Bone Strength: Current Concepts

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ABSTRACT: Bones serve several mechanical functions, including acoustic amplification in the middle ear, shielding vital organs from trauma, and serving as levers for muscles to contract against. Bone is a multiphase material made up of a tough collagenous matrix intermingled with rigid mineral crystals. The mineral gives bone its stiffness. Without sufficient mineralization, bones will plastically deform under load. Collagen provides toughness to bone making it less brittle so that it better resists fracture. Bone adapts to mechanical stresses largely by changing its size and shape, which are major determinants of its resistance to fracture. Tissue is added in regions of high mechanical stress providing an efficient means for improving bone strength. Experiments have shown that small additions of bone mineral density (BMD) (5–8%) caused by mechanical loading can improve bone strength by over 60% and extend bone fatigue life by 100-fold. Consequently, it is clear that bone tissue possesses a mechanosensing apparatus that directs osteogenesis to where it is most needed for improving bone strength. The biological processes involved in bone mechanotransduction are poorly understood and further investigation of the molecular mechanisms involved might uncover drug targets for osteoporosis. Several pathways are emerging from current research, including membrane ion channels, ATP signaling, second messengers, such as prostaglandins and nitric oxide, insulin-like growth factors, and Wnt signaling.

KEYWORDS: biomechanics; fracture; osteoporosis; mechanotransduction

BACKGROUND

The skeleton serves several functions.[1] Probably most importantly, it provides a ready source of calcium ions to maintain appropriate serum calcium levels and facilitate proper muscle function. Bones also provide acoustic amplification and impedance matching in the middle ear. But here we will focus

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on the skeleton as a structure. There are at least two key biomechanical roles for bones. First, bones shield vital organs from trauma. In the skull, mechanical energy resulting from blunt trauma concentrates mainly in the spongy bone separating the bony plates. Consequently, very little energy is transferred to the innermost bony plate and the cranial vault is preserved. In addition, bones serve as levers for muscles to contract against. To better distribute joint forces, the ends of long bones are broadened to reduce stress (load/area) and that stress is carried by trabecular bone beneath the joint surface to distribute the force into the long bone cortex.

BASIC BIOMECHANICS

There are a number of biomechanical parameters that can be used to characterize the integrity of bone. The key relationship is that between load applied to a structure and displacement in response to the load-displacement curve (FIG. 1). The slope of the elastic region of the load-displacement curve represents the extrinsic stiffness or rigidity of the structure (S). Besides stiffness, several other biomechanical properties can be derived, including ultimate force (F_u), work to failure (area under the load-displacement curve, U), and ultimate displacement (d_u). Each of these measured parameters reflects a different property of the bone: ultimate force reflects the general integrity of the bone structure; stiffness is closely related to the mineralization of the bone; work to failure is the amount of energy necessary to break the bone; and ultimate

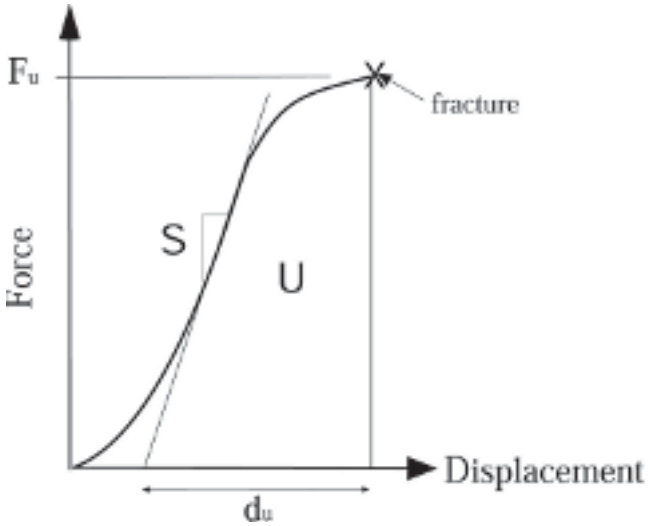


FIGURE 1. Load-displacement curve for bone tissue. The slope of the linear region of the curve represents the extrinsic stiffness or rigidity of the structure (S); the height of the curve denoted ultimate force (F_u); area under the curve is work to failure (U); and total displacement to fracture is ultimate displacement (d_u).

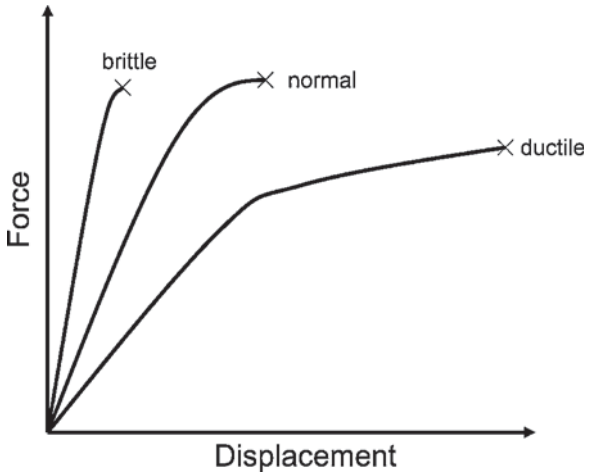


FIGURE 2. Load-displacement curves for different bone conditions. Osteopetrotic bone is brittle and thus displays reduced work to failure. On the other hand, a bone from a young child is ductile with larger ultimate displacement, resulting in increased work to failure.

displacement is inversely related to the brittleness of the bone. The biomechanical status of bone may be poorly described by just one of these properties. For instance, a bone from an osteopetrotic patient will tend be very stiff, but also very brittle, resulting in reduced work to failure and increased risk of fracture (FIG. 2). On the other hand, a bone from a young child will tend to be poorly mineralized and weak, but very ductile (large ultimate displacement), resulting in increased work to failure. Because of these properties, "greenstick" fractures, in which the bone undergoes large deformation but does not completely break, are sometimes observed in children.

When load is converted to stress and deformation converted to strain by engineering formulas, the relationship between stress and strain in bone follows a curve called the stress–strain curve. The slope of the stress–strain curve within the elastic region is called the elastic or Young's modulus (E). The Young's modulus is a measure of the intrinsic stiffness of the material. The area under the stress–strain curve is a measure of the amount of energy needed to cause material failure. This property of a material is called energy absorption or modulus of toughness or just toughness. The maximum stress and strain the bone can sustain are called the ultimate strength and ultimate strain, respectively. It should be noted that strength, as it is defined by the stress–strain curve, is an intrinsic property of bone. That is, these strength values are independent of the size and shape of the bone. The force required to break the bone is different from the intrinsic strength, because ultimate load will vary with bone size. It is important to keep this distinction in mind because intrinsic strength and ultimate load can show different trends in drug or genetic studies, especially

if the drug or gene affects the size of the bone. Strength measures that are not presented in units of stress do not represent the intrinsic strength of the material but are influenced by extrinsic factors like specimen size and shape.

The elastic strain region and the plastic strain region of the stress-strain curve are separated by the yield point (FIG. 3). The yield point represents a gradual transition, above which stresses begin to cause permanent damage to the bone structure. Post-yield strains (i.e., strains beyond the yield point) represent permanent deformations of bone structure caused by slip at cement lines, trabecular microfracture, crack growth, or combinations of these. The yield point is seldom well defined when testing bone specimens. Several methods have been proposed to determine the yield point. For instance, the yield point is often defined as the point where the stress-strain curve begins to become nonlinear.[2] Other techniques include offset methods where a line parallel with the linear portion of the stress-strain curve and offset by 0.03% to 0.2% strain is constructed.[3] The point where this line intersects the stress-strain curve is arbitrarily called the yield point.

WHY BONES BREAK

Strength and stiffness are typically used to define the "health" of a bone, but they are not as clearly related to risk of fracture as is the amount of energy

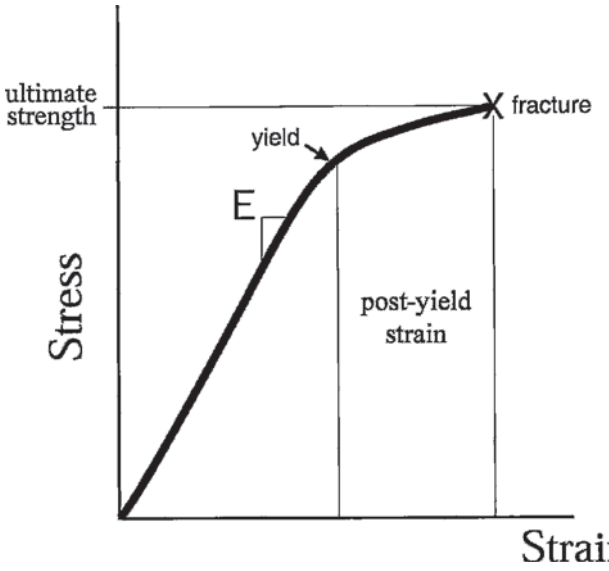


FIGURE 3. Stress-strain curve for bone. The slope of the curve is called Young's modulus (*E*). The height of the curve is the ultimate strength. The yield point represents a transition, above which strains begin to cause permanent damage to the bone structure. Post-yield strain is inversely proportional to the brittleness of the bone.

required to cause fracture. Trauma transfers energy into the bone and, if that energy exceeds what the bone can absorb, the bone will break. A bone that is highly mineralized is also stiff and brittle and will require much less energy to fracture (the area under the curve) than a bone that is more compliant. Bone mineral density (BMD) is highly correlated with strength and stiffness, but there is an inverse relationship between bone stiffness (or Young's modulus) and ultimate strain (FIG. 4). Deer antler, which is not highly mineralized, has a very high ultimate strain (ductility) but low Young's modulus. This combination of properties makes an antler exceedingly difficult to break.[4] On the other hand, the tympanic bulla of a fin whale has high mineral content, high Young's modulus, and is very brittle. The bulla is not as strong as antler or bone due to its brittleness. However, it is not designed for strength, but for acoustic properties. Like the middle ear ossicles, the bulla is highly mineralized to provide proper acoustic impedance. Long bone tissue has intermediate mechanical properties.

Cracks forming in bone tissue provide a means by which energy is released. Energy absorbed by the bone during loading builds up and is released as damage accumulates or when the bone fractures. Bone subjected to high-energy trauma, such as a gunshot wound, will form many cracks because energy accumulates quickly and must be released. High-energy trauma causes

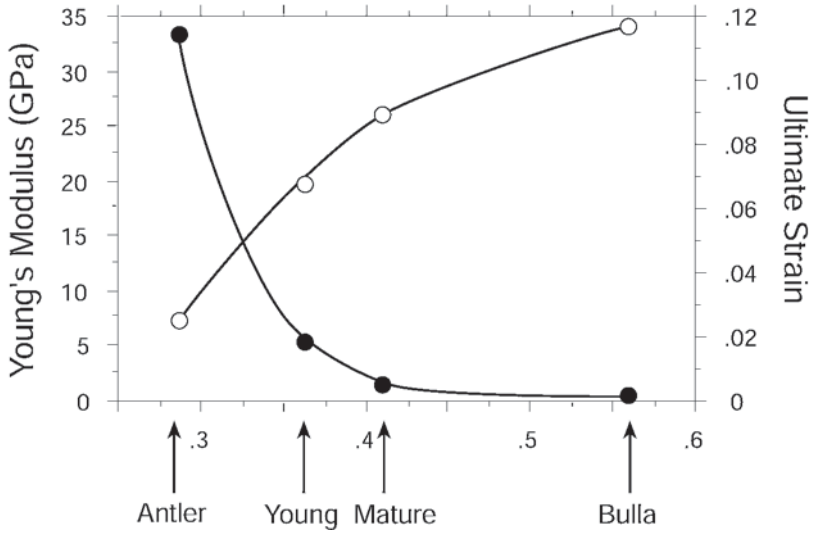


FIGURE 4. Biomechanical properties of mineralized tissues (from Currey 1990). As mineral volume fraction (x-axis) increases, Young's modulus (*open circles*) is improved but ultimate strain (*closed circles*) decreases. Deer antler is less stiff (lower Young's modulus) and less brittle (higher ultimate strain), whereas the tympanic bulla from a fin whale is very brittle and stiff. Bone tissue from young (1-year-old) cows is less stiff and brittle than tissue taken from mature (9-year-old) cows. (Reprinted from Bone Formation, F. Bronner and M.C. Farach-Carson, eds., copyright 2004, with permission from Springer-Verlag.)

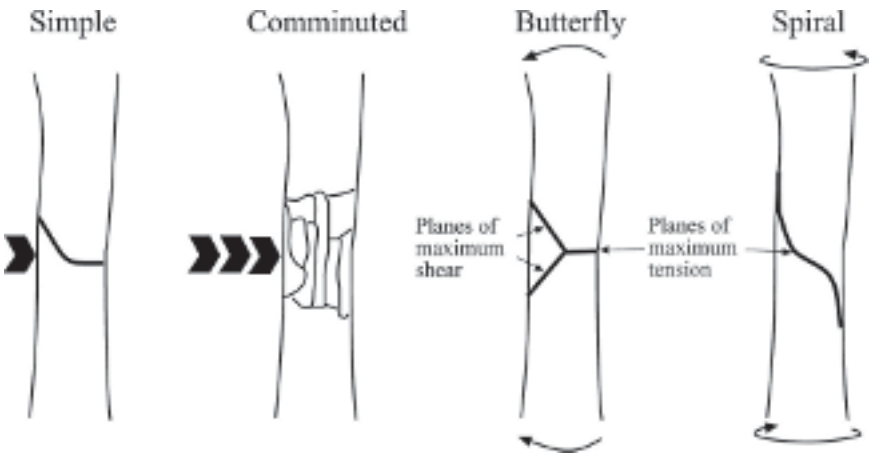


FIGURE 5. Types of bone fractures. A low-energy impact causes a simple fracture, whereas high energy causes fragmented or comminuted fracture. Bending tends to cause a butterfly fracture with fracture planes following maximum shear and tension lines. Torsion causes a spiral fracture with the fracture plane following a maximum tension plane. (Adapted from *Orthopaedic Basic Science*, 2nd Edition, American Academy of Orthopaedic Surgeons with permission.)

the bone to break into fragments. Lower energy trauma causes simple fractures, without fragmentation (FIG. 5). Bone tissue is weakest in tension or shear and strongest in compression, thus cracks tend to propagate along tension or shear planes within the bone tissue. Shear planes run at 45° angles from compressive stresses and because of this bending forces can create "butterfly" fractures. Fracture lines follow shear planes to create a fragment that resembles a butterfly wing. Similarly, a plane of maximum tension falls 45° from the shear plane, so torsional (shear) loads often cause spiral fractures that propagate along a helical plane of maximum tension.

MATRIX COMPOSITION AND BONE BIOMECHANICS

Bone tissue is a two-phase porous composite material composed primarily of collagen and mineral, with mechanical properties determined primarily by the amounts, arrangement, and molecular structure of these primary constituents. The mineral component confers strength and stiffness to the tissue. The collagen phase is tough and improves bone's work to failure or toughness.

The ratio of mineral to collagen in bone affects both bone's strength and brittleness.[5] Excessive mineral content, or a change in the stoichiometry or quality of the mineral increases brittleness and is detrimental. Collagen has a small influence on the strength and stiffness of bone, but mostly improves bone's toughness.[6] The most obvious clinical example of the mechanical effects

of a collagen defect is osteogenesis imperfecta (OI). OI is a family of heritable disorders that involve mutations in the type I procollagen genes. People with OI have a markedly increased risk of fracture, and often present with multiple fractures at a young age. This is likely due to a combination of poor bone tissue properties, together with low bone volume and thin long bone cortices.

BONE GEOMETRY AND STRONGER BONES

Long bones are for the most part thick-walled tubes. This geometry allows bones to carry loads effectively but remain relatively light. To understand the principle behind this, first consider that long bones are loaded mainly in bending.[7] Deflection of a beam in bending is given by $ML^2/8EI$, where M is the bending moment, L is length, E is the Young's modulus, and I is the second moment of area. For a given value of M, beam deflection can be reduced by shortening the beam (decrease L), stiffening the beam material (increase E), or increasing I. Anabolic therapies for osteoporosis take advantage of the latter option. For a tubular bone, the second moment of area I equals $\pi/4$ ($r_p{}^4 - r_e{}^4$), where r_p is the periosteal radius and r_e is the endosteal radius. For mammalian long bones, r_p is about 1.8 times r_e making $I = 0.71 r_p{}^4$.[8] This equation demonstrates the importance of the periosteal radius for bone structural rigidity. An 8% increase in r_p will cause the bone rigidity to increase by 36%. If we incorporate the effects of aging by increasing the endosteal radius by 35% to simulate bone resorption, the cross-sectional area of the cortex is decreased by 12% yet the bone rigidity still increases by 17% due to the modest 8% increase in periosteal radius (FIG. 6). Consequently, adding bone tissue to the periosteal surface will substantially strengthen the bone. Mechanical loading applied to skeleton preferentially increases periosteal bone formation in regions where mechanical stresses are highest causing large increases in mechanical strength.

STRUCTURAL OPTIMIZATION

Efficiency of structures is enhanced if mass can be reduced as much as possible without compromising strength or rigidity. Structural engineers have adapted several strategies to achieve optimum structure. One effective approach involves the reshaping of a structure to equalize the stresses as much as possible. In theory, one should eliminate structural elements that carry no stress, since these are superfluous and can be removed to reduce mass, and augment elements that carry high levels of stress as these are at risk of failure. Mattheck[9] illustrated this principle with the analysis of a shaft with a rectangular aperture (FIG. 7). This mechanical part developed a stress concentration in the fillet when loaded in bending. They employed an algorithm that allowed

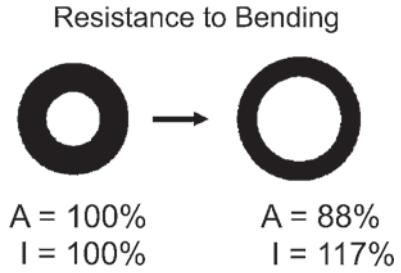


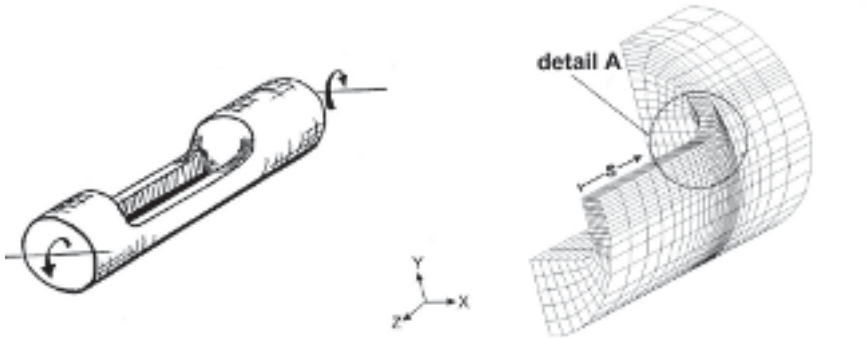
FIGURE 6. Long bones resemble hollow tubes. Under bending loads, the rigidity of a long bone is determined largely by the second moment of area (*I*). The effects of aging were simulated in the right hand cross-section by increasing the endosteal radius by 35% to simulate bone resorption. The cross-sectional area (*A*) of the cortex is decreased by 12% yet the bone rigidity still increased by 17% due to the modest 8% increase in periosteal radius.

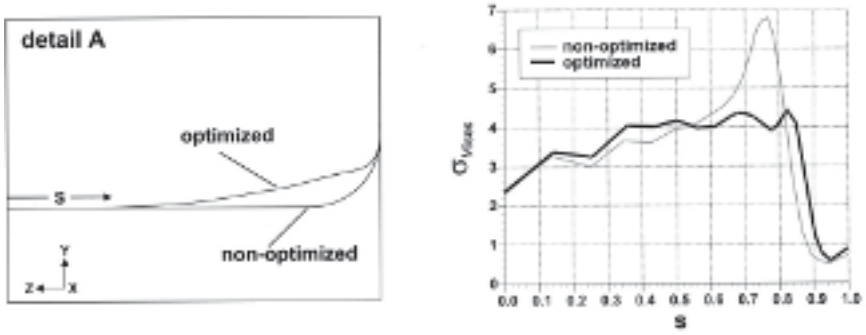
the fillet to "grow" in areas of high stress, thus changing the shape in the fillet slightly. The stress concentration was eliminated in the optimized part and mechanical tests showed that the improved design sustained over 40-fold more loading cycles before failing.

The structural optimization algorithm favored by Mattheck dictates that bone should be formed only where stresses are highest. Bone should not be formed in regions of low stress, as this adds little structural benefit and increases the risk of inappropriate bone formation that might impinge on nerves or other adjacent tissues. Recent studies[10,11] show how long bones apply this algorithm in response to loading. Cyclic mechanical loads were applied axially along the ulna of adult rats. The rat ulna has a natural curvature in the medial-lateral direction, so axial loads induce bending of the bone. Under load, the medial periosteal surface of the bone was subject to compressive stresses (or strains) and the lateral periosteal surface was under tension. The ratio of compressive to tensile strain magnitude in the loaded adult rat ulna is about 1.5, indicating that the highest strains in the ulna occur at the periosteal medial surface in compression (FIG. 8). The pattern of bone formation induced by loading

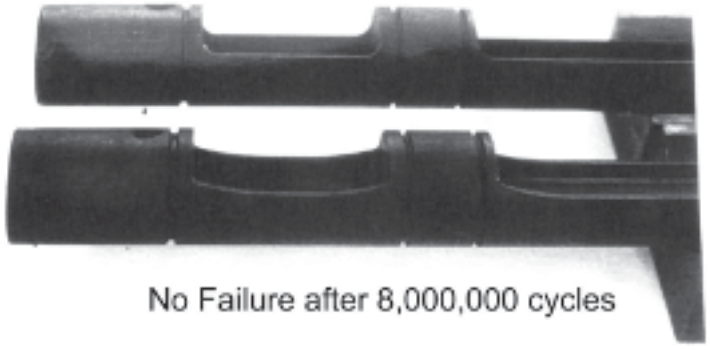
FIGURE 7. Structural optimization applied to a shaft with a rectangular aperture. The original design for the part caused a stress concentration in the fillet (*detail A*). To reduce the high stress, material was added to the fillet. Although the amount of new material added was modest (*middle left panel*), the mises stress at the fillet was reduced by about 70% (*middle right panel*). The original design failed after only 200,000 use cycles, whereas the new, optimized design lasted for over 8,000,000 cycles. This represents over 40-fold improvement in performance of the part. (Reprinted from Mattheck C. Design in Nature. Learning from Trees. Springer, Berlin. 1997, with permission.)

Shaft with Rectangular Aperture





Failure after 200,000 cycles



No Failure after 8,000,000 cycles

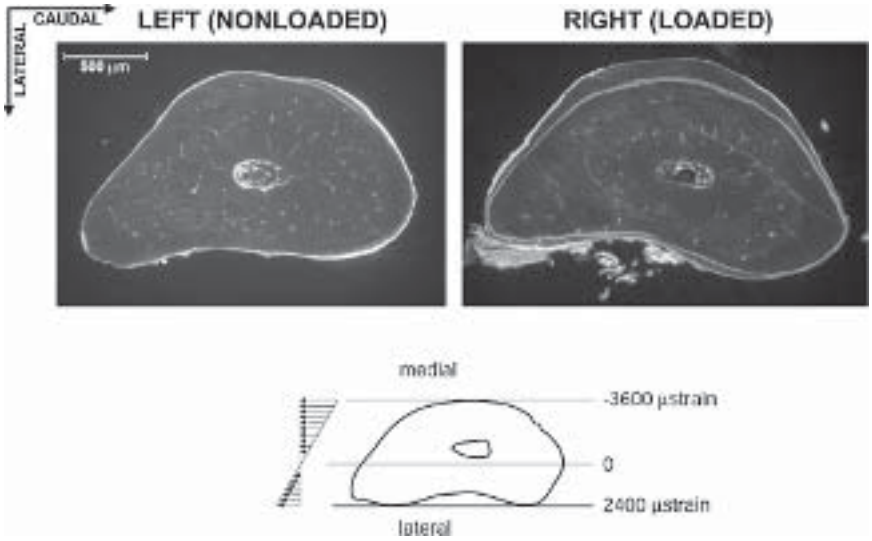


FIGURE 8. The rat ulna is strained more on the medial (*top*) surface when loaded. The bottom figure shows the strain profile across the loaded ulna. The strains are designated in units of microstrain. Positive values are tensile strain and negative values are compressive strain. Bone formation is shown in the right panel. The bright lines within the bone show labels at the beginning of loading. Little new bone was formed in the left (control) ulna, but the loaded ulna showed increased bone formation mostly in regions where the strains were of greatest magnitude. (Reprinted from Ref. 10. Used with permission from the American Society for Bone and Mineral Research.)

resembles the strain distribution, with more bone formation where the strains are highest. The improvement in bone structure is evidenced by a 64% increase in bone strength and a 100-fold increase in fatigue life, yet the improvement in areal BMD was only a modest 5–8%. Therefore, loading caused dramatic improvements in bone biomechanical properties, even with small changes in BMD. The structural efficiency of the ulna was improved by bone formation preferentially on the periosteal surface, with more bone formation in highly strained (or stressed) areas where it was most needed.

THE CHARACTERISTICS OF THE SKELETAL MECHANOTRANSDUCER

Mechanotransduction in bone involves several cell types. The cells that ultimately form or resorb bone may not be the same that transduce and respond to mechanical signals. Mechanotransduction might involve signaling through mechanically activated ion channels in the cell membrane, focal adhesions of the cytoskeleton, or a G protein-coupled mechanoreceptor. In cultured osteoblastic cells, fluid flow increases intracellular calcium within minutes and

this response is suppressed by gadolinium, a blocker of the stretch-activated calcium channel.[12] In addition, the L-type voltage-operated calcium channel probably plays a role in bone cell mechanotransduction. Studies using bone explants showed that gadolinium abolished loading-related responses in osteocytes, while a blocker of L-type calcium channels inhibited loading-related responses in osteoblasts.[13] In addition, two blockers of L-type calcium channels, verapamil and nifedipine, strongly suppress mechanically induced bone formation in rats.[14,15]

An increase in intracellular calcium is observed in osteoblastic cells seconds after a mechanical stimulus. The inositol 1,4,5-triphosphate pathway plays a key role in intracellular calcium release after a mechanical stimulus[16] and intracellular calcium signaling appears to be requisite for expression of bone matrix proteins. Intracellular calcium mobilization triggers a mitogen-activated protein kinase (MAPK) signaling pathway, which is linked to the expression of osteopontin.[17]

Osteoblastic cells attach to the bone matrix through the integrin-cytoskeleton complex. Integrins are heterodimeric transmembrane proteins that bind to the extracellular matrix (ECM) on the outside of cells, and are linked to the actin cytoskeleton via the short cytoplasmic domain of the β subunit on the inside of cells at specialized sites known as focal adhesions. Several lines of evidence obtained with various cell types, including fibroblasts, epithelial cells, endothelial cells, neutrophils, as well as osteoblasts, indicate that a key molecule in mediating linkage of actin filaments to integrin cytoplasmic domains is the protein α-actinin.[18] Fluid flow or mechanical stretch applied to osteoblastic cells induces recruitment of integrins to focal adhesions and causes the actin filaments in the cell to reorganize into large bundles of actin filaments called stress fibers.[19,20] Microinjection into osteoblasts of a 53-kDa proteolytic fragment of α-actinin, which contains the integrin-binding domain, but not the actin-binding domain, causes the competitive displacement of the endogenous α-actinin from focal adhesions and blocks fluid flow-induced gene expression.[19]

AUTOCRINE AND PARACRINE MESSENGERS FOR SKELETAL MECHANOTRANSDUCTION

Within minutes after a mechanical stimulus, a number of biochemical signaling pathways are set in motion. The interacting effects of paracrine and autocrine signaling pathways on cell to cell communication or osteoblastic activity are poorly understood. For instance, release of prostaglandins is consistently observed after loading of bone explants or the application of a mechanical stimulus to osteoblasts in culture.

Prostaglandins and nitric oxide are released from bone cells within minutes after dynamic mechanical loading.[21–24] Blockade of prostaglandin synthesis

using nonsteroidal anti-inflammatory drugs (NSAID) suppresses mechanically induced bone formation *in vivo*,[25–27] as does the nitric oxide synthesis inhibitor L-NAME.[28] Nitric oxide release from bone cells appears to be involved in cellular mechanotransduction, but it is not clear how nitric oxide affects intracellular signaling pathways in bone cells. In other cell types, nitric oxide binds to soluble guanylyl cyclase, thus stimulating the enzyme and increasing intracellular cyclic GMP and may cause similar effects in bone cells. Cyclic GMP has been suggested as a mediator of mechanical loading in osteoblastic cells.[29] Nitric oxide may play an important role as a mediator of the suppressive effects of mechanical loading on osteoclasts. Nitric oxide is known to be a strong inhibitor of osteoclast activity[30–32] and has been shown to decrease expression of receptor activator of NF-κB ligand (RANKL, a.k.a., osteoclast differentiation factor) and increases expression of osteoprotegerin (OPG, an inhibitor of osteoclast differentiation), which in turn leads to decreased recruitment of osteoclasts.[33] Mechanical stimuli applied to marrow stromal cells increases reduced expression of RANKL, which in turn decreases osteoclast number.[34,35] Consequently, cells of osteoblastic lineage appear to be mediators of the suppressive effects of mechanical stimuli on bone resorption, perhaps by releasing nitric oxide.

The two most active prostaglandins in bone cells are PGE_2 and PGI_2. Both are released from osteoblasts or osteocytes shortly after mechanical loading and have numerous effects on bone including the recruitment of osteoblasts from marrow stroma.[36] Exogenous PGE_2 administered in rats is strongly osteogenic and results in increased recruitment of osteoblasts and accelerated osteoblastic activity.[37] The anabolic effects of PGE_2 are mediated mainly through the EP_4 prostaglandin receptor,[38] but the EP_2 receptor may also be important in bone matrix synthesis.[39] There are two isoforms of prostaglandin synthase (cyclooxygenase), constitutive (COX-1) and inducible (COX-2). Selective inhibition of COX-2 using NS-398 is considerably more effective in blocking loading-induced bone formation *in vivo* than is indomethacin, which blocks both isoforms of cyclooxygenase.[26,27] Administration of NS-398 3 h before mechanical loading suppressed bone formation by 67% in the rat tibia, whereas administration of the drug 30 min after loading had no significant effect.[27] These findings demonstrate that prostaglandin synthesis is most important prior to loading, suggesting that prostaglandins must be available at the time of loading to potentiate the osteogenic response.

Adenosine triphosphate (ATP) signaling plays a role in skeletal mechanotransduction. Osteoblastic cells can communicate through autocrine or paracrine activity of secreted ATP on $P2Y_2$ purinergic receptors[40] and $P2Y_2$ signaling appears to be mechanosensitive.[41] A local mechanical stimulus initiates intercellular calcium signaling, mediated by ATP receptors, which rapidly propagates from cell to cell. In addition, the P2X family of receptors is probably an important target for mechanically derived signals. $P2X_7$ receptor knockout mice have an osteopenic phenotype that resembles the skeleton of animals

subjected to chronic disuse. $P2X_7$ signaling is important for promoting osteoblastic activity and bone formation, whereas $P2X_7$ signaling suppresses osteoclastic bone resorption.[42] Mice with a null mutation of $P2X_7$ are 60–70% less responsive to mechanical loading of the skeleton, indicating that $P2X_7$ signaling is critical for proper skeletal mechanotransduction.[43]

Wingless-type (Wnt) signaling through the Lrp5 receptor is important in osteoblast mechanotransduction. Mice with nonfunctional Lrp5 receptors respond poorly to mechanical loading of the skeleton, with 88–99% reduced bone formation compared to controls.[44] In addition, osteoblasts cultured from Lrp5-deficient mice do not express osteopontin after a mechanical stimulus. However, early mechanotransduction events are normal in Lrp5-deficient osteoblasts. In response to a mechanical stimulus, these cells release ATP and PGE_2 and extracellular-regulated kinase (ERK)1/2 (a hallmark of osteoblast mechanotransduction[17]) is activated normally. Consequently, it appears that Wnt signaling through Lrp5 is necessary to couple early mechanotransduction events that occur within 15 min after a mechanical stimulus with synthesis of matrix proteins, which occurs many hours after a mechanical stimulus.

The insulin-like growth factors (IGF) play a role in anabolic mechanical loading responses although that role has not been clearly defined. IGF-1 interacts synergistically with mechanical loading in stimulating bone formation in mice[45] yet others have shown IGF-II, not IGF-I, to mediate mechanical loading responses.[46] The diminished bone formation seen with disuse is due in part to resistance to the effects of IGF-I on bone formation[47] and IGF-I expression is increased in osteocytes and bone-lining cells within 6 h of mechanical loading.[48] Therefore, IGF-I appears to be a necessary mediator of mechanically induced bone formation yet the molecular mechanisms that link IGF-I to mechanical loading are poorly understood.

INTERACTIONS BETWEEN HORMONES AND SKELETAL MECHANOTRANSDUCTION

There are examples of hormones that might amplify the effects of mechanical loading; these include parathyroid hormone (PTH) or the 1-34 PTH fragment and estrogen. PTH(1-34) acts synergistically with mechanical loading to enhance periosteal bone formation[49] and PTH(1-34) has been shown to enhance the anabolic effect of mechanical loading on endocortical and trabecular surfaces in rats.[50] In addition, the anabolic effect of mechanical loading is abolished if the parathyroid gland is removed.[50] In cultured osteoblasts, PTH(1-34) sensitizes cells to mechanical forces possibly by enhancing the mobilization of intracellular Ca^{2+}.[15,51] PTH(1-34) differs from mechanical loading in that the former stimulates bone resorption whereas the latter suppresses it. This discrepancy was addressed by Bakker *et al*.,[52] who applied mechanical stress to primary osteoblasts in culture and observed that both nitric oxide and PGE_2

production were elevated twofold, whereas PTH(1-34) increased PGE_2 production with no effect on nitric oxide release. Thus there are opposite effects of PTH(1-34) and mechanical loading on nitric oxide production, which may explain the different actions these two stimuli have on bone resorption.

Estrogen is another hormone that may interact with mechanical loading pathways, but the nature of that interaction remains unclear. Mechanical loading increases estrogen receptor alpha phosphorylation in osteoblasts through activation of ERK 1.[53] In addition, mice deficient in estrogen receptor alpha

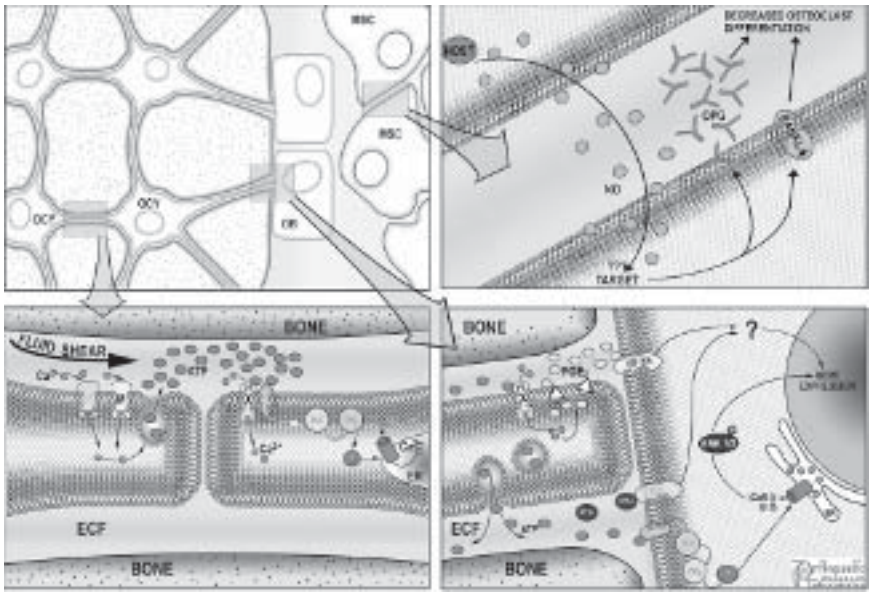


FIGURE 9. Model for mechanotransduction in bone. Fluid shear on osteocytes (OCY) induces an influx of extracellular Ca^{2+} via voltage-sensitive (V) and perhaps mechanosensitive (M) channels. Shear stress also enhances ATP release, which binds to the purinergic receptors P2X (ionotropic) and P2Y (metabotropic). Signaling through P2Y is required for Ca^{2+} release from intracellular stores via a G_q – PLC – PIP_2 – IP_3 pathway. ERK 1/2 is activated by intracellular Ca^{2+} and activated gene expression. ATP release causes PGE_2 release through signaling downstream of the $P2X_7$ receptor. PGE_2 binds and signals through one of the EP receptors, probably EP2 and/or EP4, and ultimately results in enhanced bone formation. PTH signaling also appears to be required for mechanotransduction to occur, but the intracellular pathways involved are not well understood (question mark). Wnt signaling through the Lrp5 receptor also appears to be important in mechanically induced bone formation. Pressure in the marrow cavity and/or fluid shear forces on marrow stromal cells (MSC) may stimulate nitric oxide synthase (NOS) activity and nitric oxide (NO) release. NO is a strong inhibitor of bone resorption and probably acts by inhibiting RANKL expression, while increasing osteoprotegerin (OPG) production (RANKL enhances osteoclast differentiation, while OPG suppresses this process). OCY = osteocyte; OB = osteoblast; MSC = marrow stromal cell. (Copyright by Alexander G. Robling 2004.)

expression show suppressed osteogenic responsiveness to mechanical loading.[54] In contrast, others have shown that estrogen suppresses the anabolic effect of mechanical loading.[55] These observations might be reconciled by considering that the effects of estrogen on the skeleton are site specific. Estrogen suppresses bone resorption on trabecular and endocortical bone surfaces, thus preserving bone mass. Conversely, estrogen suppresses bone formation on the periosteal surfaces.[56] Consequently, the interaction between estrogen and mechanical loading may depend upon which bone surfaces are involved.

CLOSING REMARKS

Bone strength is affected primarily by matrix composition and geometry. Increased mineralization of bone has the combined effects of stiffening the tissue while making it more brittle. This has implications for osteoporosis therapies that change bone turnover. A therapy that reduces bone turnover will increase mineralization and stiffness but at the same time bone becomes more brittle, whereas a therapy that increases bone turnover will have opposite effects. The most effective way to strengthen bone is by adding new bone tissue where bone stresses are greatest. This occurs when bone adapts to mechanical loading. Bone cells act as mechanotransducers that detect high stresses and signal locally for an anabolic response. There are a number of pathways involved in bone cell mechanotransduction (FIG. 9). Targeting these pathways using pharmacotherapy could effectively strengthen bones.

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