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Review article

A brief review for orthopedic surgeons: Fatigue damage (microdamage) in bone (its determinants and clinical implications)

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Abstract: Bone modeling can slowly strengthen bones to keep their strains below bone's microdamage (MDx) threshold. When that condition is satisfied the slow basic multicellular unit (BMU)-based remodeling can usually repair the little MDx that occurs anyway, and some always does. While this arrangement minimizes fatigue fractures of whole bones or trabeculae, they can still happen if: (A) drugs, disease, or dead bone impair MDx repair; (B) if bone loads increase faster than the sluggish modeling can strengthen bone to meet the new loads, and/or faster than remodeling can repair the increased MDx; (C) if a cyst, tumor, or surgery removes enough bone to let strains in the remaining bone reach or exceed the MDx threshold; (D) if abnormal properties of bone as a material cause too much MDx to repair; (E) if altered modeling and remodeling thresholds cause an osteopenia that lets normal activities cause bone strains in or above the MDx threshold range; (F) or if strains in the bone supporting a load-bearing implant reach or exceed bone's MDx threshold.

Key words: stress fracture, fatigue damage, microdamage, biomechanics, bone, implants

Introduction

From material in the Utah paradigm of skeletal physiology[11,18] this review summarizes the determinants of stress and spontaneous fractures of bone, and some of their clinical implications. Table 1 defines abbreviations used in the text, which provides a glossary. This review does not discuss effects of longitudinal bone growth. The emphasis is on humans.

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Some microdamage physiology

While bone is a fatigue-prone material, bones normally adapt to their voluntary mechanical usage in ways that keep that usage from breaking them, and that involves minimizing fatigue damage in them. Bone remodeling and modeling activities provide these adaptations under the control of bone strains caused mainly by muscle forces on bones.

Bone remodeling by basic multicellular units (BMUs)[11,12,16,17,31]

In an Activation → Resorption → Formation sequence a BMU makes and uses osteoclasts and then osteoblasts to replace a small "packet" of old bone with new lamellar bone. This takes 3 or more months, a time that is called the "remodeling period" (Fig. 1). Each BMU creates a small temporary hole in bone. All such holes define a bone's *remodeling space*, which normally occupies ≈4% of a bone's volume but can exceed 25% of it, and more in trabeculae than compacta. When *completed* BMUs make less bone than they resorb, losses occur mainly of bone next to marrow. This "disuse-mode" remodeling can cause an osteopenia. When BMUs equalize their resorption and formation, this minimizes losses of bone. This "conservation-mode" remodeling can turn bone over while simultaneously preventing an osteopenia, or progression of an existing one.

Strains above a *remodeling threshold* range (the remodeling threshold strain range [MESr] in the 50–100 microstrain region) can begin to turn conservation-mode remodeling ON. This occurs during normal mechanical usage, as well as during weight-lifting-type activities. Where strains stay below that threshold, as in sudden total disuse, disuse-mode remodeling removes bone, usually next to marrow. This causes a "disuse-pattern osteopenia" in which bones have less spongiosa,

wider marrow cavities, and thinner cortices than before, but unchanged outside diameters and lengths.

Microdamage (MDx), its threshold (MESp), and its repair[6,12,23,28]

Repeated strains cause microscopic fatigue damage or MDx in bone, and this damage degrades the physical integrity of the tissue's collagen. MDx begins at the ultramicroscopic level, and then progresses to cracks and delamination that can be stained and seen in the light microscope.[6] A decrease in the stiffness of an affected bone accompanies these features. Then the MDx can progress to complete fractures of an affected bone or trabecula. Larger and/or more numerous strains can each increase it, and it can reduce bone strength below 20% of normal. Normally bones detect their MDx, and then BMUs repair it by removing and replacing the damaged bone with new bone. In bone with dead osteocytes but live marrow, MDx usually escapes repair.[15] This suggested that detecting MDx depends on osteocytes. Some bone MDx always occurs in active people, and since strains cause it, anything that minimized these strains would tend to minimize MDx too.

While MDx above a limiting amount can escape repair and cause fatigue fractures, bone can apparently

Table 1.[a] Abbreviations used in the text

BMU, basic multicellular unit of bone remodeling
MDx, microscopic fatigue damage or microdamage in bone
MESr, the remodeling threshold strain range
MESm, the modeling threshold strain range
MESp, the microdamage threshold strain range
≈, "approximately equals"

[a] From[11] with permission

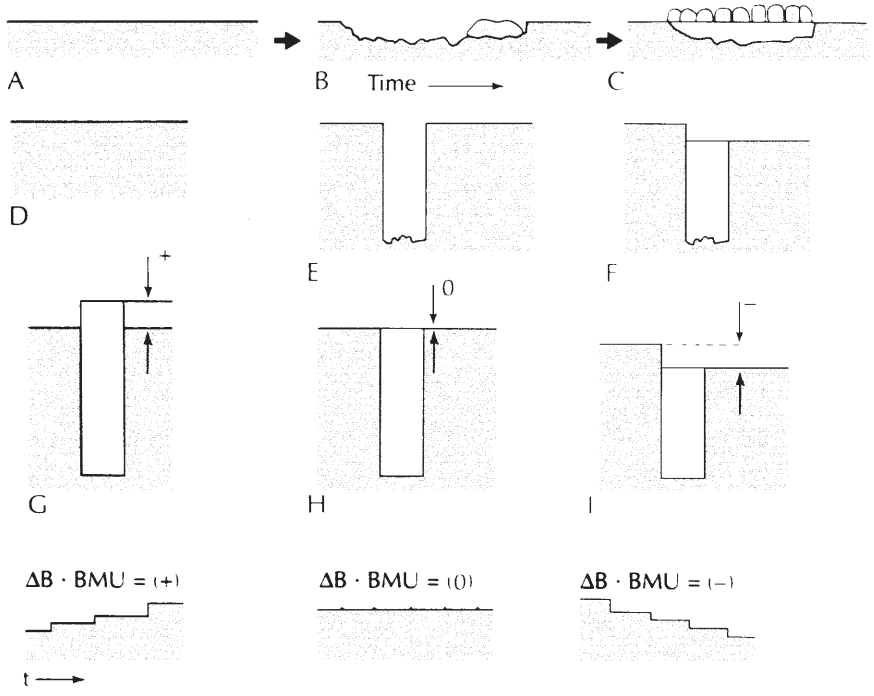

Fig. 1A–I. *Bone remodeling* basic multicellular units (*BMUs*). *Top row*: An activation event on a bone surface at **A** causes a packet of bone resorption at **B**, and then replacement of the resorbed bone by osteoblasts at **C** *on the right*. The BMU makes and controls the new osteoclasts and osteoblasts that do this, and the time taken to do it defines the "remodeling period" mentioned in the text. *Second row*: Idealized version of these events to emphasize the *amounts* of bone resorbed **E** and formed **F** by *completed* BMUs. *Third row*: In these "BMU graphs" (after Frost), **G** *on the left* shows a small excess of formation over resorption as, perhaps, on periosteal surfaces. **H** shows the "conservation mode" of equalized resorption and formation, as on haversian surfaces. **I** *on the right* shows the "disuse mode" of a deficit of formation, as on cortical-endosteal and trabecular surfaces (this could also represent an effect of estrogen deficiency[17]). *Bottom row*: These "stair graphs" (after PJ Meunier) show the effects on the local bone "mass" of a series of BMUs of the kind immediately above. BMUs are created anew when and where they are needed. They include a capillary, precursor, and "supporting" cells, and some wandering cells, as well as osteoclasts and osteoblasts. They are multicellular entities with their own functional properties in the same sense as renal nephrons and intestinal villi. The early idea that osteoclasts alone cause net bone losses is no longer tenable; disuse-mode remodeling does it instead. $\Delta B \cdot BMU$, *net* loss of bone per *completed* BMU. (Reproduced by permission from Frost HM. *Strain and other mechanical influences on bone strength and maintenance.* Curr Opin Orthopaed 1997;8:60–70)

repair lesser amounts of MDx indefinitely. The strain range that begins to cause too much MDx to repair can be defined as an operational *MDx threshold* range (the MESp centered near 3000 microstrain).[6] As the loads that originally cause 2000 microstrain only double in size, MDx in bone can increase phenomenally, more than 500 times[28] (for comparison, bone's ultimate strength as a strain ≈25 000 microstrain[22]). A BMU needs 3 or more months to repair one locus of MDx,[12] and excessive MDx would cause all so-called "spontaneous" fractures.

Agents that suppress all BMU-based remodeling would suppress MDx repair too and lead to fatigue fractures; some bisphosphonates can do this.[9] Other agents can depress some remodeling but not MDx repair, and estrogen can do this.[11]

Modeling by drifts[12,16,17,32]

Formation drifts create and use osteoblasts to add bone slowly on some bone surfaces, while separate resorption drifts create and use osteoclasts to remove bone slowly from other surfaces (Fig. 2). In this way modeling moves bone surfaces in tissue space to determine the longitudinal and cross-sectional shapes, outside diameter, and strength of trabeculae and of whole bones. Their strength determines the strains caused by the loads they carry (a bone's strength is a surrogate for its stiffness in this article). This modeling works best during growth and poorly on adult cortical bone, but it can affect trabeculae for life.

Strains above a *modeling threshold* range (the MESm centered near 1000 microstrain in most young adults) can make modeling strengthen a bone to reduce later strains towards the bottom of that range. Body weight and muscle strength keep increasing during growth, so the slow modeling-dependent increases in bone strength should lag behind the mechanical need during growth[13] and let strains exceed the modeling threshold. This helps to explain why modeling is most active during growth. In young adults, body weight and muscle strength usually plateau, so bone strength can finally "catch up" to the mechanical needs and reduce strains to the bottom of the modeling threshold. This would turn modeling OFF and let bone strength plateau too. Partly for such reasons, fractures from falls occur more often in children than in young adults,[13] and the largest bone strains from voluntary efforts range between ≈2000 and 4000 microstrain during growth, but between ≈800 and 1300 microstrain in young adults.[5,32] Strains above 3000 microstrain can also stimulate woven bone formation instead of lamellar bone formation.[4,17,22]

In sum: Since modeling normally makes bones strong enough to keep strains from exceeding the modeling threshold, and since that threshold lies below the MDx threshold, normal modeling also minimizes MDx in bone. Under this condition, remodeling can normally repair the resulting small amounts of MDx indefinitely. Other remodeling and modeling functions are not discussed here.

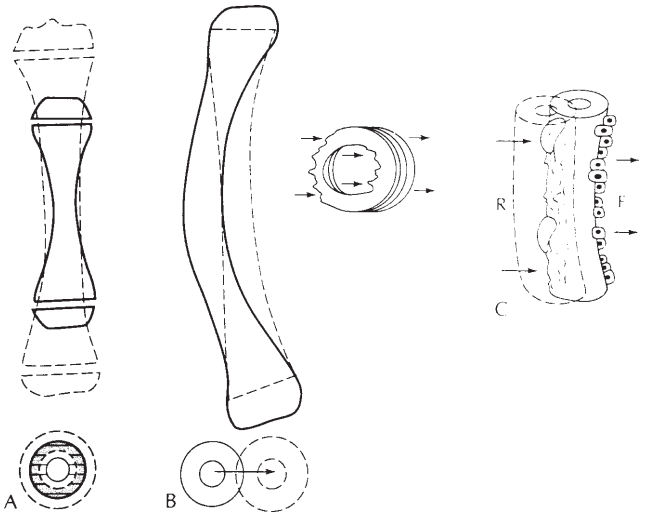

Fig. 2A–C. *Bone modeling by drifts*. **A** diagrams an infant's long bone with its original size and shape shown in *solid line*s. To keep this shape as it grows in length and diameter, its surfaces must move in tissue space as *the dashed lines* suggest. *Formation drifts* make and control new osteoblasts to add bone to some surfaces. Separate and independent ("uncoupled") *resorption drifts* make and control new osteoclasts to remove bone from other surfaces. **B** A different drift pattern can correct the fracture malunion in a child, shown in the *solid line*. The cross-section view *to the right* shows the cortical-endosteal, as well as the periosteal drifts, that do this. **C** Shows how the drifts in **B** would move the whole segment to the right. This can increase a bone's strength without necessarily increasing bone "mass" too. Large forces, as in weight-lifting, make modeling strengthen bone far better than smaller forces, no matter how frequent, as in marathon running. Drifts can also thicken and strengthen trabeculae. They are created anew when and where they are needed, and they include capillaries, precursor, and "supporting" cells and some wandering cells, besides their osteoblasts or osteoclasts. They are complex multicellular entities that have their own special functional properties in the same sense that renal nephrons and hepatic lobules do. The early idea that osteoblasts alone add to and strengthen bone is no longer tenable; global modeling does it instead. *R*, Resorption; *F*, Formation. (Reproduced by permission from Frost HM. *Strain and other mechanical influences on bone strength and maintenance*. Curr Opin Orthopaed 1997;8:60–70)

Role of muscle

Modeling responds to the typical *largest* strains of bones, and it makes bones strong enough to keep these strains from exceeding the modeling threshold range. Loads cause these strains, and muscles (not body

weight) provide the largest loads on a bone,[7,22,30,31] so they cause the largest bone strains too. This is due to the fact that to move us around on earth muscles must overcome the resistances of body weight multiplied by the bad lever arms most muscles work against. As a result it takes over 2 kg of muscle force on bones to move each kilogram of body weight around during work and play, and in a soccer game the longitudinal forces on a player's femur can briefly exceed five times body weight. Ergo, muscle strength should and does strongly influence both bone strength and bone MDx.

Muscle strength usually increases during growth, plateaus in young adults, and then declines, so that at 75 years of age, less than half the young-adult muscle strength can remain.[7] Adults who keep doing arduous physical work usually keep their young-adult muscle strength and bone "mass" better than sedentary adults,[21] so aging is not the only cause of our age-related bone loss.

In the past, physiologists thought the influence of muscle on bone strength and "mass" was secondary to the effects of such factors as hormones, calcium, vitamin D, sex, race, nutrition, and age.[21] The strong influence of muscle on bone strength and "mass" adds a new dimension to the concerns of bone physiology, orthopedics, and metabolic bone disease.[7] Not unexpectedly, this causes some controversy too.

A universal biomechanical relationship?

To recapitulate, normally the remodeling threshold (MESr) lies below the modeling threshold (MESm), which lies below the MDx threshold (MESp), which lies far below bone's fracture strain (Fx). Also, in properly adapted bones, typical peak strains ("E") from voluntary activities seem to stay within the MESr and MESm boundaries (as shown in Fig. 3).[11] Or:

$$\text{MESr} < \text{“E”} < \text{MESm} << \textit{MESp} <<< \text{Fx} \qquad \text{Relation (1)}$$

Presumably this recently recognized relationship exists in the bones of all healthy amphibians, birds, mammals, and reptiles of any size, age, and sex (in dinosaurs too?), excepting the cranial vault, ethmoids, and turbinates. Satisfying it would make bones stronger than needed for their voluntary mechanical usage; it would give them a safety factor for their strength. Dividing the ultimate strength (Fx) by the modeling threshold (MESm) expressed as stresses would provide the safety factor's value, which ≈6 (i.e, 120 mpa ÷ 20 mpa = 6).

In passing, the Utah paradigm proposes that an analogous relationship occurs in cartilage, collagenous tissue, joints, tendons, and ligaments.[11] Table 2 lists salient features of the above material.

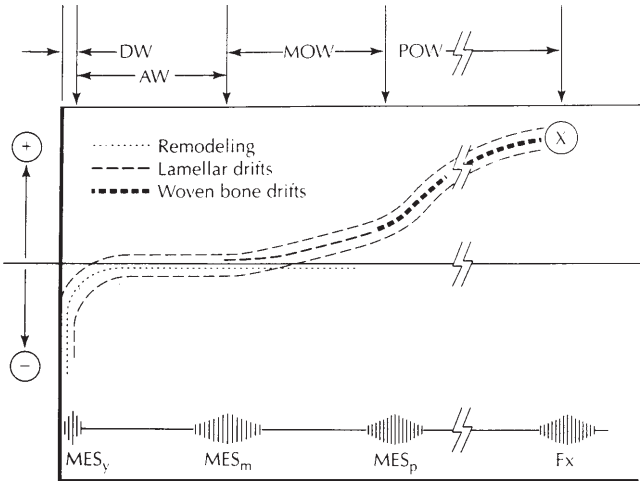

Fig. 3. *Combined modeling and remodeling effects on bone strength*. The *horizontal line at the bottom of this graph* suggests typical peak bone strains from *zero on the left*, to the fracture strain (*Fx*) on the right, plus the locations of the remodeling, modeling, and microdamage threshold ranges (*MESr*, *MESm*, *MESp*). The *horizontal axis* represents no net gains or losses of bone strength. The *lower dotted line curve* suggests how disuse-mode remodeling would remove and weaken bone where strains fall to or below the MESr range and stay there, but otherwise would tend to keep existing bone. The *upper dashed line curve* suggests how modeling responses to bone strains would begin to strengthen bone where strains enter or exceed the MESm range. The *dashed outlines* suggest the combined effects of modeling and remodeling on bone strength. In and beyond the MESp range, woven bone formation usually replaces lamellar bone formation. *At the top*, *DW* indicates disuse window; *AW*, adapted window or "comfort zone" as in normally adapted adults; *MOW*, mild overload window, as in growing mammals; *POW*, pathologic overload window.[11] (Adapted from: Frost HM. *Perspectives: A vital biomechanical model of synovial joint design*. Anat Rec 1994;240:1–18), with permission

Some clinical applications of microdamage physiology

Impaired MDx detection and/or repair

Dead bone cannot detect and repair MDx, which explains why fatigue fractures can occur in avascular autografts, in allografts and xenografts,[1] in radiation necrosis, in infarcted cortical bone, in infarcted epiphyseal or apophyseal spongiosa, and in micropetrotic bone.[10] Fatigue fractures of bones and/or trabeculae ("microfractures") often occur in these situations.

In living bone, some cell disorders could impair MDx detection and repair. Some bisphosphonates[9] and some immunosuppressor drugs used after organ transplants[20] have this effect. In osteomalacia the remodeling period prolongs markedly,[11,22] which could retard MDx repair enough to help to cause pseudofractures. MDx repair would be depressed in osteopetrosis

Table 2. Some features of microdamage physiology

(1) Suppressing all BMU-based remodeling can suppress MDx repair and cause fatigue fractures. Some agents can do this; others can depress some remodeling but let MDx repair proceed normally.
(2) Excessive MDx causes all spontaneous fractures (so they are not really spontaneous).
(3) MDx is not repaired in bone with dead osteocytes.
(4) MDx repair is rate-limited, which helps to create an operational MDx threshold.[6,11]
(5) In the cross-sectional sense, big bones are big because modeling adapted them to big loads in ways that minimized their MDx.
(6) Mainly modeling strengthens bones, and it could cure an existing osteopenia.[11,17]
(7) Disuse-mode remodeling can cause an osteopenia, and mechanical disuse usually causes one.[11,17]
(8) Normal mechanical usage of osteopenic bones could increase their MDx and their fragility enough to cause spontaneous fractures and/or bone pain.[6,22,23]
(9) When mechanical usage of osteopenic bones decreases enough to keep strains below the MDx threshold, spontaneous fractures would seldom happen.
(10) The bone loss in adult-acquired osteopenias comes mainly from bone next to marrow, so bones without a marrow cavity do not develop such osteopenias (i.e, the vomer, ethmoids, nasal bones, sphenoid alae, inner ear ossicles, turbinates).
(11) Conservation-mode remodeling can prevent an osteopenia, so anything that turns it ON should prevent one or progression of an existing one.

MDx, Microscopic fatigue damage

because the osteoclasts that BMUs need to work normally are defective in this disease. Locally inadequate MDx repair in subchondral bone would cause most cases of osteochondritis dissecans.[11,27] Excessive amounts of fluoride can also impair MDx repair.[11] Analogous impairments may happen in the true osteoporoses described next, and occasionally in people who seem quite healthy otherwise.[15]

MDx in physiologic osteopenias and true osteoporoses[14]

In response to chronically weak muscles, normal remodeling and modeling activities usually cause an osteopenia in which *voluntary* activities do not cause *spontaneous* fractures and/or *bone pain*. Of course falls could fracture these weakened bones, usually wrists and hips. The usual loss of muscle strength in aging adults,[7] and similar losses in chronic, debilitating illnesses, can cause this physiologic osteopenia; Table 3 lists examples. It is common and can affect men, women, and children. An intrinsic bone disorder should not cause it, and MDx should contribute little to its increased bone fragility.

In other people, remodeling and modeling disorders can reduce bone strength and "mass" (i.e, cause an osteopenia) so much that *voluntary* activities do cause *spontaneous* fractures and/or *bone pain*. This less common true osteoporosis affects the spine more than extremity bones (vertebral body wedging, end plate "cod fishing", spontaneous compression fractures), and women more than men or children. Of course falls can fracture extremity bones here too. An intrinsic bone disorder(s) would cause it, and MDx would contribute to its excessive bone fragility.

Those two conditions (i.e., osteopenia and true osteoporosis) were long known under other names,[21] but their biomechanical pathogeneses were recognized so recently[14] that authorities have just begun to try to account for them. Also, in some people, features of these two conditions could combine in various ways to cause combination states.

Time lag effects when MDx increases suddenly

When someone with habitually weak muscles and low bone strength starts arduous physical labor, athletics, or training in military special forces, muscle strength can increase faster than modeling can increase bone strength. This could let bone strains temporarily reach or exceed the MDx threshold and incite enough MDx to cause stress fractures or "march" fractures. The MDx could accumulate during the 3 or more months BMUs need to repair each locus of this suddenly increased MDx.[23] Given enough time — typically, several months — modeling could finally increase bone strength enough to reduce further MDx to amounts its repair could handle. In support of this idea, such fractures do occur less often at the end than at the beginning of such training,[24] while prolonging the training to decrease its intensity also reduces these fractures.[6,19]

Increased MDx increases the number of BMUs involved in repairing it, which increases the remodeling space too. This temporarily weakens affected bones. Since MDx increases over 500 times as the loads that originally cause 2000 microstrain only double in size,[28] the relatively small increase in strains from this temporary, remodeling-space-dependent weakening could create enough more MDx to cause fatigue fractures.[23]

Table 3.[a] Some conditions that cause chronic disuse and muscle weakness (and related osteopenias) in humans

Asthma	Emphysema	Pulmonary fibrosis
Renal failure	Hepatic failure	Cardiac failure
Malnutrition	Anemia	Polyarthritis
Metastatic cancer	Depression	Stroke
Muscular dystrophy	Multiple sclerosis	Alzheimer's disease
Organic brain syndrome	Huntington's chorea	Myelomeningocele
Lou Gehrig disease	Paralyses	Leukemia
Cystic fibrosis	Still's disease	Alcoholism
Drug addiction	Nursing home residence	Juvenile rheumatoid arthritis
	Aging	

In causing an osteopenia, the relative importance of the mechanical disuse and the biochemical-endocrinologic abnormalities accompanying some of these entries is uncertain at present, since few past studies of the matter tried to quantify the mechanical usage effects. The Utah paradigm suggests the mechanical effects could dominate most biochemical-endocrinologic ones

[a] Modified from[11] with permission.

Remodeling space effects following load-bearing implant procedures

In the first weeks following a total joint replacement or a spine procedure that utilizes internal fixation ("instrumentation"), the regional acceleratory phenomenon caused by the surgery,[11] plus acute disuse, can combine to increase regional BMU-based bone remodeling and the remodeling space. If full loading of the implant resumed immediately, this increased remodeling space might sufficiently reduce the amount of bone supporting the implant to cause enough MDx in the bone to loosen the implant.[23]

While antiremodeling agents, such as some bisphosphonates, should help to minimize such remodeling space increases, early resumption of motion and gradually increasing the loads by gradually increasing the frequency and vigor of voluntary activities seem to do this equally well.[15] This may partly explain why joint replacement procedures do better with this strategy than they did 25–35 years ago, when we often restricted the loading of new joints for weeks or months.[15]

Increased MDx due to loss of local bone stock (pathologic fractures)

A cyst, tumor, or operation can remove enough of a bone cortex to let strains in the remaining bone exceed the MDx threshold and incite enough MDx to cause a fatigue failure, or let a minor injury fracture it. Things that can cause such pathologic fractures include, in part, unicameral bone cysts, fibrous dysplasia, and metastatic carcinomas. Most such fractures would depend, at least in part, on increased MDx in the affected bone.

Abnormal properties of bone as a material

These abnormalities might make normal loads on normal amounts of bone still cause too much MDx to repair. This can happen in osteomalacia, partly due to the associated loss of bone stiffness, which lets equal loads cause larger strains that could help to cause pseudofractures in that disease. This can happen in fluorosis too.[25] The small amounts of fluoride put into water supplies to minimize dental caries do not have this effect. Some unusual properties of bone as a material happen occasionally in other situations,[15] a matter that needs systematic study.

Effects of altered thresholds on MDx

Some genes, hormones, vitamins, minerals, drugs, and other agents seem able to change some of the above thresholds.[11,22] Lowering the MDx threshold would make fatigue failures more likely, by making smaller strains cause more MDx. No examples of this are known yet, perhaps because they were not sought.

An elevated modeling threshold would increase the strains needed to turn modeling ON,[22] so affected bones would be weaker and develop larger strains than normal. Instead of the "MESm $<<$ MESp" relationship in Relation (1), this could create an "MESm $\approx$ MESp" relationship that might increase bone strains enough to cause fatigue fractures. This may occur in osteogenesis imperfecta,[11] perhaps due to the abnormal Type I collagen in that disease. Hyperphosphatasia may provide another example of this situation.

An elevated remodeling threshold would make disuse-mode remodeling remove bone. If normal mechanical usage continued, this would increase bone strains and MDx. Adrenalcortical steroid analogs and estrogen deficiency at menopause may have this effect.[11,22] One could argue that some factor might increase both the modeling and remodeling thresholds in true osteoporoses.[14] How aging affects these thresholds is unknown at present.

MDx and implant design

Implant design should minimize MDx in bone supporting load-bearing implants such as artificial joints and teeth, replacements of parts of whole bones, and internal fixation devices, including spinal instrumentation.[11,31] Such design should require keeping typical peak bone strains below the MDx threshold near 3000 microstrain (see "On the cited strain values," below). Curiously, no such implant marketed up to and including 1998 was intentionally designed to keep strains below this MDx threshold and thereby minimize MDx in the bone supporting the implant.[12,31] However, Branemark's dental implant system seems to have done this unintentionally.[2] When informed clinicians begin to ask manufacturers how implants handle this problem, manufacturers may try to deal with it better than they have done in the past.

MDx in aseptic necroses

An infarct of the femoral head following a hip dislocation or femoral neck fracture kills the osteocytes in that head. New tissue growing in from adjacent living bone can replace the dead marrow tissues within 3 or so months, but the osteocytes in the original trabeculae would stay dead. In about a third of such patients, from 6 to 36 months later the trabeculae supporting the articular cartilage of this femoral head begin to collapse. Accumulated MDx in these trabeculae would cause the collapse. Since the osteocytes in the original trabeculae remain dead, if they are needed to detect MDx, this could help to explain these observations.[11,22]

The roles of MDx in idiopathic aseptic necroses should be discussed at another time and place.[11]

Trabecular microfractures

Complete fractures of trabeculae can occur in vertebrae, femoral heads, and the spongiosa above acetabulae, as examples.[8,26] They would stem from fatigue failures rather than from single loads above the ultimate strength of the trabeculae. They have been implicated in the pathogenesis of some arthroses,[11,29] and in the increased vertebral bone fragility in true osteoporoses,[14] an old idea that is causing a diminishing controversy.[3]

"Stress risers"

Drill holes and the ends of saw cuts in a bone, especially in its diaphyseal compacta, can cause local stress and strain concentrations that let normal loads on the bone cause fatigue fractures. Scratches on the surfaces of some load-bearing implants can also cause such "stress risers" and lead to fatigue failures of the implants. During implantation surgeons must handle such implants in ways that do not scratch the implants.[22] Sharp changes in the contours of load-bearing implants can also cause stress concentrations and fatigue failures.

On the cited strain values

While the strain values cited above concern compression or tension parallel to lamellar bone's "grain", shear strain probably helps to control bone modeling and remodeling too, but how this occurs is currently unknown and under study. Biomechanicians can also express strain as "strain energy density" and in other ways. Until further research resolves these matters, the longitudinal strains cited above can provide useful indices of shear and strain energy density, as well as reliable evidence of the size and nature of the loads on bones. Thus, when this text cites such a longitudinal strain, the qualifier, "or equivalent" is always understood.

Glossary[a]

Since some terms have vague or even different meanings in the medical literature, and since some terms in this text come from different skeletal science fields, their meanings in this text follow.

BMU. The basic multicellular unit of what is now called bone remodeling. See Fig. 1. In 3 or more months and in a biologically coupled Activation → Resorption → Formation or "ARF" sequence, a BMU turns over ≈0.05 mm^3 of bone. New osteoclasts created locally provide the resorption, and new osteoblasts created locally and in the same place provide the formation. When a BMU makes less bone than it resorbs, this tends to remove bone permanently, usually where it touches marrow. Healthy adult humans may create and complete about three million new BMUs annually, but in disease and some other circumstances this number can be over more than five times smaller or larger.

Bone "mass". The amount of bone tissue in a bone or skeleton, preferably viewed as a volume minus the marrow cavity. In absorptiometry, as by dual energy X-ray absorptiometry (DEXA) it does not mean mass as used in physics. When used in quotes in this text it has the absorptiometric meaning.

Disuse. Its meaning may seem clear to us, but bones need a specific way to define and recognize it. When a bone's peak strains down-shift into the remodeling threshold region (as seen in Fig. 3), for that bone, this would represent disuse and signal its existence, no mat-

[a] From[11] with permission

ter how small or big the bone. In such situations disuse-mode remodeling usually turns ON to remove bone next to marrow. "Disuse" would be the relationship between the bone's strength and its usual loads. The resulting strains and the remodeling threshold would provide the criteria that could "recognize" disuse.

Drift. See Fig. 2. While drifts seem to use the same kinds of osteoblasts and osteoclasts found in remodeling BMUs, drifts and BMUs are different mechanisms that can even respond in opposite ways to the same stimulus.

Fatigue fracture. Here, any fracture that follows two or more load applications. Commonly, such fractures follow thousands to many millions of load applications.

Fatigue life. A measure of strength in fatigue. It would include the number of loading cycles needed to cause a fatigue fracture at a given strain or stress. When repeatedly loaded at loads that originally cause 2000 microstrain bone has a fatigue life ≈10000000 cycles, but at loads that originally cause 4000 microstrain, its fatigue life can fall below 20000 cycles.

Fragility, increased. More easily fractured, whether by voluntary activities or by an injury.

Load. Any mechanical force on a bone. Trauma excepted, the largest loads come from muscle contractions, and smaller ones from body weight.

Mechanical usage. All the forces or loads applied to bones by our usual voluntary physical activities. Among these loads one should separate the very large ones caused by weight-lifting or equivalent activities, from lesser loads applied more frequently, as in long distance running.[12,13] Bones adapt their strength to the largest loads, and seem to be little influenced by smaller ones, no matter how frequent or numerous.

Microdamage (MDx). Microscopic physical damage in bone due to materials fatigue. It weakens a bone without affecting its size, shape, content of material, or appearance. It can reduce a bone's strength below 20% of normal. To increase the fatigue life of inanimate structures, engineers usually add more structural material. But bone can detect and repair limited amounts of fatigue damage to keep it from accumulating, so it needs only enough strength to keep strains below the level that could cause larger amounts of MDx. It can carry loads that cause smaller strains indefinitely. It was recently proposed that skeletal design may aim to minimize MDx in skeletal tissues (this is one meaning of *Relation 1* in the text).

Microdamage threshold (MESp). The strain range above which the amount of new MDx exceeds the ability of remodeling to repair it, so it begins to accumulate and can cause a spontaneous fracture. It should center near 3000 microstrain.

Microstrain. See "strain" below.

Modeling. The biologic processes that produce functionally purposeful sizes and shapes to skeletal organs. Chiefly independent, uncoupled resorption and formation modeling drifts do it in bones. The chief purpose of modeling seems to lie in fitting these organs to their mechanical usage in ways that prevent that usage from breaking them or making them hurt, and for life.

Modeling threshold (MESm). The minimum effective strain range (or equivalent factor) that can turn mechanically controlled bone modeling drifts ON. It seems to center near 1000 microstrain in most young adults, which corresponds to a bone stress of ≈20 megapascals. The author inferred its existence before studies of in vivo strains verified it. Biomechanicians currently ponder how to express it mathematically.

Osteopenia. Less bone than usual for most healthy people of the same age, height, weight, sex, and race. Or, also, less bone at a given age than previously in the same person. It need not represent a disease or stem from an intrinsic bone disorder. Since affected bones would usually have less strength than comparable normal ones, injuries such as falls could fracture them more readily.

Osteoporosis. The 1997 "standard" for diagnosing an "osteoporosis" consisted of a bone mineral "density" or content more than 2.5 SD below the applicable norm.[21] Some have also suggested that an "osteopenia" consisted of a reduction in bone "mass" between 2.0 and 2.5 SD below the applicable norm. This classification does not account for the osteopenia's biomechanical cause(s), yet effective treatment could depend on such causes.[14] Reviews published after 1985 show that many authors find the often used "Type I, Type II" terms confusing.[21]

Remodeling. Turnover of bone in small packets by the above BMUs. Pre-1964 literature did not distinguish modeling from remodeling and lumped them together as remodeling. Some authors still do this, which can be confusing. However, while drifts and BMUs seem to create and use the same kinds of osteoblasts and osteoclasts to do their work, in different parts of the same bone at the same time the osteoblasts and osteoclasts in drifts and BMUs can even respond in opposite ways to the same stimulus.

Remodeling period. The length of time between beginning a typical BMU and its final bone formation. Equal to 3 or more months in healthy humans, it can be prolonged to several years in some diseases, including osteomalacias and some true osteoporoses. Many bisphosphonates prolong it.

Remodeling threshold (MESr). The minimum effective strain range (or equivalent factor) that helps to control BMU-based remodeling. Where strains exceed it, BMU creations usually begin to decrease, and completed BMUs begin to make and resorb equal amounts of bone. This defines conservation-mode remodeling. When strains stay below the MESr, BMU creations increase, and completed BMUs next to marrow make less bone than they resorb. This defines the disuse-mode remodeling that removes bone mainly where it touches marrow (i.e., spongiosa and endocortical bone). This little-studied threshold may center near 50–100 microstrain, which would correspond to a tension or compression stress of ≈1–2 megapascals.

Resorption. Some authors use this term to mean *net* bone loss, and in this sense discuss "antiresorption agents". While often called antiresorption agents, estrogen and the bisphosphonates really depress BMU creations and remodeling. Initially this decreases resorption, but later, and due to the ARF sequence, a usually equal decrease in bone formation occurs too. These are really "antiremodeling agents". Others and this text use "resorption" to mean bone resorption by osteoclasts, and refer to net losses of bone as such and separately.

Safety factor. How much stronger a skeletal organ is than is needed to endure its voluntary mechanical usage. The ultimate strength divided by the modeling threshold can provide a numerical value for this factor for any structural tissue. In stress terms for lamellar bone it ≈6.

Stiffness. The resistance to straining under a load. Stiff materials strain less than less stiff (more "compliant") ones under the same load. Dividing the load or stress by the corresponding strain can define stiffness. The resulting number is often called "Young's modulus". Stiffness is not the same as strength. For example, blackboard chalk is quite stiff but weak, while rubber is far less stiff but far stronger. Since bone's materials properties, including, stiffness, vary little with age, sex, species, and disease, a whole bone's strength can provide a useful surrogate for its stiffness.

Strain. The deformation or change in dimensions and/or shape caused by a load on any structure or structural material. Strain can include stretching, shortening, twisting, and/or bending. Special gauges can measure bone strain in the laboratory and in vivo. Loads always cause strains, even if very small ones. Biomechanicians often express strain in microstrain units, where 1000 microstrain in compression would shorten a bone by 0.1% of its original length, 10000 microstrain would shorten it by 1% of that length, and 100000 microstrain would shorten it by 10% of that length (and break it).

Strength. The load or strain that, when applied *once*, usually fractures a bone (also called the *ultimate strength*). Normal lamellar bone's fracture strength expressed as a strain ≈25000 (c.v. ≈0.25) microstrain, which corresponds to a change in length of 2.5%, i.e, from 100% of its original length to 97.5% of that length under compression, or to 102.5% of it under tension. In normal lamellar bone under parallel-grain loading, 25000 microstrain corresponds to an ultimate or fracture stress of ≈17000 pounds per square inch or ≈120 megapascals. Strength can be expressed in other units too. Strength in fatigue is defined differently (see "fatigue life" above).

Stress. The elastic resistance of the intermolecular bonds in a material to being stretched by strains. Loads cause strains, which then cause stresses. Three "principal" strains and stresses include tension, compression, and shear. We cannot measure stress directly, but must calculate it from other information that often includes strain. Bone's stress-strain curve is nonlinear. While some think stress causes strain, this is like saying a lake causes the rivers that fill it.

Typical peak strains. During a period of 1 week, the strains large enough to turn modeling ON would comprise far less than 0.1% of the total number of strains during that week. For example, counting each systolic pulse in the marrow as a loading event on a hollow bone like the femur, in a week it would strain over 725000 times. Yet only ≈100 strains during that week (strains caused by peak voluntary muscle forces) would be large enough to reach or exceed bone's modeling threshold. The bone would adapt its strength to these ≈100 events and pretty much ignore all others. This has been verified experimentally.[4,5,11,32] Failure to understand this concept explains the tendency to assume that a bone's strength should adapt to some average of all its loads or strains during a week or more.

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