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EDITORIAL

Bone quality

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Introduction

This supplement contains the proceedings of a workshop aimed at defining the material, cellular, and structural basis of bone fragility. This meeting brought together investigators with expertise in bone's trabecular and cortical macroscopic and microscopic architecture, its inorganic, organic, and cellular composition, bone modeling and remodeling, the local and systemic regulators of bone cell differentiation and function, extracellular matrix proteins, angiogenesis, mechanisms of mechanotransduction, biomechanics, and genetic research. The purpose of the meeting was to unify these highly specialized areas by directing each topic toward a better understanding of the pathogenesis of bone fragility.

The principles of bone remodeling and the current status of drug therapy are discussed by Robert Heaney and Robert Lindsay, respectively. John Bilezikian discusses bone quality in metabolic bone disease, in particular primary hyperparathyroidism. The inorganic and organic composition of bone in relation to its strength is discussed by John Currey. Dr. Currey contrasts the effects of alterations in the proportions of mineral, organic, and water content on the stiffness and toughness of bone tissue. Increasing mineral increases the stiffness of bone tissue, while decreasing collagen reduces the toughness of bone material. The contribution of collagen to strength may be less in cortical than in trabecular bone.

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The organic constituents of the extracellular matrix are discussed by Caren Gundberg. Dr. Gundberg reviews the role of matrix proteins in the nucleation of mineral, remodeling, recruitment and attachment of cells, storage of growth factors, bone formation, and transduction of mechanical stimuli. The nature of the mineral phase of bone and methods of its measurement are discussed by Adele Boskey and Georges Boivin, respectively. Dr. Boskey emphasizes that extremes of crystal size reduce the mechanical properties of bone and reviews the effects of drug therapy on the size and distribution. Dr. Boivin reviews the effects of disease states and drug therapy on the degree of mineralization of bone tissue, which in turn may influence bone strength independent of its structure. Janet Rubin discusses the cell types critical to bone strength, the critical role of loading in regulating bone remodeling and the importance of integrin receptors, guanine regulatory proteins, ion channels, kinases, and nitric oxide as signals transducing strain. The neglected area of angiogenesis in the role of bone formation and bone strength is discussed by Dwight Towler. Dr. Towler points out that anabolic responses are accompanied by angiogenesis and endothelial, and mesenchymal cell interactions. He discusses the role of microvascular smooth muscle cells (pericytes) as mesenchymal progenitors that contribute to bone formation and the role of vascular endothelial growth factor in bone formation.

The architecture and structure of cortical and trabecular bone is discussed by David Dempster. He clearly distinguishes between the effects of antiresorptive agents, which stabilize the structural decay of bone, and anabolic agents, which contribute to the reconstruction of the skeleton. Karl Jepsen and Ralph Müller continue the discussion of bone structure and methods used in its assessment. Dr. Jepsen discusses the complexities contained within the words "cortical bone strength" and the fact that this is determined by the mode of loading, its rate, direction, cycle number, and other factors as well as the resistance of bone to damage produced by the interfaces stemming from cement lines and lamellar

structure within the osteons. The role of periosteal apposition in maintaining bone strength in the face of continuing endosteal bone loss is discussed by Tom Beck. The topics of microdamage and the role of remodeling in microdamage repair are discussed by David Burr and Mitchell Schaffler, respectively. The importance of microdamage in fracture remains uncertain. Factors initiating cracks, factors determining crack growth, and the cessation of progression of cracks and their removal are discussed. Genetic studies in animals are addressed by Robert Shmookler Reis and Robert Ebert, while genetic studies in human subjects are discussed by Sergio Ferrari.

The overview that follows briefly reviews the development and decay of the material and structural determinants of bone strength and attempts to place some of the topics discussed below into a clinical context. I would like to thank Dr. Stephen Morris and Dr. Mary Bouxsein for their initiative in organizing this meeting and Aventis Pharmaceuticals for providing an unrestricted grant that made this meeting possible. We hope that these proceedings, the transcripts of the discussions, and the extensive bibliography that follows each presentation narrows the gulf between the seemingly disparate and inaccessible worlds of basic science and clinical bone biology, making each accessible and meaningful to the reader.

Bone fragility is a problem in biomechanics

Bone tissue must have contradictory properties to serve the differing functions of the skeleton. Bone must also be light for speed of movement, yet strong for load-bearing. It must be stiff, able to resist deformation for load-bearing and propulsion against gravity, yet flexible—able to absorb the energy imparted during impact loading by changing shape (deforming) or releasing it by fracturing (as energy cannot be destroyed). As fracture is not a desirable alternative, nature finds a compromise between stiffness and flexibility, lightness and bulk, by selecting the material composition and structural features most suited to the usual functions of bone.

Nature varies the stiffness of bone material by modulating the concentration of the crystals of hydroxyapatite-like mineral in the triple helix of type I collagen matrix. Higher mineral content increases stiffness but at the expense of flexibility. If the mineral content is excessive in relation to the loads usually imposed upon it, brittleness results; cracks occur even with slight deformation. For example, vibrating ossicles are 90% mineral. While the high degree of stiffness is suited to their function as sound transducers, their low flexibility causes them to crack even if slightly loaded. By contrast, antlers, structures that are not weight-bearing but used for head-butting to fight off other suitors during the mating season, must be flexible and spring-like, so that they can absorb energy by bending. They have a tissue mineral content of only about 30%, conferring the flexibility needed for the function they are designed to fulfill. If the mineral content of this appendage were to be increased, deer would soon be extinct, as fractured antlers in a suitor are a disincentive to a doe. Human bone is about 45% mineralized; if undermineralized (due to high remodeling states), bone becomes too flexible and will reach its peak tolerable strain, bend too much in loading, and crack. If overmineralized (if remodeling is greatly suppressed), it will become brittle and crack.

This material is fashioned into three-dimensional geometric and architectural masterpieces of biomechanical engineering—minimal mass optimized in size and shape according to whether the main function is as a lever or a spring. For load-bearing and leverage, the need for stiffness and lightness is favored over flexibility by the fashioning of mineralized tissue into long bones with a marrow cavity displacing the mineralized cortex distant from the neutral bone axis. Vertebral bodies, spring-like shock absorbers, in which stiffness and peak load-bearing are sacrificed for flexibility, show an open-celled porous cancellous structure able to deform and return to its original size and shape without cracking. Thus, nature selects the material and structure most suited to their usual function by varying the mineral content of the material and the degree of porosity: minimal in cortical bone, and maximal in trabecular bone.

These material and structural properties degrade with age because the mechanisms constructing (modeling) and reconstructing (remodeling) the skeleton fail. Remodeling repairs microdamage but during aging less bone tissue is deposited than is removed in each remodeling of the basic multicellular units (BMUs). After menopause, increased remodeling with a more negative bone balance in the many BMUs removes more bone more rapidly from an ever-diminishing and architecturally disrupted bone. The high remodeling and negative bone balance produce bone loss, trabecular thinning and loss of connectivity, cortical thinning, and porosity. Older, more densely mineralized interstitial bone, distant from surface remodeling, has reduced osteocyte numbers and accumulates microdamage, while more superficial bone is replaced with younger, less-mineralized bone, reducing stiffness. Bone modeling by periosteal apposition reduces compressive stress (load per unit area) by distributing loads on a larger area, and so partly maintains bending strength. It may be impaired due to abnormalities in periosteal osteoblast production, function or life span, osteocyte signaling, or deficiency.

A rational approach to intervention using drug therapy requires the unambiguous definition of the material and structural determinants of strength embraced by the word "quality" and the mechanisms responsible for the decay of these material and structural properties. These mechanisms may include abnormalities in one or more of the categories of bone size, cortical thickness, porosity, trabecular number, thickness, connectivity, bone tissue mineral content, microdamage production, progression, cessation and removal, rate of remodeling, extent of resorption and formation in each

BMU, osteocyte number and distribution, and periosteal apposition. There is progress in these areas.

Nature selects material for function

Long bones are levers that must have the contradictory properties of strength yet lightness, and stiffness yet some flexibility. Bone must be strong for load-bearing, yet light to allow movement [1]. Resistance to bending (stiffness) can be achieved with bulk, like the pylons of the Parthenon, but bulk takes time to grow, is costly to maintain, and difficult to move. If bones were flaccid rather than rigid, objects could not be lifted, supported, or moved against gravity during muscle contraction. However, flexibility is also needed to absorb the energy of impact loading. The elastic properties of bone allow it to absorb energy by changing shape without structural failure. Provided displacement occurs in the elastic zone, no permanent structural damage occurs. If the imparted energy produces displacement which exceeds the zone of elastic deformation, plastic deformation occurs but at the price of microdamage and permanent change in morphology. If the displacement exceeds the elastic and plastic zones of deformation, the imparted energy must be dissipated by fracture—not a good option for the host who must move to catch dinner or avoid becoming it.

Nature chooses the material and the amount of material for the function needed. A most important material property of bone is the degree of mineralization of its tissue. The greater the tissue mineral content or ash density, the greater the stiffness and the peak stress the bone will tolerate [2]. But more is not necessarily better: 100% mineralized bone is brittle and will not give during impact-loading. Increasing mineral content is associated with declining toughness. Deer antlers are modestly mineralized so that they are suited to their function in the animal's fight with suitors for a mating partner; they are not weight-bearing, so flexibility (''toughness'') rather than stiffness is needed. The impact energy imparted by an impala, for example, must be absorbed by the antlers in bending without cracking—strength is reflected in the ability to deform before breaking [3]. The ossicles of the ear, as another example, are transducers of sound and thus need to be 90% mineral for stiffness.

Nature selects structure for function

Strength and lightness are also achieved by architectural design. Long bones are weight bearing and should not bend too much, that is, stiffness is favored over flexibility. Bone tissue is fashioned into long bones with a medullary canal, and cortex of mineralized tissue placed distant from the central long axis, a geometric feature which confers greater resistance to bending than the same unit area placed near its long axis. The resistance to bending (the moment of inertia) is a function of the fourth power of the distance from this long axis [4].

By contrast, the vertebral bodies are structures consisting of an open porous ''spongiosa'', a mineralized interconnecting honeycomb of plates that function like springs able to store energy by deforming in compression. This structural adaptation achieves lightness by its porous network, with strength in tolerating greater peak strains than cortical bone while sacrificing peak stresses (load/area) compared to cortical bone. The trabecular structure withstands larger deformations to facilitate flexion, extension, and rotation of the whole vertebral skeleton of the upper body.

The construction (modeling) of the skeleton by growth in size, shape, and architecture

As long bones grow in length and diameter, the mass of bone inside the periosteum increases and is fashioned into a cortex by creation of a marrow cavity which effectively moves the cortical shell further and further from the neutral or long axis of the long bone. The absolute and relative movements of the periosteal and endosteal envelopes determine the diameter of the long bone, the mass of cortical bone, its cortical thickness, cross-sectional area (CSA), and the distance this cortical mass is placed from the neutral axis of the bone.

Growth builds a bigger, wider, and longer long bone in males than in females, but the thickness of the cortex is similar or only slightly greater in males (after height and weight adjustment) so the volumetric apparent bone mineral density (BMD) of long bones such as the femur is constant and independent of age and sex [5]. The main sex difference in bending strength is achieved, not by the thickness of the cortex, but by the placement of the cortex further from the neutral axis in males than in females. This greater radial displacement of the cortex also produces a larger CSA upon which compressive loads can be distributed. So the larger bone in males has a larger CSA upon which larger muscles exert the same load per unit area—that is, stress on the bone CSA is no different in young males and females because of this scaling in nature.

Vertebral bodies increase in length, width, and depth. The length and thickness of the trabecular plates increase in proportion to the enlarging vertebral body. At puberty, trabecular apparent BMD increases to a similar degree in boys and girls, so that males and females have the same vertebral body, trabecular number, and thickness at peak [6]. Growth builds a bigger vertebral body in males, not a more dense vertebral body, so that the greater peak load tolerated in males is due to the larger size, not higher density, and the load per unit area in young males and females is no different.

The reconstruction (remodeling) of the skeleton during adulthood—emergence of fragility

Bone fragility is the result of abnormalities in bone remodeling and modeling, the two processes that

maintain the material and structural elements in a pristine state. During aging, bone remodeling occurs at discrete BMUs on the trabecular, endocortical, and intracortical components of the bone's endosteal envelope. One of the functions of remodeling is to remove older damaged bone and replace it with younger bone.

At some time before menopause, bone balance starts to become negative due to a reduction in the amount of bone formed in each BMU [7]. The negative bone balance within each BMU is the basis of bone loss which produces structural damage—cortical thinning and intracortical porosity, trabecular thinning, complete loss of trabecular plates, and loss of connectivity. The same loads on bone are imposed on a structure diminished in CSA so that the load per unit area increases the predisposition to buckling, microdamage, and ultimately fracture.

Women and men lose similar amounts of trabecular bone during aging [8]. However, trabecular thinning predominates in men, while loss of connectivity dominates in women [9]. The residual strength of the vertebrae decreases more with loss of connectivity than with thinning. Loss of connectivity is the result of the accelerated loss of bone in women due to estrogen deficiency, which increases remodeling intensity and may aggravate the imbalance in the BMU as the life span of osteoclasts increases and that of osteoblasts decreases [10].

While the imbalance in the remodeling produces structural damage, abnormalities in the rate of remodeling affect the material properties of bone, particularly the bone tissue mineral content. If the remodeling rate increases, older, more mineralized bone is replaced by younger, less mineralized bone. This reduces the stiffness of bone or its resistance to bending. If remodeling is very slow, more time is available for secondary mineralization and thus bone stiffness increases, that is, the resistance of bone to development and progression of microdamage (toughness) decreases (bone becomes brittle).

Microcrack progression is prevented by the composite nature of the bone material created by differing mineral density and differing direction of the mineralized collagen fibers. Cracks require energy to progress through bone, and when the mineral density is high and distribution of the tissue mineral density is homogeneous, less energy (derived from deformation) is needed for microdamage progression. Reduced remodeling also reduces the removal of microdamage. Thus, the microdamage burden increases as a result of both increased production and reduced removal of microdamage [11].

Construction (modeling) by periosteal bone formation during aging

Age-related periosteal bone formation offsets endosteal bone loss. Greater periosteal bone formation in men offsets endosteal bone loss more than in women [12]. The lower net decrease in BMD at the spine in men than in women is due to deposition of more periosteal bone rather than the removal of less endosteal bone [13].

Fragility fractures are uncommon in young adults because loads are well below the ability of the bone to withstand them. Structural failure emerges during aging because periosteal bone formation fails to completely offset the fragility produced by bone loss and architectural destruction inside the bone. Greater periosteal apposition in men during aging decreases the load per unit area on bone more than in women because the load is more widely distributed, while architecture is less disrupted in men. A lower proportion of elderly men than elderly women have bone size and architectural and material properties, such as microdamage, tissue mineral density, loss of connectivity, porosity, trabecular and cortical thinning, below a critical level (or fracture threshold), where the stresses are greater than the bones ability to resist them.

Goldilocks, Mama, Papa and Baby Bear: keeping the porridge just right

Bone quality is a vague term. Progress in understanding the pathogenesis, prevention, and reversal of bone fragility depends on the unambiguous definition of the material and structural properties of bone that determine its resistance to structural failure: bone size, cortical thickness, trabecular number, thickness, connectivity, tissue mineral content, microdamage burden, osteocyte density, porosity, and properties of collagen such as its crosslinking.

Age- and menopause-related abnormalities in remodeling rate and BMU balance produce loss of the material and structural properties that keep bone "just right" for the species-specific functions it must perform. High remodeling reduces the mineral content of bone tissue and thus its stiffness. Low remodeling increases bone stiffness and microdamage production, and reduces microdamage repair. Sex hormone deficiency increases the volume of bone resorbed and reduces the volume of bone formed in each BMU, producing bone loss and structural damage.

The challenge for the future is to measure each of these material and structural determinants of bone strength. In doing so, it may be possible to identify women at risk for fractures more accurately and to improve approaches to drug therapy. The purpose of the Bone Summit was to try to define these structural and material properties so that investigators of materials, biomechanics, engineering, and biology begin to talk the same language. We hope that the reader enjoys the subjects covered in this series.

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