Bone 56 (2013) 127–138

Contents lists available at SciVerse ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Functional integration of skeletal traits: An intraskeletal assessment of bone size, mineralization, and volume covariance

Stephen H. Schlecht [a,*], Karl J. Jepsen [b]

[a] Department of Orthopaedic Surgery, University of Michigan, 2148 Biomedical Science Research Building, 109 Zina Pitcher Place, Ann Arbor, MI 48109, USA
[b] Department of Orthopaedic Surgery, University of Michigan, 2007 Biomedical Science Research Building, 109 Zina Pitcher Place, Ann Arbor, MI 48109, USA

ARTICLE INFO

Article history:
Received 22 February 2013
Revised 8 May 2013
Accepted 10 May 2013
Available online 27 May 2013

Edited by: David Burr

Keywords:
Bone
Robustness
Functional morphology
Cortical area
Mineralization

ABSTRACT

Understanding the functional integration of skeletal traits and how they naturally vary within and across populations will benefit assessments of functional adaptation directed towards interpreting bone stiffness in contemporary and past humans. Moreover, investigating how these traits intraskeletally vary will guide us closer towards predicting fragility from a single skeletal site. Using an osteological collection of 115 young adult male and female African-Americans, we assessed the functional relationship between bone robustness (i.e. total area/length), cortical tissue mineral density (Ct.TMD), and cortical area (Ct.Ar) for the upper and lower limbs. All long bones demonstrated significant trait covariance ($p < 0.005$) independent of body size, with slender bones having 25–50% less Ct.Ar and 5–8% higher Ct.TMD compared to robust bones. Robustness statistically explained 10.2–28% of Ct.TMD and 26.6–64.6% of Ct.Ar within male and female skeletal elements. This covariance is systemic throughout the skeleton, with either the slender or robust phenotype consistently represented within all long bones for each individual. These findings suggest that each person attains a unique trait set by adulthood that is both predictable by robustness and partially independent of environmental influences. The variation in these functionally integrated traits allows for the maximization of tissue stiffness and minimization of mass so that regardless of which phenotype is present, a given bone is reasonably stiff and strong, and sufficiently adapted to perform routine, habitual loading activities. Covariation intrinsic to functional adaptation suggests that whole bone stiffness depends upon particular sets of traits acquired during growth, presumably through differing levels of cellular activity, resulting in differing tissue morphology and composition. The outcomes of this intraskeletal examination of robustness and its correlates may have significant value in our progression towards improved clinical assessments of bone strength and fragility.

Introduction

Variation in whole bone stiffness is directly linked to the functional adaptation process. Increasingly, this variation in stiffness appears to be established during growth and maintained throughout the aging process via the coordination of morphological and compositional traits acting through biomechanical pathways [1–7]. These traits include, but are not limited to, diaphyseal size, tissue mineralization, and cortical area. These three interacting traits account for 73–79% of whole bone bending stiffness [9], making them important determinants of whole bone strength. Additionally, these traits are clinically convenient for assessing fracture risk in that they are non-invasively measured. Previous studies demonstrated that total cross-sectional area of the diaphysis relative to length (i.e. robustness) varies along a biological continuum from slender to robust, in which the cross-sectional diameter varies from narrow to wide, irrespective of body size [1,8–10]. Slender bones, though smaller in cross-sectional diameter, have proportionally thicker cortices and greater mineralization (i.e. tissue stiffness) compared to robust bones, which demonstrate relatively thinner, less mineralized cortices [9,11,12]. This covariance between robustness, cortical area, and mineralization is present both between and within sexual cohorts [1,2,12] and populations [9,10]. Given the observed range in bone size and stiffness, one of the ongoing questions surrounding bone is how this tissue ascertains and preserves adequate stiffness throughout growth and aging to accommodate static and dynamic loading associated with body mass and physical activity. Resisting peak strains within the normal physiological range, which may differ between skeletal regions, is one primary objective. As new evidence comes to light, it appears that variation in bone size and an individual's susceptibility to fracture results from genetic and environmental perturbations [13–20]. To better understand how this variation is established and modified throughout growth and development it is important to look past population means in assessing function [21], which mask the variation within, and begin focusing on an individual's unique trait set that may lie on the slender or robust periphery of the population average. No single trait defines whole bone stiffness. Thus,

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* Corresponding author.
E-mail addresses: sschlech@med.umich.edu (S.H. Schlecht), kjepsen@med.umich.edu (K.J. Jepsen).

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http://dx.doi.org/10.1016/j.bone.2013.05.012

understanding covariance among traits is essential towards identifying genetic and environmental factors that impair the development of stiffness, while enhancing evaluations of skeletal growth.

Bone robustness appears to be established early postnatally in both males and females [2], with this relationship between subperiosteal expansion and longitudinal growth persisting to adulthood despite fundamental sex differences in growth patterns [1]. Thus, we must consider that robustness naturally varies within a population and that geometric strength parameters based on habitual loading patterns do not fully explain this phenomenon. Given that there is a covariant pattern as to how traits establish function (i.e. a bone that is sufficiently stiff and strong to support physiological loads) during growth, variation in bone stiffness may be better defined by the specific combination of traits acquired by adulthood and maintained during aging. Having a slender phenotype does not necessitate lower habitual loading or a bone that is poorly adapted, as there may be a selective advantage of constructing a bone that minimizes mass while maximizing stiffness to perform particular functions [22].

The functional morphology of bone is complex, and compounded by genetically guided structural and tissue level mechanical properties that fluctuate over time [20]. Thus, individuals within a population are at risk of fracturing their bone for different life history, temporal, and genetic reasons. Despite this understanding, the systemic nature by which traits covary has yet to be fully investigated. Previous human populational research into bone size and tissue level trait variants, as discussed above, have been largely limited to radiographic and computed tomography scans comprised of individuals who are physically fit [9,23–25], and those of European ancestry with moderate to high socioeconomic standing [1,2,17]. The following investigation seeks to complement these studies while both confirming and enhancing our understanding of functional morphology and the systemic nature of robustness trait sets throughout the human skeleton. Specifically, are patterned trait interactions previously reported for robustness, tissue modulus, and cortical bone area, consistent among weight bearing and non-weight bearing bones? All long bones are subjected to loading, albeit in differing manners, and as a result they are functionally adapted relative to habitual loading regimes. Understanding the intraskeletal variance of complex trait sets, and determining whether robustness and its correlates behave systemically throughout the skeleton, has significant clinical value towards predicting variation in bone stiffness and strength using data obtained from a single skeletal site.

To progress towards this goal, the upper and lower limbs from a population of African-American individuals of low socioeconomic standing were analyzed. The specific aims of this study were threefold: 1) to confirm the presence of a significant negative relationship between skeletal robustness and tissue modulus (i.e. as robustness increases for a given bone, tissue modulus decreases) relative to body mass and bone length 2) to confirm the presence of a significant positive relationship between skeletal robustness and cortical area (i.e. as robustness increases for a given bone, tissue volume increases) relative to body mass and bone length; and 3) to assess the intraskeletal relationship of all bones examined in respect to skeletal robustness, tissue modulus, and cortical area. Better understanding these patterns for different bones and an ethnic group that is not predominately of European origin, will benefit efforts aimed at understanding loading patterns across ethnic groups, which is fundamental for the continual advancement of clinically assessing fracture risk, and the behavioral interpretation of prehistoric and historic osteologic material.

Materials and methods

Sample

The sample used in this study was comprised of 52 women and 63 men of African-American ethnicity obtained from the Hamann-Todd Osteological Collection that was amassed between 1910 and 1940 from dissecting room cadavers in Cleveland, Ohio and is now curated by the Cleveland Museum of Natural History. This population was chosen specifically because it is predominantly comprised of indigents of low socioeconomic status that were a subjugated people during early 20th century urban industrialism. Moreover, this population was undoubtedly susceptible to health-related factors stemming from nutritional deficits and disease [26–29], presumably accounting for many of these individuals' young age-at-death. We acknowledge the limitation of the sample chosen and the 'osteological paradox' [30] considerations associated with a sample of this nature. However, this sample was intentionally chosen to complement previous investigations into robustness trait variants in healthy Caucasians of higher socioeconomic status, determining whether the covariation of traits remains significant amid environmental considerations that may impact longitudinal and transverse skeletal growth [31,32]. Thus, this sample provides us with a starting point for looking at individual differences within populations that we hope to build upon in future work.

All individuals selected had stated ages of 20–30 years, and they were devoid of any gross or radiologically observable skeletal pathology that may have impacted bone structure and/or tissue level mechanical properties. The left upper and lower limbs of each individual were used in this study and included the humerus, radius, second metacarpal, third metacarpal, femur, and tibia. Body weight was documented at time of autopsy for each individual; however, these data may not be reliable. Todd and Lindala [33,34] noted that the condition of the bodies varied greatly at the time they were received, and that reported weights were not always directly measured but also estimated. However, regression equations given for the estimation of body weight are widely variable, occasionally reliant upon mean data and/or self-reported weights, contingent upon varying morphological indicators and quantification methods, and useful only for the population from which they were derived. Thus, rather than introduce further bias in the application of body weight estimation equations, documented body weight, along with femoral head breadth as a proxy, are used in this study. Despite the uncertainties in this variable, our analyses below will demonstrate that body weight has little influence on the significance of the relationships reported.

Data acquisition methods

Robustness and tissue moduli estimations were quantified for each bone using peripheral quantitative computed tomography, or pQCT (XCT 2000; Stratec Medizentechnik, Pforzheim, Germany). Each bone was axially scanned with an in-plane pixel size of 0.10 mm × 0.10 mm. To ensure quality and consistency of images generated, a calibration scan was performed daily using a standard phantom with known densities.

Scans were taken at the 50% midshaft of each bone according to length. Length was measured parallel to the longitudinal axis of each bone using a standard osteometric board in accordance with Ruff [35]. Femoral head breadth was measured using standard calipers, with an offsetting attachment, and was quantified along the anterioposterior axis. Each long bone was placed in two custom holders designed to hold the bone along the proximal and distal metaphyses. This facilitated the orienting of each bone along the anterioposterior and mediolateral axes in a similar manner to that described by Ruff and Hayes [36]. The design of the holders allowed each bone to be oriented in a consistent, reproducible manner that accounted for variation in bone width and curvature. Each bone was positioned with the distal end facing away from the gantry opening. To make certain each slice obtained from the midshaft was perpendicular to the longitudinal axis of the bone, a line level was placed on the anterior surface of the bone and the holders on either end