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Mapping the natural variation in whole bone stiffness and strength across skeletal sites

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ABSTRACT

Traits of the skeletal system are coordinately adjusted to establish mechanical homeostasis in response to genetic and environmental factors. Prior work demonstrated that this 'complex adaptive' process is not perfect, revealing a two-fold difference in whole bone stiffness of the tibia across a population. Robustness (specifically, total cross-sectional area relative to length) varies widely across skeletal sites and between sexes. However, it is unknown whether the natural variation in whole bone stiffness and strength also varies across skeletal sites and between men and women. We tested the hypotheses that: 1) all major long bones of the appendicular skeleton demonstrate inherent, systemic constraints in the degree to which morphological and compositional traits can be adjusted for a given robustness; and 2) these traits covary in a predictable manner independent of body size and robustness. We assessed the functional relationships among robustness, cortical area (Ct.Ar), cortical tissue mineral density (Ct.TMD), and bone strength index (BSI) across the long bones of the upper and lower limbs of 115 adult men and women. All bones showed a significant ($p < 0.001$) positive regression between BSI and robustness after adjusting for body size, with slender bones being 1.7–2.3 times less stiff and strong in men and 1.3–2.8 times less stiff and strong in women compared to robust bones. Our findings are the first to document the natural inter-individual variation in whole bone stiffness and strength that exist within populations and that is predictable based on skeletal robustness for all major long bones. Documenting and further understanding this natural variation in strength may be critical for differentially diagnosing and treating skeletal fragility.

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1. Introduction

The natural variation in skeletal robustness (specifically, total cross-sectional area relative to length) is a mechanically and clinically important trait. The broad range in bone robustness, as defined by Martin and Saller [1], is well tolerated within and between populations. Bone is a 'complex adaptive system,' which is a term used to describe systems that coordinately adjust multiple traits in response to genetic and environmental perturbations in order to establish system-level homeostasis [2–7]. For bone, the homeostasis of clinical interest refers to the biological processes that are involved in establishing and maintaining mechanical function. However, the flexibility in how bone establishes mechanical function, or stiffness [8], comes at a clinical cost, with individuals acquiring reduced fracture resistance through various biomechanical and biological pathways [9]. This phenomenon raises two primary issues that should be considered to better define and expand our ability to identify individuals with increased fracture risk. First, the adaptive process is not perfect [10]. Biological constraints in cellular activity (e.g. osteoclastic/osteoblastic driven modeling and remodeling) limit the degree to which traits can be adjusted to mechanically offset the natural variation in bone robustness. This in part explains why slender bones, those that are narrow relative to length, are less stiff and strong in relation to body size compared to more robust bones that are wide relative to length [10]. This natural variation in stiffness and strength, or functional inequivalence, has only been quantified for the tibia and has not been explicitly incorporated into clinical studies. Fully defining the magnitude of how bone stiffness and strength naturally vary is important. Both slender and robust bones perform adequately well under routine loading conditions [9,10]. However, slender bones are more at risk of fracturing when subjected to extreme loading conditions, such as military training and falls in the elderly [11–14]. Therefore, a segment of the population (i.e. individuals with a skeleton comprised of slender bones) is at risk of fracturing despite their bones being as well adapted as biologically possible to maximize stiffness while minimizing mass [15]. Second, cortical area (Ct.Ar) and cortical tissue mineral density (Ct.TMD) naturally vary relative to robustness [9,10,16], resulting in a circumstance wherein variations in Ct.Ar and Ct.TMD are superimposed on the natural variation in robustness. Understanding this variation is important for determining when

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the covariation between traits is impaired, resulting in reduced fracture resistance. Furthermore, how this covariation between morphological and compositional traits impacts clinical bone mineral density (BMD) assessments has yet to be defined.

Previously we found that the slender or robust phenotype of an individual is consistently represented throughout the appendicular skeleton. This suggests that the covariation among robustness, Ct.Ar, and Ct.TMD is system wide (Fig. 1) [17]. Moreover, slender bones, after adjusting for body size, demonstrated a 25–50% lower Ct.Ar and a 5–8% greater Ct.TMD, relative to robust bones, depending on the long bone considered [17]. However, this prior work did not establish whether the covariation of these skeletal traits resulted in similar strength differences across skeletal sites. Our previous work found that the slender tibiae of young adult men and women were two to three times less stiff compared to those with robust tibiae [10]. To put this 100–200% natural variation in bone stiffness into a clinical context, work by others reported 6.5–40.8% reductions in bone strength between fracture and non-fracture groups, depending on the skeletal site considered [13,18,19]. Therefore, the natural variation in stiffness we previously documented overshadows the mean differences others have reported in bone strength within and between men and women, and has yet to be clinically defined or acknowledged. How this variation presents itself across the major long bones of the appendicular skeleton is unknown. Taking our previous findings into consideration, the goals of the current study are to quantify the natural variation in whole bone stiffness and strength across the major long bones and to systematically evaluate how this natural variation in strength can be attributed to the degree to which skeletal robustness, Ct.Ar, and Ct.TMD covary. We further tested whether a person showing less Ct.Ar or Ct.TMD for robustness at one skeletal site demonstrates this same deficit across all major long bones. This would provide insight in the degree to which impairments in the adaptive process are systemically versus locally influenced. Though diaphyseal fractures are much less frequent than those of metaphyses, the diaphysis provides us with a relatively simple model from which to establish basic principles of how the skeletal system coordinately adjusts multiple traits to establish mechanical homeostasis. These principles can then be translated to the metaphysis in future work, since these cortico-cancellous regions pose their own unique challenges [20,21].

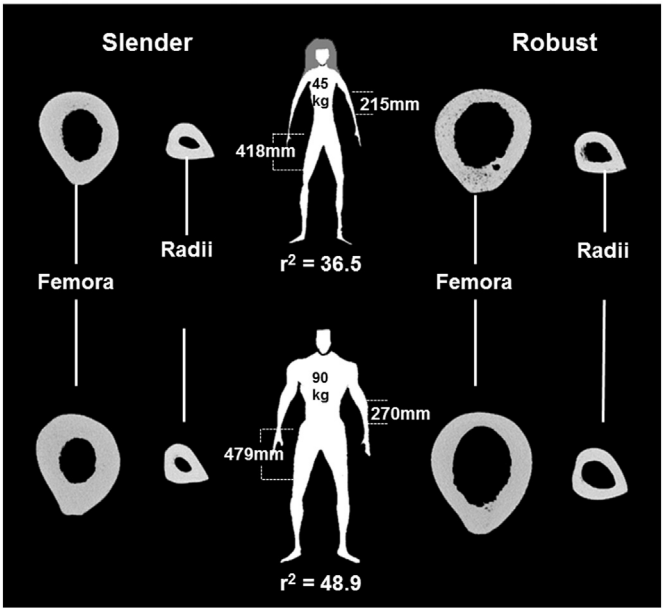

Fig. 1. Example of systemic intraskeletal covariance of traits for four individuals within the study population. Bone length and body mass are similar between each set of men and women.

2. Materials and methods

2.1. Sample

The sample used in this study consisted of 63 men and 52 women of African-American ethnicity. These individuals died in the Greater Cleveland area of Northern Ohio between 1910 and 1940, and their skeletal remains are presently curated by the Cleveland Museum of Natural History within the Hamann–Todd Osteological Collection. Individuals comprising this collection are predominately indigent and of low socioeconomic standing for this young 20th century region of early urban industrialism. This sample was specifically chosen due to its scientific value. It is rare to acquire substantial data from multiple human skeletal sites from which to estimate whole bone stiffness and strength based on engineering theory. These volumes of data, at such a high scan resolution (e.g. 100 μm voxel size), are not obtainable from most clinical and/or research databases given the expense and well-documented risks of radiation exposure. Moreover, anatomical collections are readily available for analysis, opposed to the time and expense required to collect multiple skeletal elements of substantial number from modern donors. Furthermore, this sample was potentially subject to a large amount of environmental noise, as they demonstrate a high propensity for acute infections and degenerative diseases [22–26]. Therefore, these individuals are expected to demonstrate a wide range of variation in how well skeletal traits were functionally adapted, increasing our ability to test to what degree variation among covariant traits is systemically affected. This complements our prior work focused on healthy, modern men and women of predominately European ancestry [9,10].

Individuals selected for this study were from 20 to 30 years of age, and consisted of no observable skeletal pathology that potentially impacted bone morphology and/or tissue level mechanical properties. Their cortices demonstrated no endocortical or intracortical resorption uncharacteristic for their age. This adult age range was chosen because the skeletons of these individuals represent the end product of the functional adaptation process during growth, wherein bone loss should be minimal. Skeletal elements in this study consisted of the left humeri, radii, second and third metacarpi, femora, and tibiae. Body height and weight were also documented for each individual at the time of autopsy; however, there may be inaccuracies in the data. Deceased individuals appropriated for this osteological collection were not necessarily received immediately following death, leaving some individuals to have measured weights below their actual weight due to variable fluid loss and decomposition [27]. Moreover, documented weights were comprised of both direct measurement and estimates [28]. Notwithstanding the potential inaccuracies in the documented data, we chose to use reported body weight, along with a femoral head breadth measure obtained at the time of our analysis to serve as a complementary proxy for body size [29]. We previously reported that body weight minimally influenced the associations among covarying traits, and that using other proxies to estimate body weight (e.g. height and femoral head breadth) was suitable [17]. Comparisons between individuals included in this study and those of known body weight from our previous study [10] confirm that the effects of body weight minimally influence the expected associations among traits. Moreover, regression-based estimations of body weight, which are useful only for the population from which they are derived, would potentially introduce additional statistical error when using these values to adjust traits for body size.

2.2. Data acquisition and statistical analyses

Quantification of skeletal traits for each long bone was conducted using a pQCT, or peripheral quantitative computed tomography system (XCT 2000, Stratec Medizentechnik, Pforzheim, Germany), as described previously [17]. Briefly, a single axial scan was taken at the 50% midshaft of each bone, as defined by longitudinal length (Le). Bone length was quantified in accordance with Ruff [30]. Images were acquired at

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