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The importance of mechanical loading in bone biology and medicine

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Abstract

This paper discusses the premise that the skeleton is primarily a mechanical organ, and reviews the reasons that mechanical factors play a major role in bone biology. It begins by considering three basic observations: (1) Galileo's observation that bone proportions become more robust as the species' overall size increases; (2) da Vinci's observation that larger structures are inherently weaker than smaller structures subjected to the same stress; and (3) the general observation that each unit of bone mass provides structural support for about 15 units of soft tissue organ mass. Together, these observations lead to the concept that it can be advantageous to minimize bone mass, consistent with constraints on other factors. This premise is discussed here in relation to the phenomenon of bone remodeling, which is seen to serve two purposes: the adjustment of bone mass and geometry to maintain peak bone strains at their maximum tolerable values, and the continual removal of fatigue damage produced at those strain levels. Finally, it is observed that bone remodeling apparently originated ~250 million years ago when the first vertebrates of substantial size became weight-bearing on land, suggesting that mechanical forces associated with weight-bearing were instrumental in the evolution of bone remodeling.

Keywords: Bone Remodeling, Mechanostat, Bone Volume, Microdamage, Evolution

Introduction

From a medical perspective the skeleton is often considered to be a mineral reservoir. It indeed serves this function, particularly with respect to calcium and phosphorus, but this ignores the role of mineralized bone in skeletal function *per se*: that is, providing a mechanical structure able to transmit force and/or motion from one part of the body to another. In order to serve their mechanical functions, bones need to have considerable resistance to deformation under load, and this has been neatly achieved using hydroxyapatite as the stiffening mineral. Certainly the evolutionary selection of this particular mineral was influenced by the fact that it contains calcium and phosphate ions, essential for muscle function and a variety of other cellular processes.

However, thinking of the skeleton as primarily a mineral reservoir is rather like believing that the function of a battery in an automobile is to provide electricity to the radio. It occasionally serves that function, but it is secondary to the battery's primary function, which is to power the starter, the electric motor that starts the engine. Once it is running, the engine supplies the energy for the radio and all the car's other power needs. Similarly, the skeleton acts as a *temporary* source (or reservoir) for calcium and phosphorus ions, but from a mechanical perspective, those minerals are essential to make bones stiff and strong. Their withdrawal from bone during long-term dietary insufficiency would have dire implications for the skeleton.

Thus, in the same way that a stagehand may periodically serve as a minor actor in a play, the skeleton acts as a mineral reservoir, periodically exchanging (withdrawing *and* replacing) a very small fraction of its mineral content with the rest of the body. However, the great mass of bone mineral is essential for its contribution to mechanical properties. Bones provide structure to the body, organizing its components in space, and transmitting muscle forces from one part

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of the body to another, or to the environmental surroundings: e.g., standing erect to get a better view, holding an infant in one's arms, or throwing an object. In addition to numerous other mechanical functions, bones are particularly important in enabling locomotion, as in walking, swimming, or climbing. From this perspective, bone biology may be viewed as largely mechanically driven.

In addition to making bones stiff, the relative abundance of mineral has another mechanical consequence: it makes bone heavy. Bone tissue is approximately twice as heavy per unit volume as other body tissues (about 2 gm/ml vs. 1 gm/ml). This makes the metabolic energy required for repeatedly and rapidly moving bones during locomotion and other activities sensitive to bone mass as a major component of body weight, especially in the limbs. Consequently, reducing bone mass decreases the associated metabolic energy requirement, whatever the vertebrate's evolutionary niche. In the following analysis this concept is pursued in the context of three fundamental mechanical problems that bones must overcome.

Three fundamental problems for bones

Problem 1: Bone tissue is metabolically expensive

The very fact that bone tissue is twice as heavy as soft tissues means that it is metabolically expensive, and that is the first fundamental problem that vertebrates face. A certain muscle mass consuming energy at a certain rate is required to cyclically move the bones within a limb at a given frequency. Furthermore, because the density of bone is approximately twice that of other body tissues (~ 2 gm/cm^3 vs. 1 gm/cm^3), muscle weight must generally increase in proportion to skeletal weight. In turn, more muscle mass dictates that the cardiovascular and pulmonary systems, as well as other physiologic organs, must increase in size to deal with the required energy and waste products. Consequently, total body weight strongly depends on musculoskeletal weight. From this perspective it appears that, by devising a system for minimizing skeletal mass in relation to a species' functional requirements, bone biology has evolved cells and strategies producing remarkable mechanical efficiencies. For example, the skeletons of young human adults weigh only about 6% or one sixteenth of total body weight[1]. Conversely, an ounce of bone costs about a pound of everything else: i.e., the tissues of the cardiovascular, digestive, and neuromuscular systems, and so forth, that keep everything else functioning along with the skeleton. This is not to claim that minimizing bone mass is the "golden rule" of bone biology. It is obvious that there have been and continue to be evolutionary advantages for large as well as small vertebrates in many environments. However, because the metabolic energy required for survival is a direct function of muscle mass and bone mass, however large or small the skeleton may be, keeping it as light as possible relative to the size of the animal should be advantageous.

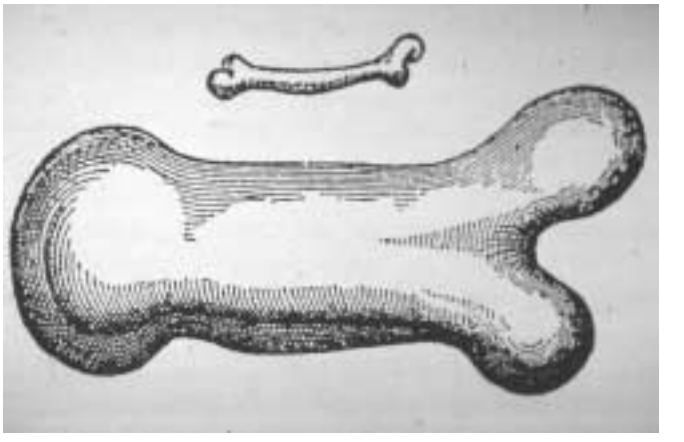

Figure 1. Galileo's illustration of a typical relationship between bone size and anatomical shape.

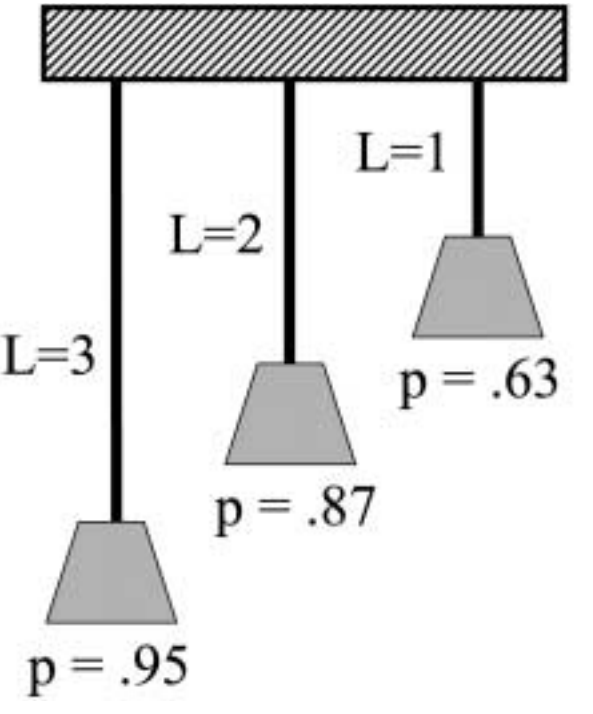

Figure 2. da Vinci's demonstration of a volume effect in the strength of iron wires.

Problem 2: Squares, cubes, and proportions

The next mechano-volumetric skeletal problem considers how the *proportions* of bones are affected by the overall size of the animal. The earliest discussion of this on record seems to be that of Galileo Galilei (1564-1642). Galileo observed that mechanics govern bone anatomy, and in particular the proportions of bones. The bones of larger vertebrates are

"stout" (Figure 1): their diameters are large relative to their length. Furthermore, he proposed that this happens because the weight of the animal increases as the cube of its general size, but the cross-sectional area of its bones only increases as the square of its size. Because the stress in a structure loaded in simple compression is the applied force per unit cross-sectional area, and the forces acting on the extremities of vertebrate skeletons are primarily due to body weight, the stresses within them should increase in approximate proportion to the animal's size. Galileo proposed that larger vertebrates have disproportionately stouter (i.e., increased diameter relative to length) bones to keep stress at a tolerable level. Thus, the limbs of an elephant have different proportions than those of a gazelle, and the same is true of their bones.

Problem 3: Bones contain flaws

The third problem for bones and skeletons is that bone tissue, like other structural materials, contains flaws that cause locally high stresses when it is mechanically loaded. These flaws consist of microscopic or sub-microscopic (molecular) irregularities that constitute local weaknesses capable of initiating microcracks or more diffuse kinds of damage when mechanically loaded[2]. From a statistical perspective, the more molecules there are in a structure, the greater the probability of a flaw occurring that is capable of precipitating a crack that initiates a fracture. Consequently, other things being equal, when larger volumes of bone are subjected to a given mechanical environment, they are more likely to contain microstructural or nanostructural flaws capable of initiating and propagating a crack leading to fracture.

Leonardo da Vinci demonstrated this phenomenon some 500 years ago[2]. He tested the tensile strength of iron wires by hanging weights from them. The wires were of the same diameter, and therefore the same cross-sectional area, but of varying length (Figure 2). The stress in the wire depends only on its cross-sectional area and the applied force; thus, each wire experienced the same tensile stress for a given test weight. However, the results showed that longer wires failed at lower stresses than shorter wires. As noted above, the modern interpretation of these results is that the longer wires had larger volumes and were therefore more likely to contain a flaw of critical size capable of precipitating fracture. Centuries later Weibull[3] developed a mathematical theory capable of predicting these effects based on a "weakest link in the chain" principle, and this approach to strength of materials analysis is now supported by a substantial body of theoretical and experimental research[4].

Application of the Weibull theory to bone has been limited[5], but during the last decade Taylor and co-workers have provided evidence that volume effects may be significant in bone[6-8]. The potential implications for bone mechanics and biology are substantial for the following reasons. While the strains (and stresses) in bones are remarkably uniform across species[9], the volumes of individual bones and skeletons vary widely across species, as noted above. For example,

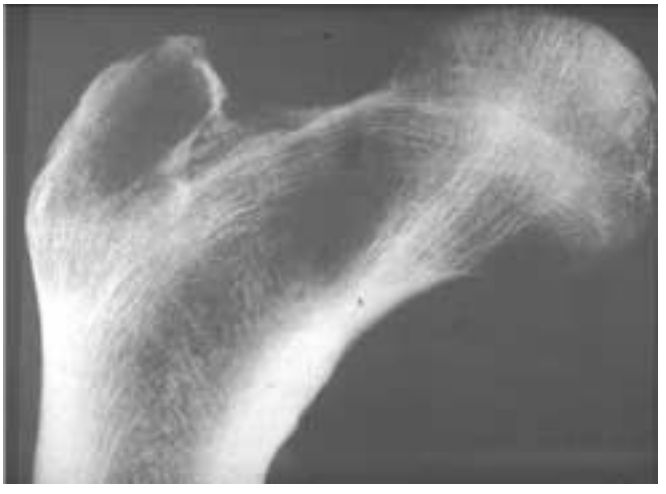

Figure 3. Typical bony architecture in the proximal human femur.

the volume of an elephant's femur is about 30,000 times greater than a shrew's femur. Weibul theory predicts that this difference in volumes would lead to stark reductions in bone strength. Using data describing the physiologic strains normally occurring in human tibias and other bones, Taylor and Kuiper[8] calculated that the fatigue life of a human tibia should only be about three years. The implication is that our tibias do not usually fracture because microcracks constantly occurring in them are being removed by remodeling. This theory is consistent with (1) the observation that microdamage and remodeling are consistently found in larger vertebrates, from ferrets to horses, but not in mice and other small vertebrates, and (2) the repeated demonstration that microdamage activates remodeling *in vivo*[10-12].

Consequently, Problems 1 (weight) and 2 (proportions) are aggravated in larger vertebrates by Problem 3, the effect of volume on flaws. From an evolutionary perspective, one can understand why both large and small vertebrates can find their size advantageous for certain behaviors in a particular environment. However, whether a vertebrate is very small, very large, or in between, having smaller bones relative to its overall size provides advantages with respect to the energy required to survive. If "volume effects" weaken bone, how can this enormous range of successful skeletal sizes be explained? How can the disadvantages of bone "large size problems" be ameliorated?

Remodeling and bone volume problems

Figure 3 shows a radiograph of a proximal human femur. The often cited archetypal trabecular architecture in this region is an example of a general phenomenon seen in all vertebrate skeletons: the creation of local microscopic architectures that are mechanically efficient in terms of strength relative to weight[13]. This phenomenon is the result of "remodel-

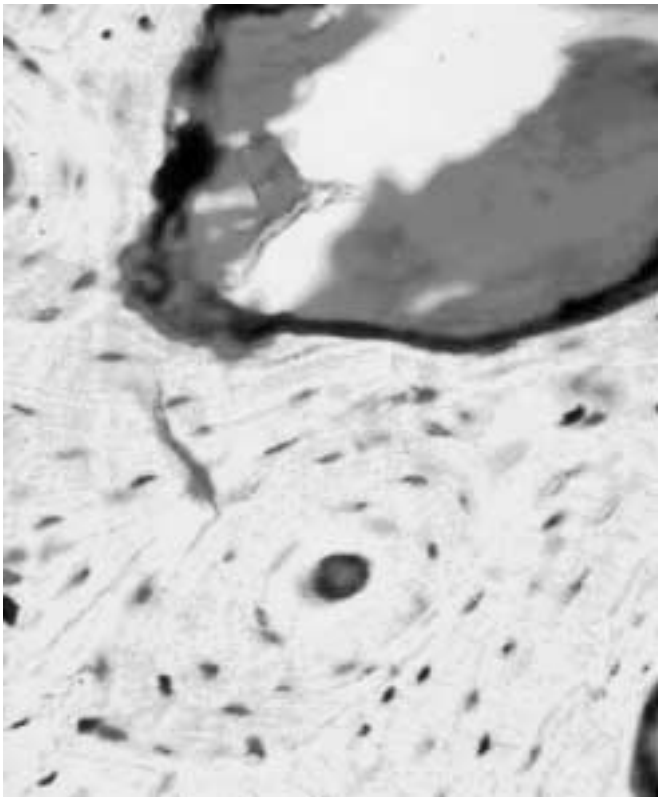

Figure 4. Remodeling resorption space adjacent to a microcrack in human femoral bone.

ing" carried out by the teams of cells that Frost named Basic Multicellular Units (BMUs)[14]. Current theory holds that BMUs remove and replace small volumes of bone, and in doing so build an efficient microstructure, i.e., one in which the amount of bone is adjusted to maintain maximum strains at a "set point" value[9,15,16]. According to the Weibull theory the reduction in the volume of bone tissue should reduce the probability of a flaw leading to microdamage accumulation and failure. Thus, this bone remodeling automatically and simultaneously controls both bone density (to keep the skeleton light) and fatigue damage that occurs routinely because the strains in the light skeleton are relatively high.

Figure 4 shows the initial resorptive phase of remodeling adjacent to a typical fatigue crack. Such microdamage produces signals that activate remodeling, which is the only way to remove it. Figure 5 shows that the mean lengths of microcracks in human femoral diaphyseal cross-sections diminish in proportion to the numbers of BMU resorption spaces per mm^2. The fact that a significant decrease in crack *numbers* (as opposed to *length*) did not occur with increased remodeling activity in these specimens (data not shown) suggests that BMUs serve to control the sizes of cracks rather than their numbers. The energy required to propagate a crack decreases in proportion to its $length^2$. It is therefore more important to reduce crack lengths than to completely remove them. Consequently, minimizing bone mass boils down to maintaining a fine balance between reducing skeletal weight and controlling fatigue damage.

Frost pioneered interest in the biological control system that maintains this balance, and Figure 6 sketches the present author's concept of how this system may function, based on concepts put forth by Frost and a number of other authors[13,15,17-20]. At upper right, a bone having a certain anatomical shape and size is assumed to be acted upon by external forces. The box beneath it represents the interior bone tissue and the effects of remodeling. The bone's anatomical structure determines the stress at any given location produced by the external force, and the bone tissue's elastic modulus at that point determines the local strain. If the strain is too high, microdamage is produced.

At left is another box representing the osteocyte syn-

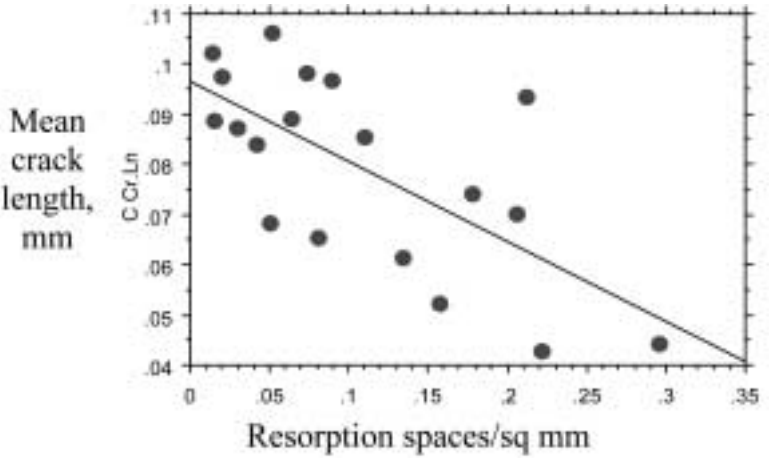

Figure 5. Demonstration that microcrack lengths in human femoral bone decrease in proportion to the intensity of bone remodeling.

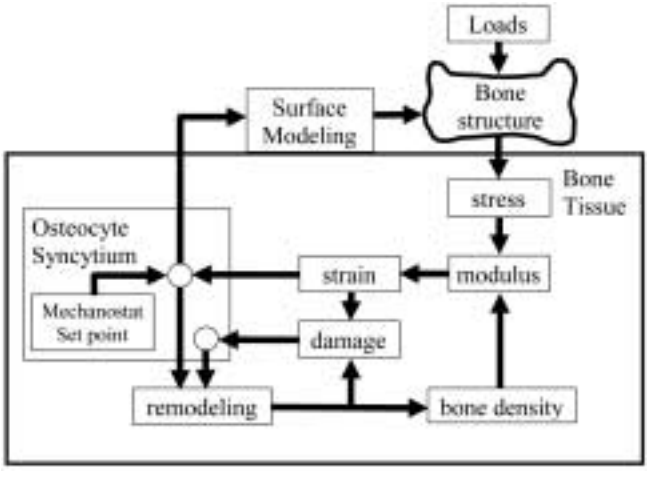

Figure 6. Diagram of putative mechanostat system. See text for details.

cytium distributed through the bone tissue, thought to activate remodeling in response to either low strain or microdamage. In the former case, strain is compared to a "set point", and if the two do not agree, bone remodeling is initiated to correct the strain. In addition, remodeling may be adjusted within the bone tissue to increase or decrease the bone volume fraction (BVF), thereby altering the elastic modulus so that the bone strain corresponds to the set point. Finally, the osteocytes distributed throughout the bone matrix have the ability to detect microscopic fatigue damage and activate local remodeling to remove the damaged material and replace it with new bone. As suggested by the diagram, the components of this feedback control system are interlinked and work in conjunction with one another.

The mechanostat set point is not yet understood, but appears to be encoded somewhere in the osteocyte syncytium. Osteocytes experience *apoptosis* (programmed cell death) at either end of the strain scale: when average strains are excessively low, or when they are so high as to produce microdamage. Both result in the activation of remodeling and the removal of accumulated microdamage and/or bone mass, depending on the circumstances. Together, the strain set point and the loads carried by individual skeletons determine their bone mass and risk of fracture. A low strain set point results in a more robust skeleton that presumably is less likely to fracture but weighs more and is metabolically more expensive. Conversely, a high strain set point weighs less but is more likely to fracture. Presumably, various species and groups within a species have evolved different strain set points that improve their ability to survive in a given environment. Recent examples of families having "high bone mass genes" have provided evidence for such a "mechanostat" in bone cells, and clues to its location and mechanism[21,22].

When did this remarkable remodeling-mechanostat system, that enables a skeleton to be simultaneously light and fatigue-resistant, evolve? The answer to this question may be sometime prior to the Permian era, 245-286 million years ago, because the fossil record shows that bone remodeling existed in relatively large vertebrates of that era. Published work shows relatively large marine vertebrates (about the size of small alligators) that were apparently amphibious and weight-bearing on land at that time: Archeria, Edpos, and Eryops. The bones of these vertebrates clearly exhibit cortical bone remodeling[23-25]. The fact that the skeletons of these animals are characteristic of amphibians is significant because skeletal weight would become more important when the buoyancy of a marine environment was lost. Larger bones would be needed to support gravitational forces, and that in turn would bring "volume effects" into the vertebrate bone equation for the first time. In any event, the phenomenon of bone remodeling apparently evolved when relatively large vertebrates became weight-bearing, and has persisted during the subsequent hundreds of millions years.

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