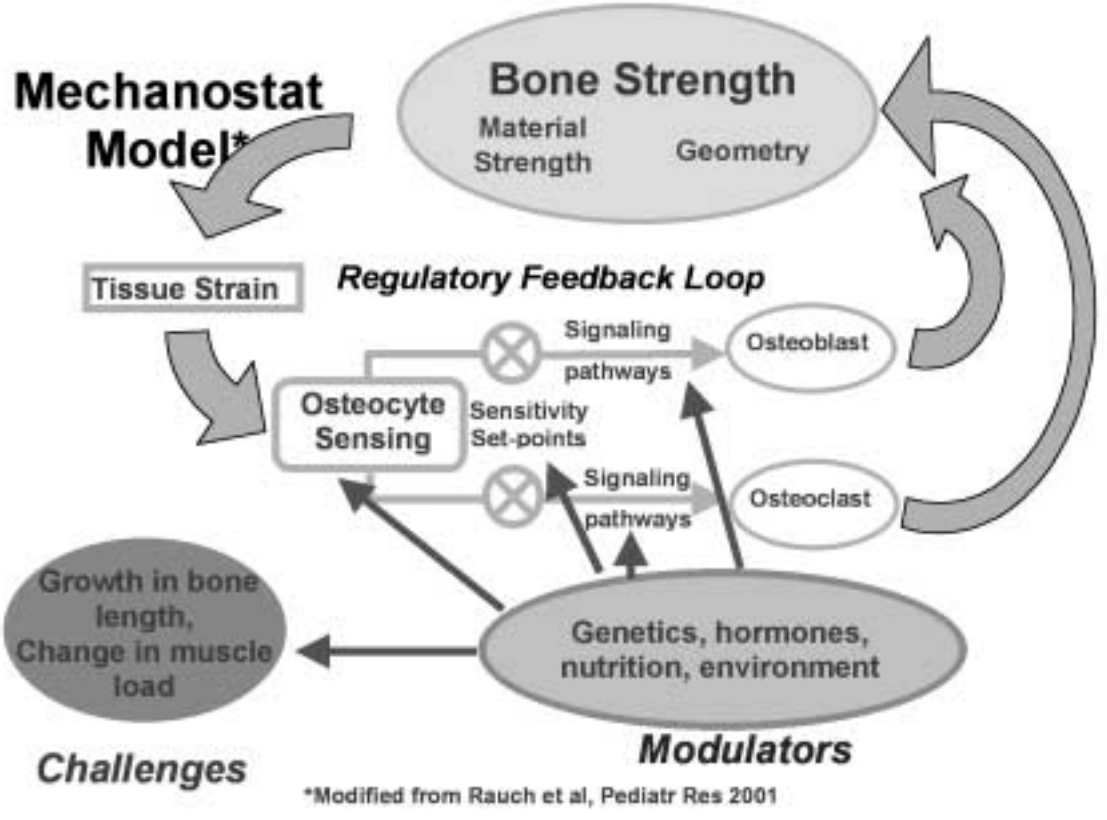

Figure 2. A functional model of bone development based on the mechanostat theory. The central piece of bone regulation is the feedback loop between bone deformation (tissue strain) and bone strength. During growth this homeostatic system is continually forced to adapt to external challenges. Factors shown below modulate various aspects of the central regulatory system. Bone strength is dependent on the material and geometric properties. [Adapted from Rauch and Schoenau, Pediatr Res 2001[17]].

cally not high enough to exclude small pores. Hence, once again one cannot reliably distinguish between differences in tissue porosity and mineralization. A more direct alternative method for measuring elastic modulus is ultrasound critical reflectometry (UCR)[26,27]. This method may be useful to assess the elastic modulus *in vivo*, but the technique is not fully developed yet and laboratory results are somewhat contradictory. Thus, although there is good potential to measure material properties non-invasively in the future, material properties, including bone mineralization, *cannot* be measured with any non-invasive technique currently available.

This latter statement may come as a surprise, given that the literature is full of DXA and pQCT studies that claim to have measured "bone mineralization". However, mineralization is a physiological process whereby bone mineral is incorporated into existing bone matrix[28]. The "degree of mineralization" is the extent to which the organic bone matrix has been filled with mineral. The spatial resolution of DXA and pQCT is by far insufficient to distinguish bone matrix from the mineral. Consequently, these techniques cannot provide information on the degree of matrix mineralization.

This concept can be further understood by explaining some basic principals of X-ray based techniques. These methods are based on attenuation using a source of X-rays on one side of the patient, and one or more X-ray sensitive detectors on the opposite side. Attenuation is greater in mineralized than in non-mineralized tissues because bone is denser than soft tissues and because it contains much more of the heavier elements: calcium and phosphorous. Soft tissues produce less attenuation since they are less dense and mainly composed of lighter elements: carbon, hydrogen, oxygen and nitrogen.

A single pixel (the 2-D picture element) value in a conventional DXA scan sums the mineral mass along a straight path between the X-ray source and detector expressing the result in g/cm^2 of hydroxyapatite (HA). The meaning of a pixel value of say 0.5 g/cm^2 is that attenuation is equivalent to a layer of 0.5 g of HA over a 1 cm x 1 cm area. BMD is the average pixel value in a region and thus represents the average mass thickness (Figure 4). BMC is the sum of the HA mass in the region expressed in g and can be derived by multiplying the total area of bone pixels in the region by the BMD. Because a pixel value sums mass along a ray path, it contains no information about how the mass is distributed along the path. The mineral atoms could be loosely distributed anywhere between the X-ray source and the detector or

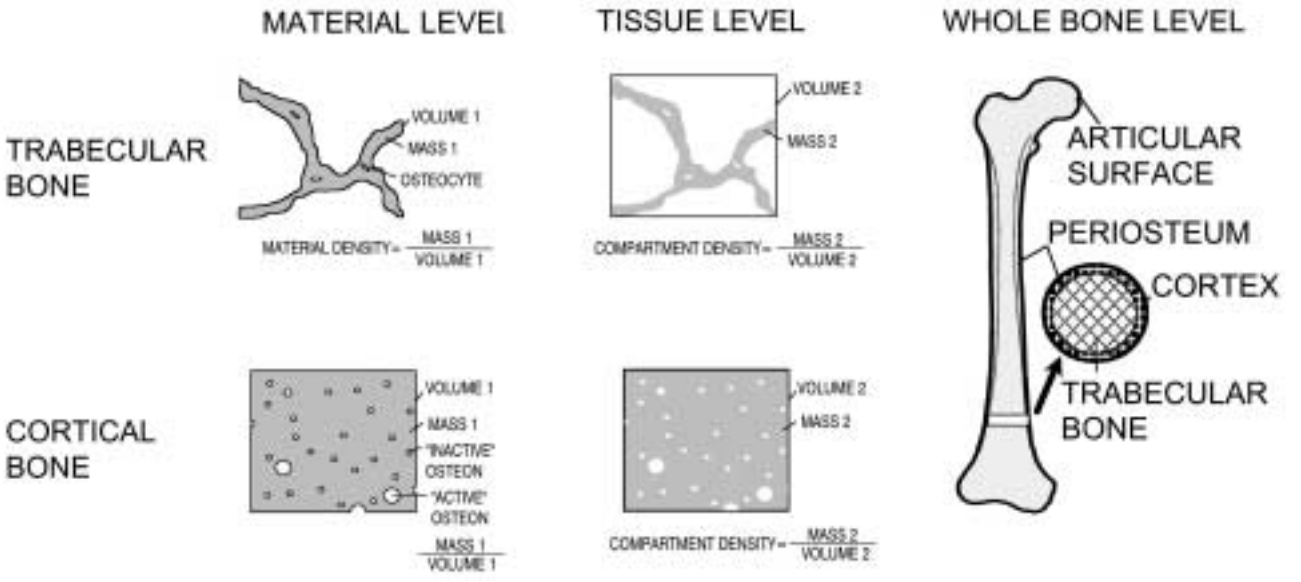

Figure 3. Definitions of various types of mineral density and compartments. Material and tissue mineral density in trabecular and cortical bone. The mass of mineral (in grey) determining material and tissue mineral density is identical (Mass 1 = Mass 2), but the volume (encircled by black lines) differs (Volume 2 > Volume 1). Therefore, material mineral density is higher than tissue mineral density. At the whole bone level, total mineral density is defined as the mass of mineral divided by the volume enclosed by the periosteal envelope. This definition can be applied to the entire bone, part of the bone (e.g., distal or proximal end) or a cross-section through the bone, as shown. The cross-section can be analyzed for geometric properties as discussed in the text. [Figure from Rauch and Schönau, JBMR 2001[1]].

they could be compacted into a solid block of bone. It is true that reduced mineralization (the fraction of HA in the organic collagen matrix) will reduce the DXA pixel value, but *it is impossible to distinguish altered mineralization from changes in the amount of normally mineralized bone.* This means that a decreased BMD value by DXA can mean one of three things: 1) a reduced amount of normally mineralized bone tissue 2) reduced tissue mineralization; or 3) the bone is expanded in diameter so that the amount of mass is averaged over a larger projected area. These represent very different clinical conditions of osteopenia and osteomalacia, respectively, in the first two cases, and potentially healthy but with a thinner cortex in the last case.

Other material properties. We have established that while DXA and pQCT measurements are influenced by mineralization, one cannot reliably determine whether measurements differ by the level of tissue mineralization or by the quantity of bone tissue. Since the dual energy mathematics of DXA subtracts out organic materials, collagen properties cannot be measured either. Since pQCT results are little affected by the collagen content of bone tissue, the same can be said of pQCT. The resolution of DXA and pQCT are clearly inadequate to measure micro-cracks (which are probably not of high importance in pediatric bone fragility anyhow) so one can rule out that these non-invasive techniques directly measure any material strength characteristic.

Tissue level properties

What to measure. At the tissue level, bone can schematically be separated into trabecular and cortical bone compartments[1] (Figure 3). In trabecular bone, mineralized tissue makes up 10 to 35% of the total tissue volume, whereas it occupies more than 90% of the volume of cortical bone[1,12]. Conceptually, trabecular bone is made up of trabeculae (you guessed it), whereas cortical bone consists of osteons. The distinction between compartments is useful in evaluating certain metabolic effects that disproportionately influence trabecular bone. In the trabecular compartment, volumetric BMD is mainly determined by the thickness of trabeculae and the average spacing between them, although it is also influenced by trabecular tissue mineralization. In cortical bone, BMD is determined by the number and average size of osteonal canals (porosity) and the mineralization density.

Other tissue properties of trabecular bone that have been found useful can be summarized under the heading "microarchitecture". This generally refers to parameters commonly measured in histomorphometry such as the orientation of trabeculae, the distribution of vertical and horizontal trabeculae and the amount of connections between trabeculae ("connectivity"). Among these tissue properties, only tissue BMD can be assessed non-invasively at present. Non-invasive methods to assess other tissue properties based

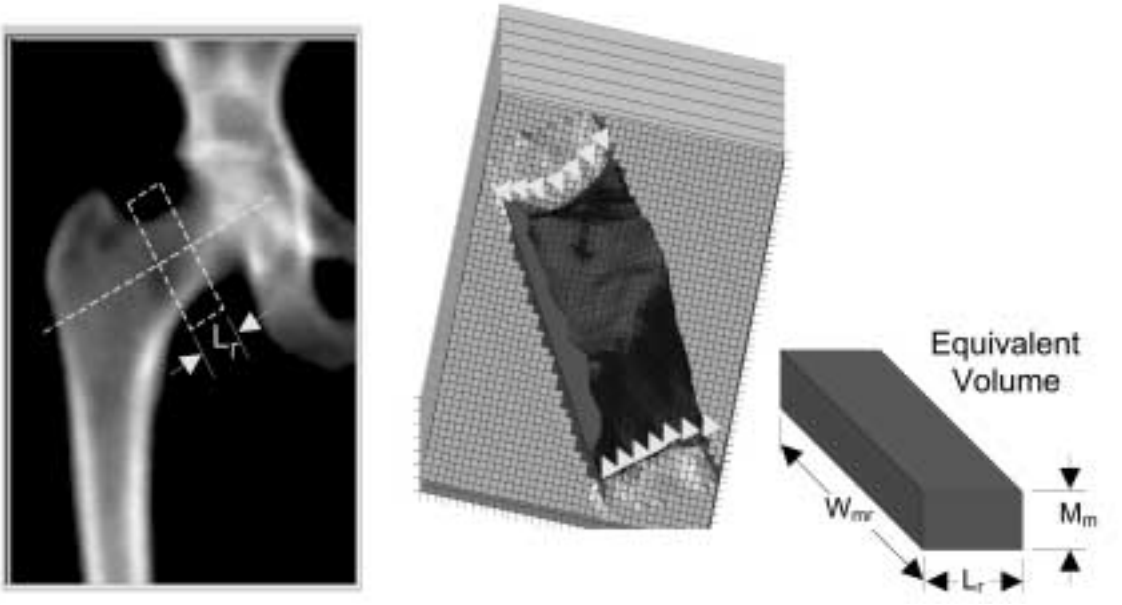

Figure 4. Extracted mass distribution from femur neck region. Length of region (L_r) is fixed by the software, and width varies along length of region (between the grey arrows) due to location of mass threshold. BMD is actually mean mass thickness (M_m) of the region. W_{mr} is the average thickness of the mass in the region. Region volume is equivalent to a block with dimensions L_r x W_{rm} x M_m.

on ultra high-resolution QCT and MRI methods are under development and are currently available only in certain research settings.

How to measure. The ability to distinguish bone compartments and to measure density volumetrically rather than over projected areas as in DXA, are considered important advantages of (p)QCT methods. In a QCT image, the pixel (2-D picture element) corresponds to a tiny box-like volume element (voxel) extending through the thickness of the measured cross-section. Numerically, the QCT pixel value is a measure of the average X-ray attenuation of the tissues within the voxel. Unless voxels are extremely tiny (tens of microns on a side) they often contain a mixture of low-attenuating soft tissues and higher attenuating bone tissue. Depending on the proportion of the two tissues within the voxel, the pixel values range between that of the soft tissues and that of pure bone (this is commonly called the partial volume effect). When voxels near cortical margins are included or when cortices are quite thin, partial volume effect can artificially reduce cortical density and should be accounted for[29].

When calibrated appropriately, the QCT pixel value reflects the average amount of mineral in the voxel and is readily expressed as mineral density, typically in mg/cm^3. This is exploited in measurements of cortical and trabecular density by averaging pixel densities over regions. From a mechanical perspective only the bone tissue provides any significant influence on bone mechanical strength.

The trabecular and cortical tissue BMDs measured by pQCT then represent the amount of mineral averaged over the volume of the trabecular and cortical compartment, respectively. As trabecular and cortical bone tissues do not only include mineralized bone but also unmineralized soft tissue, the tissue BMD is always lower than the material BMD (Figure 3)[1]. Since the trabecular compartment contains more soft tissue than the cortical compartment, trabecular BMD is correspondingly lower than cortical BMD, even though the material BMD is similar (but not identical[14]) in the two bone compartments.

Bone geometric properties: Whole bone level

What to measure. Certainly things would be easier if only we could just measure areal BMD by DXA or volumetric BMD by pQCT and be done with it. Why can't we? After all, areal BMD is correlated with whole bone strength in the laboratory[30]. However, there are several problems with this construct in adults, and even more issues in children. Aside from the fact that BMD (areal or volumetric) is *not* a mechanical strength property, there are scaling problems that are introduced in both growing and aging bones that complicate the interpretation of such simple constructs. For example, adult bones continually expand in diameter throughout adult life, apparently in adaptation to the changing mechanical demands[31,32]. An expanding periosteal diameter, will reduce the BMD by increasing the volume (QCT) or area (DXA) over which the mass is averaged - but it does not have the same effect on structural dimensions of cross-sections. As shown in the scaled drawing of bone cross-sections in Figure 5, the same bone bending strength (section

Areal BMD (DXA)	1.00	0.53	0.36
Volumetric BMD (QCT)	1.00	0.46	0.27
Section Modulus	1.00	1.00	1.00
Bone CSA or BMC	1.00	0.66	0.53

Figure 5. Schematic representation of 3 bone cross-sections with expanding periosteal diameter (from A-C) and constant section modulus. The areal BMD (by DXA) or volumetric BMD (QCT) is reduced (A-C) despite the same bone bending strength (section modulus). This is because the contribution of bone surface to the section modulus varies exponentially with distance from the center of mass of the cross-section; as diameter is increased, less material is needed for the same bending stiffness.

			% change
Cortical BMD by CT (g/cm^3)	0.918	0.855	-7%
Area BMD by DXA (g/cm^2)	0.398	0.417	+5%
Volumetric BMD by CT (g/cm^3)	0.844	0.591	-30%
BMC by CT (g)	0.048	0.075	+58%
Cortical thickness (cm)	0.215	0.200	-7%
CSA (cm^2)	0.260	0.440	+69%
Section modulus (cm^3)	0.021	0.064	+207%

Figure 6. A schematic of bone development at the femoral midshaft from birth to six months of age. At birth, the external bone diameter is about 6.0 mm and cortical thickness is 2.15 mm. At 6 months of age, BMD (volumetric by CT) has dropped by 30% and cortical thickness has decreased. However, the external bone diameter has increased to 9.0 mm. Therefore, the mineral mass (BMC by CT) in a 2 mm thick slice of bone has increased by 58%. Geometrically the axial strength (CSA) increases by 69% and the bending strength by 207%. See text for further explanation. [Figure adapted from Rauch and Schönau, JBMR 2001[1]].

modulus) can be achieved in bones of increasing outer diameter but reduced areal or volumetric BMD. This is because the contribution of bone surface to the section modulus varies exponentially with distance from the center of mass of the cross-section; as diameter is increased, less material is needed for the same bending stiffness.

These geometric effects are important in adults but *critical* in children; not only are bones changing in outer dimensions but also in the lengths of the lever arms (i.e., limb length) that are actuated by muscles in normal activities. Bone lengthening in growth requires compensatory increases in the cross-sectional dimensions to maintain strength. An example of the type of change seen in the shaft of a normal infant's femur from newborn to 6 months, using data derived from the literature[1,33-37], is shown in Figure 6. Depending on what you measure you get a very different picture of the bone status over this rapid growth period. Looking at cortical BMD, volumetric BMD or even cortical thickness one would conclude that the bone is getting weaker. The slight increase in areal BMD suggests an improvement. Of conventional densitometric parameters, only the change in BMC comes close to the actual improvement in strength. Geometrically the axial strength (CSA) increases by 69% and the bending strength by 207%. Clearly, densities have little value in this case and only BMC is at least consistent with the geometric reality.

In the medical literature it is often stated that bone mineral mass (BMC) is the primary contributing factor to bone strength. While this is only crudely true (bigger bones are stronger and contain more mineral mass), the measurement of BMC may be the most direct means for getting at the strength of a child's bones by DXA methods. Hence, the growing popularity of BMC as an assessment in children[38,39]. However, if one can measure the structural geometry of cross-sections at specific sites, specifically bone cross-sectional area (CSA) and section modulus, these parameters provide a more direct evaluation of strength. The reason that BMC has proven useful is that when measured in a region that traverses the bone axis, it is linearly related to the area of bone surface in the corresponding cross-section (bone CSA[**]). For bones that are axially loaded in compression (like columns) the strength in compression (or tension) is inversely related to bone CSA[40,41]. Long bones, though, act as muscle actuated levers and bending forces dominate except in cross-sections near joint surfaces. In this case, the amount of bone surface in the cross-section is important but its distribution is much more so.

The distribution of area is captured in the cross-sectional moment of inertia (CSMI, *I* in the engineering literature). A bone or any strut-like object with an irregular cross-section is stronger when bent in certain directions than in others. For

** Note that *total* CSA (the area enclosed within the outer periosteal boundary), is not a mechanical property because it includes the surface area of non-supporting soft tissues enclosed within. *Bone* CSA and BMC exclude these tissues.

example, the distal femoral neck is roughly elliptical in cross-section. The cross-section is stronger when bent in the mediolateral (widest) direction than in the narrower anteroposterior direction; this is quantified in terms of its principal moments of inertia. The principal moments of inertia (I_{max} and I_{min}, respectively) are by definition 90° apart and their sum is called the polar moment of inertia (J). J is important in determining stress in torsion[41,42]. However, maximum stress in bending is inversely related to the section modulus (Z)[40,43], a useful parameter for evaluating bending strength of long bones. Section modulus is derived by dividing CSMI by the maximum distance from the bending axis (center of mass of cross-section) to the outer surface, in the plane of bending.

For practical purposes, the section modulus (bending strength) and bone cross-sectional area (compression or axial) should be the primary geometric strength outcome parameters because physiologic loads to which bones adapt, as well as those associated with common fracture types are dominated by a combination of axial compression and bending. Other geometric parameters such as cortical thickness, outer diameters, total bone area or circumference while not mechanical properties *per se*, can be useful in explaining how two bones differ or change over some interval.

How to measure. Although limited by two-dimensional properties of a conventional DXA image, cross-sectional geometry can be measured from DXA images of long bones using a principle first described by Martin and Burr[44]. Basically, the distribution of mineral mass in the profile of pixels traversing the bone axis is a projection of mass in the corresponding cross-section, and its dimensions can be partially described from the distribution[45-47]. Pixel mineral mass (g/cm^2) is converted to linear thickness by dividing by the average mineral density of fully mineralized bone tissue: thus generating a thickness equivalent to solid cortical bone with all pores and spaces collapsed out. The bone CSA is then the summation of pixel spacing multiplied by the thickness along the profile. After locating the center of mass of the profile, the CSMI is measured as the summation pixel spacing times thickness weighted by the square of the distance from the center of mass.

The Hip Structure Analysis (HSA) program that incorporates these principles[46] has been widely applied to epidemiological studies in adults[31,48-50] and more recently in studies of children[51-53]. The program was designed to help interpret the plethora of existing DXA data in a more mechanically meaningful way than using BMC or areal BMD alone. The main limitation of this method is that it only measures the CSMI and section modulus in the plane of the image[54]. Inconsistent positioning in sequential scans can change projected dimensions so that it can be difficult to distinguish dimensional changes from positioning error. An additonal limitation when applying this method to pediatric DXA scans is that children's bones are typically less mineralized than adults, thus use of an adult mineralization assumption results in underestimates of cross-sectional geometry. Future QCT studies may help to resolve this issue.

Importantly, DXA was not designed to assess geometry and the images are not of good enough quality to do so accurately for a given *individual*. Recently, DXA software for analysis of geometry has also become commercially available. However, it is not always clear what assumptions are made in the algorithms, so users should interpret results with a healthy dose of skepticism.

(p)QCT is especially useful for the measurement of the cross-sectional dimensions that define stress magnitudes, because they provide an image of the cross-section from which those dimensions can be derived. Several outcome variables are available from pQCT software. Bone cross-sectional areas and apparent densities of the total bone slice and of the cortical and trabecular bone separately can be measured, periosteal and endosteal circumferences, cortical thickness, and various strength measurements including moments of inertia, section modulus, and the strength-strain index (SSI). Which should we report? First, let us clarify some misperceptions. In addition to the common statement that pQCT measures bone "mineralization" (a misperception we dispelled earlier), it has been stated that pQCT provides bone geometry in "three dimensions" in comparison to planar DXA measurements. While it is true that pQCT has the benefit over DXA of measuring bone volume (and volumetric tissue density), the third dimension – slice thickness – is held constant. Thus, pQCT geometry outcomes are "area" measurements: the total bone area (ToA) which is the result of subcortical, trabecular (TrA) and cortical (CoA) bone areas (all in mm^2). Since pQCT is a relatively new modality for assessment of pediatric bone, there are no standardized data acquisition and analysis protocols. Thus, different protocols and variables reported to date make it difficult to compare results across studies. For example, bone circumferences have been previously reported to assess growth in the tibia. Increased periosteal or endosteal circumferences by pQCT can simply reflect a change in bone shape during growth with or without a concomitant change in ToA or CoA. We therefore recommend using measurements of bone areas by pQCT to describe changes in bone size.

In addition to section modulus, the strength-strain index (SSI) is a strength estimate calculated from pQCT. SSI incorporates both geometric properties (CSMI) and a reasonable surrogate of material properties of cortical and trabecular bone (tissue level BMD), and is able to predict whole bone breaking strength in laboratory testing[55,56]. Measurement at the relevant region of interest is important[57] but in general, section modulus or SSI along with ToA and CoA give a good picture of bone geometry and overall bending strength[58].

Bone muscle strength indices: What we really want to know

"*Muscle and bone, for instance, are inseparably associated and connected; they are moulded one with another; they come into being together and act and react together*" – D'Arcy Wentworth Thompson, 1942.

What to measure. Assessment of bone alone, even if we can measure the right strength properties, still does not tell us whether a child's bone strength is adapted to his or her needs. For the past decade, the focus has been on developing normative data and attempts to control bone variables for body size, sex, and/or maturity. Various combinations of these variables such as height, weight, age, Tanner stage, change in height or weight, bone area, or height[1,5], or log transformed, each used alone or in endless combinations have been used to "adjust" DXA outcomes especially, but also pQCT variables. In a recent review, it was suggested that "BMD results using DXA should be interpreted in light of several potential confounding factors including bone size, skeletal age, pubertal maturation, and body composition"[59]. The one thing that is clear about this long list of adjustment variables is that it can cause headaches to pediatricians dealing with DXA. It is less certain that this inconvenience is counterbalanced by improved patient management.

If we take a step back and approach bone from a functional perspective, what we really want to know is "how strong are the child's bones relative to physiologic load demands?" We might restate the clinical question as: Is the child's bone strength appropriate for his or her size? If not, is this because the bone has adapted to a reduced or absent mechanical stimulus? If the mechanical stimulus is normal, is there an induced or heritable defect in the material or its ability to respond to load?

Through skeletal growth and development, bones must continually adapt to the loading forces imposed upon them, or in the process of achieving adaptation. Muscles multiply the loads that gravity exerts on the skeleton, because they act against unfavorable lever arms. Therefore, it has been proposed that bone be assessed relative to indices of muscle force such as muscle cross-sectional area or lean body mass. Any anomalies in adaptation should alter the muscle-bone relationship thus making bones stronger or weaker than demands require. If the relationship can be reliably measured *in vivo*, it should provide a child-specific strength assessment.

How to measure. The idea of adjusting bone strength for the forces on it is hardly a new concept. Similar approaches have been used in anthropological and mechanical literature for decades[40,60]. Ideally we would measure: 1) bone strength (both material and geometry), and 2) loads on bone at the site measured (i.e., bending moments in specific bone cross-section and force of muscle that activates the bone being measured).

Several reasonable approaches to incorporate forces on bone have been recently reported in the literature[61-64]. In each case, some estimate of bone "strength", an estimate of muscle force, and lever arm should be used. Incorporating surrogates for muscle force (usually lean mass by DXA or muscle cross-sectional area by pQCT), bone strength (section modulus, bone strength index, or BMC), and lever arm (height or limb length) into regression models or to a ratio (called the functional muscle-bone unit[63], bone muscle strength index (BMSI)[61], or relative bone strength (RBS)), can give a reasonable estimate of the bone strength relative to a load for an individual child. These approaches are based on the idea that muscle provides the largest forces on bone and taking into account the lever arm (which can crudely be represented by height or limb length). Muscle load is a function of muscle strength and activity level. Since muscle strength generally scales with muscle size, an appropriate size measurement should suffice.

It is interesting that when we assess bone in this way, using surrogates for the forces imposed on it, other variables (height, weight, Tanner stage, etc.) become less important. That is, once some index of muscle force (either total body lean mass or muscle CSA) and lever arm (tibia length or height) are controlled for, other size or maturity variables are no longer significant[64,65]. Group differences that appeared before – such as overweight and obese children having "high bone mass", are no longer true[65]. In clinical pediatric populations, this approach has been very useful as well[66-68] and allows clinicians to distinguish between bone and muscle abnormalities. We strongly encourage assessment of the muscle-bone unit in all studies and in clinical settings to improve diagnosis.

That said, we are some distance away from an ideal standardized method for measuring the strength of a child's bones relative to the loads it experiences. Technologies are yet inadequate and our approaches thus far are necessarily crude. Clearly the actual forces on bone in any given loading condition are far more complicated than simple assessment of muscle area and limb length can provide. Surrogates used for muscle force and lever arm are crude indices of the actual forces on bone (at the bone cross-section measured) in any given loading condition. Even research using animal models or anthropology emphasizes the need for further research to understand these forces and how bone adapts to them[41,69]. Attempts to understand and apply the body of work on scaling bone and bone adaptation to mechanical loading[41,69-72] should improve our approach to examining the developing bone.

Conclusion

This is an interesting and often confusing time for researchers and clinicians who examine the developing bone. Bone strength is dynamically changing during growth as dimensions rapidly change and the tissues develop. Normal heterogeneity in these non-linear processes make it difficult to determine what is normal. Rapid changes in linear and cross-sectional dimensions alter the structural geometry that controls stresses under loads and dynamic changes in bone tissue influence the material capacity to withstand those stresses. Ideally one should be able to measure the structural geometry and the material strength directly to determine if they are normal but our capability for doing so remains rudimentary. Available technologies and software are mainly based on a density paradigm developed to evaluate adult osteoporosis. Despite this somewhat dismal condition there is light on the horizon. Mechanically meaningful measures of

bone geometry (bone cross-sectional area, section modulus, or SSI) are available with non-invasive techniques such as (p)QCT and some DXA software. It remains uncertain whether available methods for measuring bone geometry by either method are sufficiently accurate or precise for use outside the research setting. Further improvements in software and scanner technology are needed especially for pediatric applications. Much more experience is needed to develop standardized scan protocols appropriate for children as well as reference standards of normality. Ultimately, reliable bone geometry measurements should become available to the pediatric clinician. While some ultrasound methods show promise, reliable, non-invasive methods for measuring bone material strength remain further over the horizon. The ability to do so is probably more important in pediatrics than in adults since certain pediatric disorders are known to alter material strength. As we go forward in this evolving scenario we strongly encourage researchers and clinicians to consider not only the absolute bone strength, but also the strength of bone relative to the physiologic loads it encounters. Interpreting bone strength in light of the loads incurred during growth (particularly muscle force) is critical for an accurate diagnosis and interpretation of the growing bone.

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