

Why bones bend but don't break

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Abstract

The musculoskeletal system is adept at dissipating potentially damaging energy that could accelerate fracture consequent to multiple loading cycles. Microstructural damage reduces bone's residual properties, but prevents high stresses within the material by dissipating energy that can lead to eventual failure. Thus skeletal microdamage can be viewed as an adaptive process to prevent bone failure by dissipating energy. Because a damaged bone has reduced strength and stiffness, it must be repaired, so bone has evolved a system of self-repair that relies on microdamage-stimulated signaling mechanisms. When repair cannot occur quickly enough, low energy stress fractures can occur. The regulating effects of muscle also prevent failure by controlling where high stresses occur. Acting synergistically, muscle forces dissipate energy by appropriately regulating accelerations and decelerations of the limbs during movement. When muscles become fatigued, these functions are constrained, larger amounts of energy are imparted to bone, increasing the likelihood of microstructural damage and fracture. Thus, healthy bones are maintained by the ability of the musculoskeletal system to dissipate the energy through synergistic muscular activity and through the maintenance of microstructural and material properties that allow for crack initiation, but also for their repair.

Keywords: Microdamage, Energy, Fatigue, Muscle, Remodeling

Introduction

Most structures that sustain loads and bear stresses – bridges, airplane wings – eventually fail at loads below those they could normally sustain when they were new. Bone, however, sustains millions of loading cycles over the course of a lifetime and rarely breaks without a major traumatic event. It can sustain large deformations, sometimes at rapid rates, and yet emerges intact to function another day. It accomplishes this remarkable feat both through structural means – the organization and composition of the material itself – as well as through physiological means in its capacity as a self-repairing structure.

From an evolutionary perspective, an inability to prevent failure

from low energy events would exert a strong selective pressure against the organism. Although bones could adapt by simply adding more material, increasing mass, there is a tipping point at which this would not be selectively advantageous. It is well known that bone can adapt by altering its geometry, providing the strongest structure possible with a minimum amount of material. But strength is not always the end-goal, and strong bones are not always those that are least at risk for fracture. For instance, the capability to withstand high stresses, a measure of bone strength, may be accompanied by a smaller amount of energy absorption in fracture, as in the case of osteopetrotic bone (Figure 1). People with osteopetrosis have very dense and very strong bones, but are also at high risk for fracture because their bones are fragile as the result of high mineralization. The mechanical strength of a bone does not necessarily equate to its resistance to fracture because a bone that is very strong, defined mechanically as one that breaks at a high stress, may absorb less energy (the area under the stress-strain curve) before it breaks than a bone that breaks at a lower stress (Figure 1). It is the amount of energy that can be absorbed before it breaks that defines a bone's resistance to fracture. Mechanisms by which our bones adapt at the tissue level, and the manner in which they function physiologically, are designed to prevent overt fractures from low energy loading. For fracture prevention in bone, as in airplane wings, maximum strength is not the design

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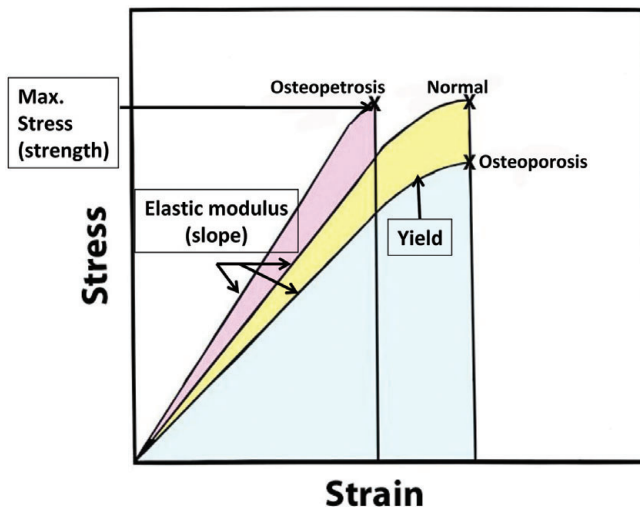


Figure 1. Maximum yield stress defines the strength of bone, while the slope of the initial part of the curve represents elastic modulus, or tissue stiffness. The amount of energy the bone can absorb prior to failure is defined by the area under the curve. Highly mineralized osteopetrotic bone is stronger at yield and stiffer than healthy bone, but it breaks soon after it reaches its yield point; it does not absorb as much energy prior to fracture as healthy bone. Osteoporotic bone, on the other hand, is neither as strong nor as stiff as healthy bone, and absorbs less energy prior to fracture than healthy bone, but much more than osteopetrotic bone. This is because it absorbs more energy after the yield point (the bend in the curve) than does osteopetrotic bone (i.e., it can deform more in the post-yield region). Bones that do not sustain much post-yield deformation/strain, are brittle. Therefore, although osteopetrotic bone is stronger and stiffer than osteoporotic or normal bone, it is brittle, absorbs less energy, and breaks more easily. (Adapted from Ref 76).

goal; energy absorption that prevents or delays fracture is the goal.

Evolutionarily, our musculoskeletal system has adapted multiple mechanisms to prevent fracture by dissipating energy that could cause the bone to break. Microscopic heterogeneity may facilitate formation of microcracks within the bone, releasing energy that otherwise might build up and create an overt fracture. The heterogeneity of the system also prevents crack growth, providing time for the body to repair the damage. This requires a signaling system, putatively provided by the osteocyte-canalicular system, that informs the bone when and where damage has occurred. The signaling system allows remodeling to be targeted efficiently to the locations of damage. Muscles also dissipate energy that would otherwise be imparted to the bone. When muscles are ineffective at dissipating energy, high levels of stress and strain can be generated in the bone that create levels of microdamage that overwhelm the body's ability to repair it quickly. This can lead to a degradation of bone's mechanical properties over time, resulting in a stress fracture. These mechanisms of bone damage, repair and energy dissipation will be explored in the sections below to provide a more holistic understanding of why bones bend under load, but rarely break.

What do cross-species comparisons tell us about mechanisms bone uses to prevent failure?

Cross-species comparisons can be instructive in pointing us towards the skeletal mechanisms that prevent fractures. Bones are designed to withstand loading, and loading is primarily exerted by muscular and gravitational forces that are applied during movement. Therefore, one might expect that animals that move in different ways demonstrate different adaptive mechanisms.

At the tissue level, bone has developed a heterogeneous structure in many different species as an adaptation for more prolonged and impulsive loading¹. Animals that do not live for a long time (decades), those that do not place large loads on their bones, and those that do not have a need for ballistic activity tend to have bone that is more homogeneous at the microscopic level. This can be seen in rats and mice, for instance, short-lived animals that have fibrolamellar bone with unorganized collagen, and which is devoid of structural topography when viewed under a microscope (Figure 2 A). Even in non-human primates, which typically have more lamellar bone and greater organization in collagen structure, there is a wide range of microscopic morphology¹, and the nature of the morphology is largely related to the manner in which the animal moves (Figure 2B,C). Arboreal and terrestrial quadrupeds that spend much of their day trying to eat sufficient amounts of leaves, insects, fruits and nuts just to survive, are not known for rapid or sustained movement. These animals have low cortical bone remodeling rates, and consequently do not develop cortical bone that appears very heterogeneous²⁻⁵. Primates that use arm-swinging behaviors, however, subject their limbs to greater impulsive (e.g. high strain rate) behaviors, and these animals remodel more rapidly and develop bone that is much more similar to human bone. From an evolutionary perspective, humans have adapted to environments and diets in which it was necessary to travel long distances on two legs, sometimes at great speed. We, too, have developed the capacity to remodel rapidly when necessary, creating structures within our bone – secondary osteons in cortical bone and hemiosteons in trabecular bone – that are heterogeneous with respect to lamellar organization, orientation, size and geometry (Figure 2D). These two features of our skeletons – the capacity to remodel, and the ability through that remodeling mechanism to create a heterogeneous tissue that controls damage – are related to each other and function in a complementary way to prevent bone failure. For that to become apparent, however, it was necessary to demonstrate that microscopic damage occurs in bone, that osteons and hemiosteons are important in controlling crack growth, and that there is a mechanism in bone that can signal for their repair.

The mechanical role of microdamage

It is clear now, and more widely accepted than it was 20 years ago, that microdamage in bone is a naturally occurring event, and that it is probably important in some way for skeletal health. The mere existence of microdamage was not always

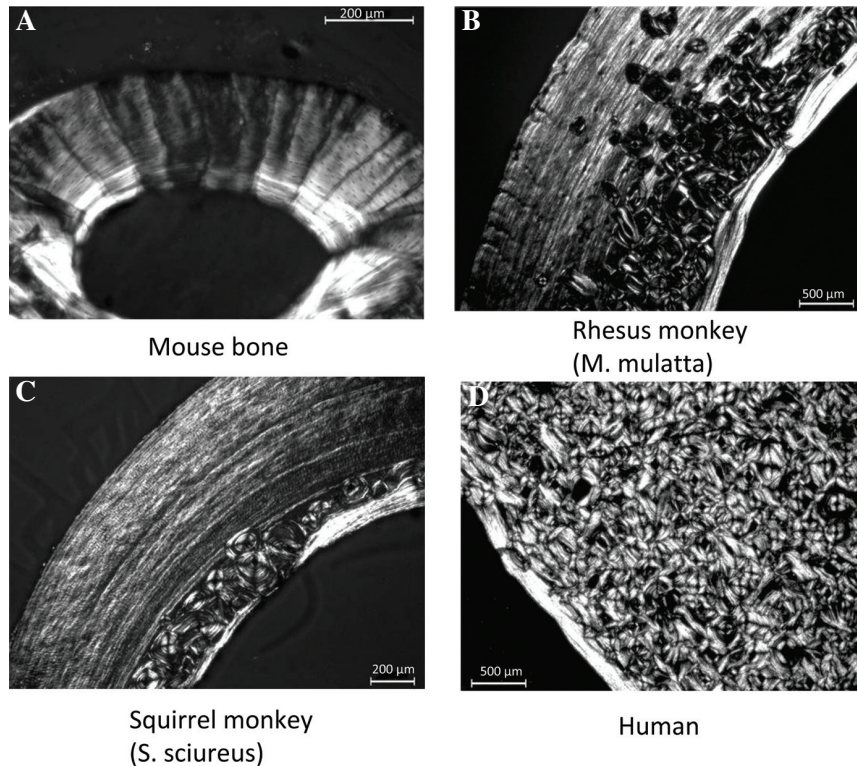


Figure 2. Photomicrographs taken under polarized light showing greater heterogeneity of structure in nonhuman primates than in mouse, and more heterogeneity in human bone than in primates that use less impulsive movements, have shorter territorial ranges, or are shorter lived. These traits are all related to the capacity to form damage and the need to remodel.

Mouse bone is fibrolamellar and has no osteonal bone. It is very homogeneous, which is not detrimental because mice do not place large strains/strain rates on their bones, and do not live for a long time. They do not need the capacity to prevent cracks from growing, or to repair them. The radial structures are vascular canals.

The squirrel monkey (*Saimiri sciureus*) is an arboreal quadruped. It is a small primate (BW: 365-1135 g) which is classified as a quadrupedal climber and seldom leaps. They do not use impulsive movements, and their bone is largely laminar, unremodeled, and quite homogeneous.

Macaques (*Shown here: Macaca mulatta*) are terrestrial quadrupeds (although they also spend time arboreally) that do not often move quickly. They tend to have more osteonal bone in their cortex, but retain large amounts of primary lamellae. Their bone remodels more intracortically and is more heterogeneous than that in squirrel monkeys, but less so than in humans.

Humans (*H. sapiens*) are larger bodied, longer-lived animals that tend to engage more often in high strain rate activities (walking long distances and running). By virtue of their behaviors and lifespans, it is more important that they have osteons to prevent microcracks from growing to critical size, and that they be able to repair microcracks with osteonal remodeling. Consequently, they have bone that is highly remodeled, with many secondary Haversian systems. Interestingly, larger bodied, longer-lived chimpanzees (not shown) also have bone that is highly remodeled with osteons intracortically.

accepted as a physiological feature of bone. There was substantial controversy from the time that Harold Frost first introduced the concept in 1960⁶ until at least the early 1990's about whether bones were subject to microscopic damage, even though it was well known by engineers that any cyclically loaded structural material would sustain damage over time. Over the past 20 years, because the phenomenon of microdamage has been observed in multiple labs using different techniques, there is less controversy now that damage occurs⁷, although the debates about its mechanical and physiological importance continue to rage on.

Microdamage is not all created equal, nor does all perform the same mechanical function. There are at least three distinct varieties of "microdamage," which can be identified as linear

microcracks, diffuse microdamage, and microfractures⁸. These "types" are distinguished by the way they form and their morphology; the nature of the stimuli that cause them to form as well as their location; and the manner in which they are repaired (Table 1).

Linear microcracks (Figure 3A-C) represent planes of separation within the bone tissue. They are three dimensional elliptical structures in that their dimensions will differ in each plane. In cross-section, they are about 40-100 microns long, and perhaps 1-2 microns wide, but can run longitudinally within the bone for 300-500 μm ^{9,10}. They tend to form preferentially in response to compressive stresses¹¹, and are indicative of bone tissue that deforms more before it cracks¹². Consequently, the preponderance of them are found within the more highly min-

	Shape/ Dimensions	Stress mode	Tissue properties	Predominant location	Age	Repair
Linear Microcracks	Elliptical ~80 x 1 x 300 μm	Compressive	More brittle	Interstitial	Older	Remodeling
Diffuse Microdamage	$\approx <10 \mu\text{m}$ wide Unknown length	Tensile	More ductile	Within trabecular packets and osteons	Younger	Remodeling ¹
Microfractures	Complete fracture	Bending/shear	Off-axis orientation	Trabecular	Older	Endochondral ossification

¹*It is not entirely clear that diffuse microdamage is repaired by targeted remodeling. It is possible that cracks must be of a certain length in order to create the physiological signals needed to produce a response⁷⁵.*

Table 1. Types of damage and their characteristics.

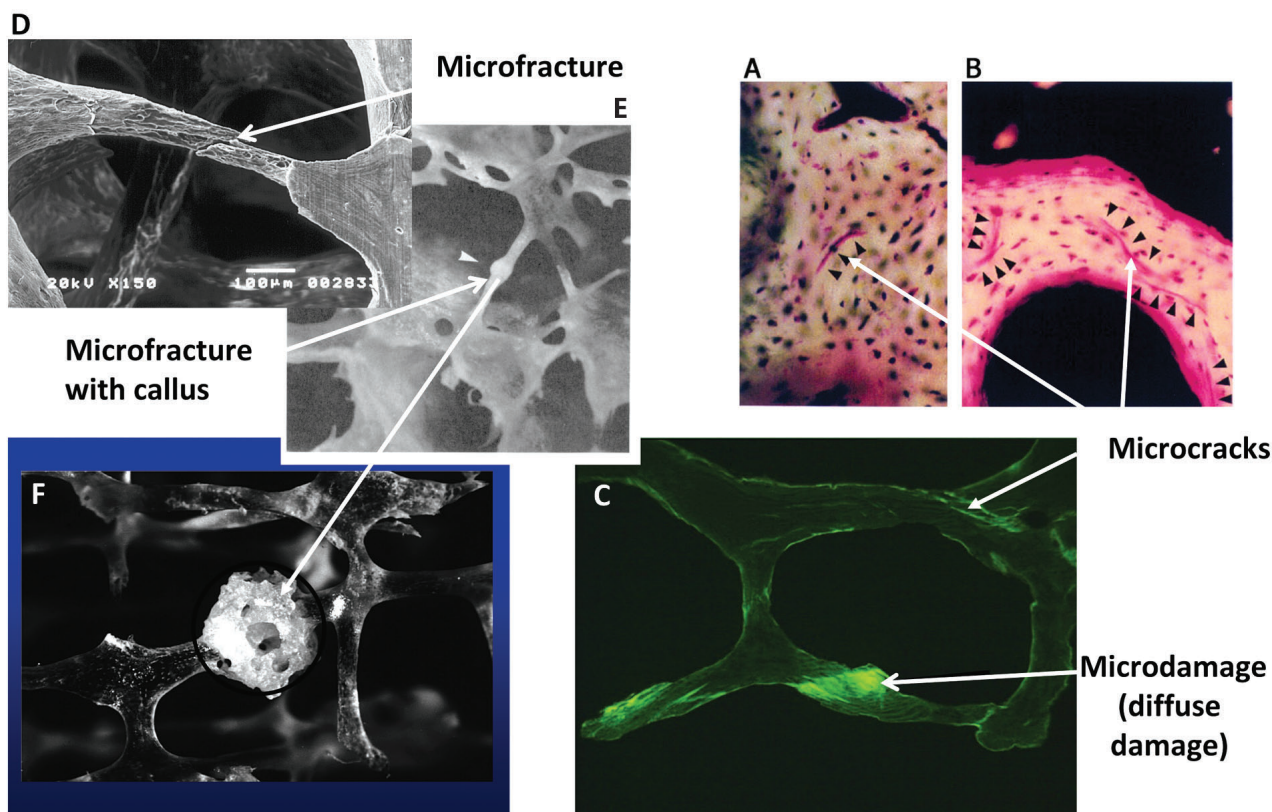


Figure 3. Linear microcracks, diffuse microdamage and microfractures are distinct features in bone. They differ by morphological appearance, location, mechanical consequences, and by the manner in which they are repaired. (D-F used with permission from Dr. Nick Fazzalari, Institute of Medical and Veterinary Science, Adelaide; Figure 3F also used with permission of Oxford University Press, www.oup.com, from Ref 77).

eralized interstitial bone¹⁵⁻¹⁶, and they tend to occur more frequently than other forms of microdamage in older people¹². Diffuse microdamage (Figure 3C) consists of collections of numerous small cracks, each $<10 \mu\text{m}$ wide and of unknown length¹⁷⁻¹⁸. They tend to form in areas under tensile stress¹¹ and can best be viewed through a confocal microscope. Using standard staining methods, such as basic fuchsin or en bloc staining with a fluorochrome, their presence is often signaled by an in-

creased patch of diffuse staining without clear visualization that cracks are present. These stains work by diffusion, damage of any sort will increase the diffusion gradient around itself, and therefore more stain appears in the area even when cracks cannot be seen. Microfractures, on the other hand, are entirely different than these forms of damage. Microfractures occur within cancellous bone, and represent complete fractures of one or more trabec-

ulae (Figure 3 D-F). Whether microfractures are the end-stage of linear or diffuse damage in cancellous bone is not known, and still somewhat controversial. However, these are full fractures, not cracks, and are clearly distinct from other forms of damage. The term should not be used as a general descriptor for linear microcracks, although it often is.

These forms of damage are not only distinct in their morphology, but heal by completely different mechanisms. Linear microcracks and diffuse damage both repair through normal coupled remodeling processes, although signaling for remodeling may differ between them with linear microcracks having greater potential to initiate a repair response¹⁹⁻²³. They are removed by resorption, and new bone is laid down where the damage once was. Microfractures, on the other hand, are repaired through normal fracture healing mechanisms which involve endochondral ossification (Figure 3F). A cartilage or woven bone callus is formed over the broken area; these can be readily observed through a dissecting microscope in nearly any hemi-sectioned femoral head/neck from a middle-aged or older person. The callus eventually remodels to re-establish the normal lamellar structure of the trabecula.

The presence of microdamage within bone tissue has mechanical effects on the residual properties of bone, and this is one reason that it is important to the skeleton to remove it and replace it with undamaged bone. By definition, the residual stiffness of damaged bone tissue is less than in undamaged tissue. In fact, this is the definition – reduced stiffness – that engineers use to define damage in structural materials which cannot be evaluated microscopically. Moreover, the introduction of microdamage reduces the bone's future capacity to absorb energy prior to fracture, and in this sense deteriorates the mechanical properties of bone. However, the paradox of this is that the initiation and growth of microcracks in itself dissipates energy and delays a catastrophic complete fracture from occurring^{24,25}. It is a truism that materials that perform well under cyclic loading conditions tend to be heterogeneous at the microscopic level. These materials delay complete failure not by preventing the initiation of damage, but by reducing its ability to grow to catastrophic size through microarchitectural organizations that stop cracks from growing^{26,27}. Thus, although we typically think of microdamage as “bad,” it has a positive role to play in preventing fracture. Particularly in a self-repairing structure like bone, any adaptation of the microarchitecture that can stop a crack from growing long enough to allow for its repair is an adaptation that will promote survival of the individual, and will tend to proliferate in the genome. This presumes that the damage will be repaired in an efficient manner, before significantly more damage can be created. This requires a signaling mechanism, and suggests a physiological role, not just a mechanical one, for bone microdamage.

The physiological role of microdamage

There is a tendency to think of microdamage only as a mechanical event, but it is possible that its role in mechanics is less important to skeletal health than its physiological role. Two

kinds of remodeling have been proposed: stochastic and targeted²⁸⁻³². Stochastic remodeling functions primarily to maintain mineral homeostasis, whereas targeted remodeling serves a mechanical function in removing microdamage from bone^{19-23,33}. Frost⁶ was the first to propose the concept that microcracks in bone signal for their own repair, suggesting that damage to the osteocyte's canalicular network could be responsible.

To address this question more methodically, Burr et al.³³ originally defined a probability function based on a comparison between the number of cracks in association with resorption spaces (n_{obs}), compared to the maximum possible number of cracks and resorption spaces (n_{max}). Targeted remodeling was defined by $n_{\text{obs}}/n_{\text{max}} > 1.0$, indicating that more cracks were observed associated with resorption spaces than expected by chance alone. In an experiment in which dog radii were loaded for 10,000 cycles to generate microdamage in the bone, they found that $n_{\text{obs}}/n_{\text{max}}$ was between 6.2 and 44. This suggested that microcracks were more likely to be found near resorption spaces than not, leading to the conclusion that the damage was eliciting a remodeling response. However, that initial experiment was not able to separate those cases in which the cracks pre-existed the resorption spaces, from those in which the resorption space preceded the crack. In other words, it still could be possible that the stress concentrations caused by active remodeling sites caused the cracks to form at those locations, and that the cracks were not eliciting the resorption response at all.

A second experiment was performed in which the right dog radius was loaded to create microdamage, as in the previous experiment, eight days were allowed to pass to permit the initiation of new remodeling, then the left radius of the dog was loaded, and the animal killed immediately after¹⁹. If the cracks were eliciting the repair response, then the proportion of cracks found in association with remodeling sites (Figure 4A) should be greater in the limb that was loaded first. Indeed, in this experiment, $n_{\text{obs}}/n_{\text{max}} = 4.05$ (Figure 4B), suggesting that following loading, cracks were found in association with resorption spaces four times more often than expected under a model of stochastic remodeling; this was not the case in the limb that was loaded immediately before sacrifice. In fact, the ratio of crack density (Cr.Dn) to resorption space density (Rs.Dn) was nearly the same in the limb that had been allowed to generate a repair response as it was in control limbs of other dogs that were not loaded at all, whereas the ratio Cr.Dn/Rs.Dn was 3 times higher in the limb that had not been allowed to mount a repair response (in other words, cracks were generated, but were not allowed to repair) (Figure 4C). This showed almost certainly that microcracks were signaling for their own repair, and also suggested that there was normally an equilibrium between the microdamage burden and the activation of bone remodeling (This was determined from a 2D analysis, and it is fair to point out that in three dimensions it is possible that a different proportionality would be found. Subsequently, Martin³² made the mathematical argument that it is at least theoretically possible that all remodeling in cortical bone of the long bones is targeted remodeling).

A more definitive set of experiments was performed by Schaffler and his colleagues. Normally, rats do not remodel

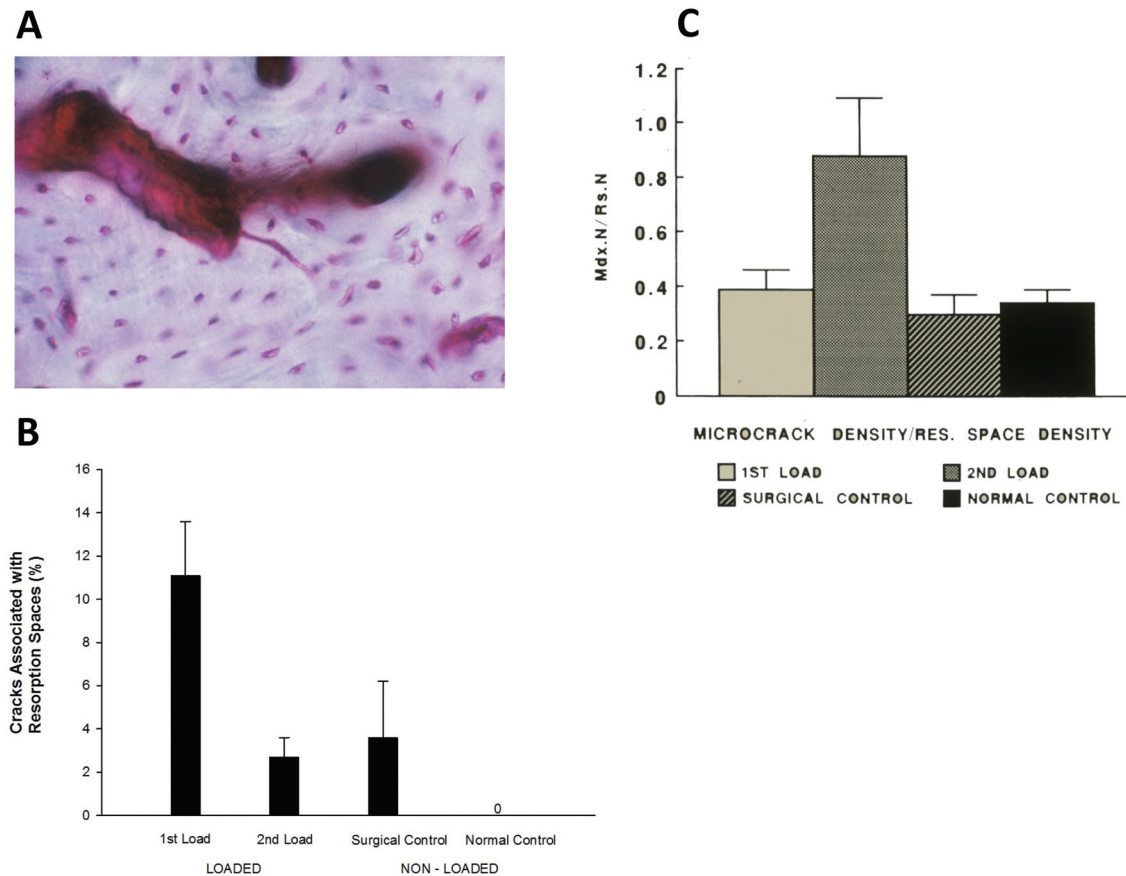


Figure 4. Microcracks signal for their own repair. **(A)** A resorption space removing a microcrack from bone. **(B)** Loading to create microdamage in a dog forelimb demonstrated that microcracks signal for remodeling to repair themselves. The left forelimb of a dog loaded on Day 1 and sacrificed 8 days later has about 4 times more microcracks close to resorption spaces than the forelimb of the same dog that was loaded immediately before sacrifice. A separate group of dogs whose forelimbs were not loaded served as controls. Surgical controls had a strain gage attached but no load applied, whereas normal controls had neither. **(C)** The ratio of microcracks to resorption spaces in these same groups of dogs shows the progression of repair. Eight days following loading, there are fewer microcracks compared to the number of resorption spaces than in dogs sacrificed immediately after loading. This is because much of the damage already has been resorbed within the week following the damage-initiating event. Dogs that were not loaded still have some naturally occurring microdamage, and have ongoing remodeling, and the ratios of damage to resorption spaces is about the same as that in the dogs allowed some time to repair damage that was induced. (Adapted from Ref 19).

their bone intracortically, but are capable of doing so under extreme conditions of low calcium or disuse. Bentolila et al.²¹ used the rat ulnar axial loading model to create microdamage within the cortical bone of the rat ulna. If damage signaled for its own repair, then the damage created in the rat ulna should stimulate a remodeling response; and indeed it did. In a subsequent set of experiments, Verborgt et al.²⁰ showed that the initiation of remodeling mounted in response to microdamage was linked both spatially and temporally with the apoptosis of osteocytes. Within one day following the initiation of damage by cyclic loading of the ulna, there was evidence of osteocyte apoptosis in regions that were within 100 μ m of the microcracks, but no increased apoptosis even after 10 days in distant regions (>100 μ m) without damage. Within the next week, resorption spaces appeared in these same regions. This experi-

ment not only confirmed the existence of targeted remodeling, but suggested that osteocyte death might be part of the signaling mechanism. When damage was created by cyclic loading but osteocyte apoptosis was prevented using caspase inhibitors, no remodeling response occurred²², confirming the vital role played by osteocyte apoptosis in the signaling mechanism.

Most recently³⁴, these investigators have demonstrated that this signaling is related to the RANKL/OPG axis. Three days after cyclic ulnar axial loading to a pre-determined damage level, the RANKL/OPG ratio in the rat ulna increased by six times, and was further increased after one week. However, those rats that were given a pan-caspase inhibitor to prevent osteocyte apoptosis did not have elevated RANKL/OPG ratios. They further spatially localized the osteocytic response, discovering that RANKL was low in regions near the location of the damage

where osteocytes were apoptotic, but increased at distances of 100-500 μm from the damage, where there were few apoptotic osteocytes. The response depends on the size of the microcrack, with larger cracks eliciting a greater increase in RANKL and greater decrease in OPG than smaller cracks³⁵. In combination these studies suggest that osteocyte apoptosis is the signal for the initiation of bone remodeling, but that it is the healthy osteocytes at a distance from the damage that provide the protein necessary for osteoclast differentiation and activation.

Summary of the role of microdamage in bone

We have learned from these studies over the past 30 years that microdamage is not an artifact of histological preparation, but occurs naturally in bone, and that in the healthy skeleton the production of microdamage is in equilibrium with its repair by bone remodeling. The presence of microdamage in bone reduces the bone's residual strength, stiffness and energy to fracture. However, the paradox is that the initiation and growth of microdamage reduces the risk of fracture by releasing energy that would otherwise cause the bone to fail. Thus, microdamage prolongs bone's integrity and is a selectively advantageous evolutionary mechanism to preserve an animal's functional capabilities. However, because it reduces residual properties, it is important to repair the damage. Indeed, the primary role and importance of microdamage in bone may be its physiologic function in stimulating the remodeling system to renew the bone matrix through bone turnover. It is absolutely clear now that this important physiologic function of microdamage in stimulating bone remodeling occurs mechanistically via a cellular signal from dying osteocytes in the area of the bone damage, and that the activation of resorption is subsequently caused by an increased osteocytic production of RANKL, most likely by non-apoptotic osteocytes at some distance from the damage.

Normally there is an equilibrium between damage and repair, and as long as that equilibrium is maintained bone continues to function. However, bone does fail sometimes from cyclic loading over long periods of time, resulting in nondisplaced fractures called stress fractures. Understanding why these occur, ie whether they represent an increased microdamage burden solely from overuse, or a failure of the repair system to remove damaged bone, is critical to understanding their pathogenesis and ultimately their prevention.

The causes and prevention of stress fracture

It has never been shown definitively that the microdamage burden in human bone is sufficiently high under most conditions to significantly reduce the mechanical properties of bone to the extent that it will increase the risk of fracture. Large amounts of damage can be induced in the laboratory, and at these levels can be shown to degrade the mechanical properties of the bone. However, these levels of damage are rarely or never found *in vivo* in bone. Yet the suspicion is that damage accumulation underlies at least some kinds of fractures, especially those that

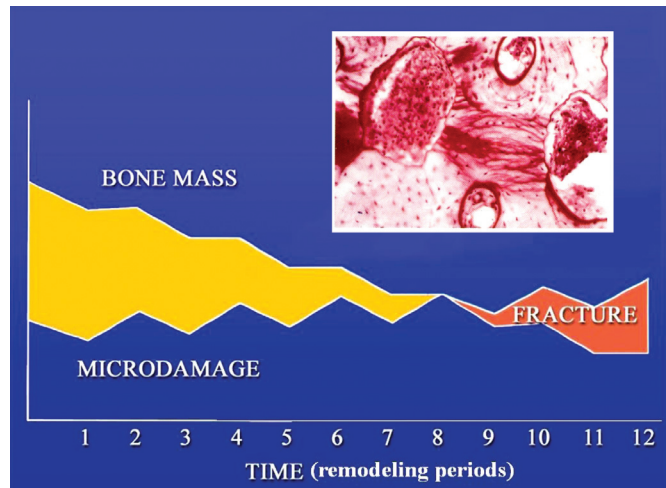


Figure 5. If microdamage initiates the repair process, then the development of a stress fracture could be the result of positive feedback between damage initiation, and the loss of bone mass caused by attempts at repair. Each time a crack is initiated, remodeling is activated. The initial stage of remodeling is resorption, but as bone is removed, there is less mass available to support loads, potentially initiating a new cascade of damage. Because it takes much longer to form bone than to remove it, taking this to its logical conclusion suggests that continued loading might result in a stress fracture when the critical threshold for stress or strain is reached. Inset: Biopsy of a stress fracture showing the remodeling reaction to microdamage. (Ref 78; Used with permission from CRC Press and Dr. Satoshi Mori).

occur spontaneously with low amounts of energy^{36,37}.

Cyclic loading studies of cow bone performed many years ago showed that at what were considered to be physiological strains (1200 $\mu\epsilon$ in tension) and strain rates (0.01-0.03/sec), bone could sustain literally millions of cycles without failure³⁸. This experiment was flawed in that it was run under strain control rather than load control so that as bone lost stiffness, the stresses also decreased. Even so, the inability to cause bone to break after 45 million cycles still did not seem consistent with the observation that stress fractures do occur frequently, and can occur in athletes and soldiers with many fewer cycles. One thought was that the strains on bone were higher than those used in this experiment, at least on an occasional basis. This stimulated us to initiate a series of experiments in which strain gages were placed on human bone *in vivo* in regions at risk for stress fractures, and strains monitored during a series of activities, including vigorous activities³⁹⁻⁴¹. These studies showed that strains were not particularly high in either the tibia or the metatarsus for most activities, ranging from 800 $\mu\epsilon$ in tension to -1200 $\mu\epsilon$ in compression during walking, to approximately -1500 $\mu\epsilon$ or so during running on a flat surface. Strains on the order of -2000 $\mu\epsilon$ could be achieved running up and downhill. Strains up to -5000 $\mu\epsilon$ occur in the metatarsus in landing from a jump about a meter high^{42,43}, an activity that no one performs routinely for very long.

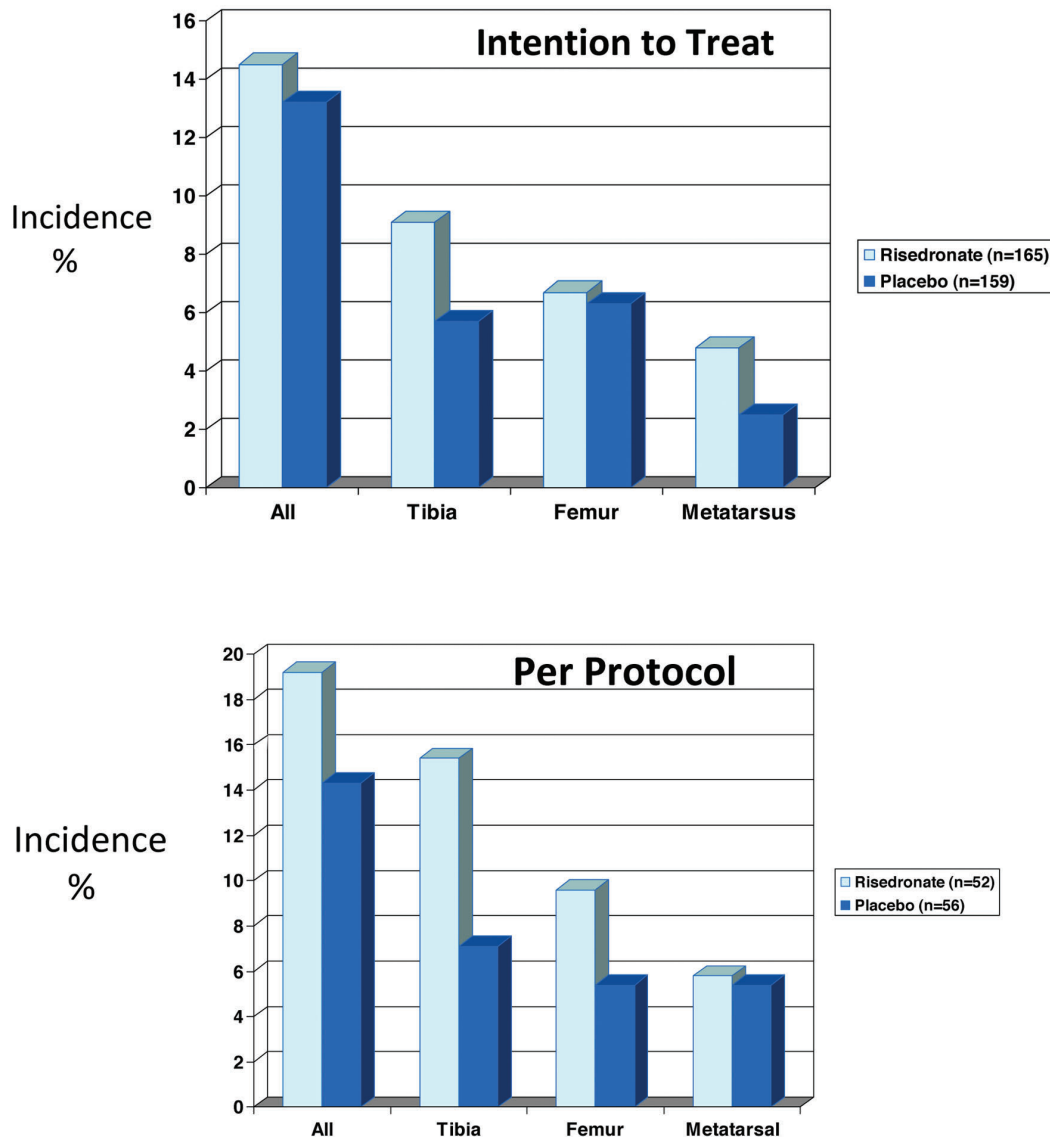


Figure 6. Reducing remodeling rate in soldiers during basic training in the military did not decrease the incidence of stress fractures at any site, suggesting that bone remodeling was not part of the pathophysiology for the development of a stress fracture. (Data from Ref 44).

Because these strains were not sufficiently high to cause bone failure in a reasonable number of cycles, we hypothesized that the physiological response of the bone to microdamage might be part of the pathophysiology for stress fractures. Knowing that microdamage initiation would activate the remodeling system, and that this begins by active resorption of bone, we hypothesized a positive feedback loop between damage production, loss of bone mass through initiation of resorption and remodeling, and eventual stress fracture (Figure 5). The active involvement of remodeling activation in stress fracture physiology could be tested by suppressing bone turnover in a well characterized group at high risk for developing stress fractures – soldiers in basic training – by giving an agent that suppresses remodeling and reduces the repair of damage that

occurs. If remodeling were a part of the pathophysiology of these fractures, then suppressing it should result in fewer stress fractures following the 14 week basic training program.

A blinded, randomized trial of Israeli soldiers in basic training was performed in which 165 soldiers began to take a bisphosphonate prior to basic training, while 159 soldiers were given a placebo⁴⁴. Although there was substantial dropout due to some negative publicity during the trial (52 and 56 soldiers in the treatment and placebo groups respectively, completed the regimen), the results definitively showed, using both intention-to-treat and per-protocol analyses, that reducing the repair of microdamage did not significantly reduce the incidence of stress fractures overall, or at specific risk sites including the tibia, femur and metatarsus (Figure 6). In fact, reducing repair

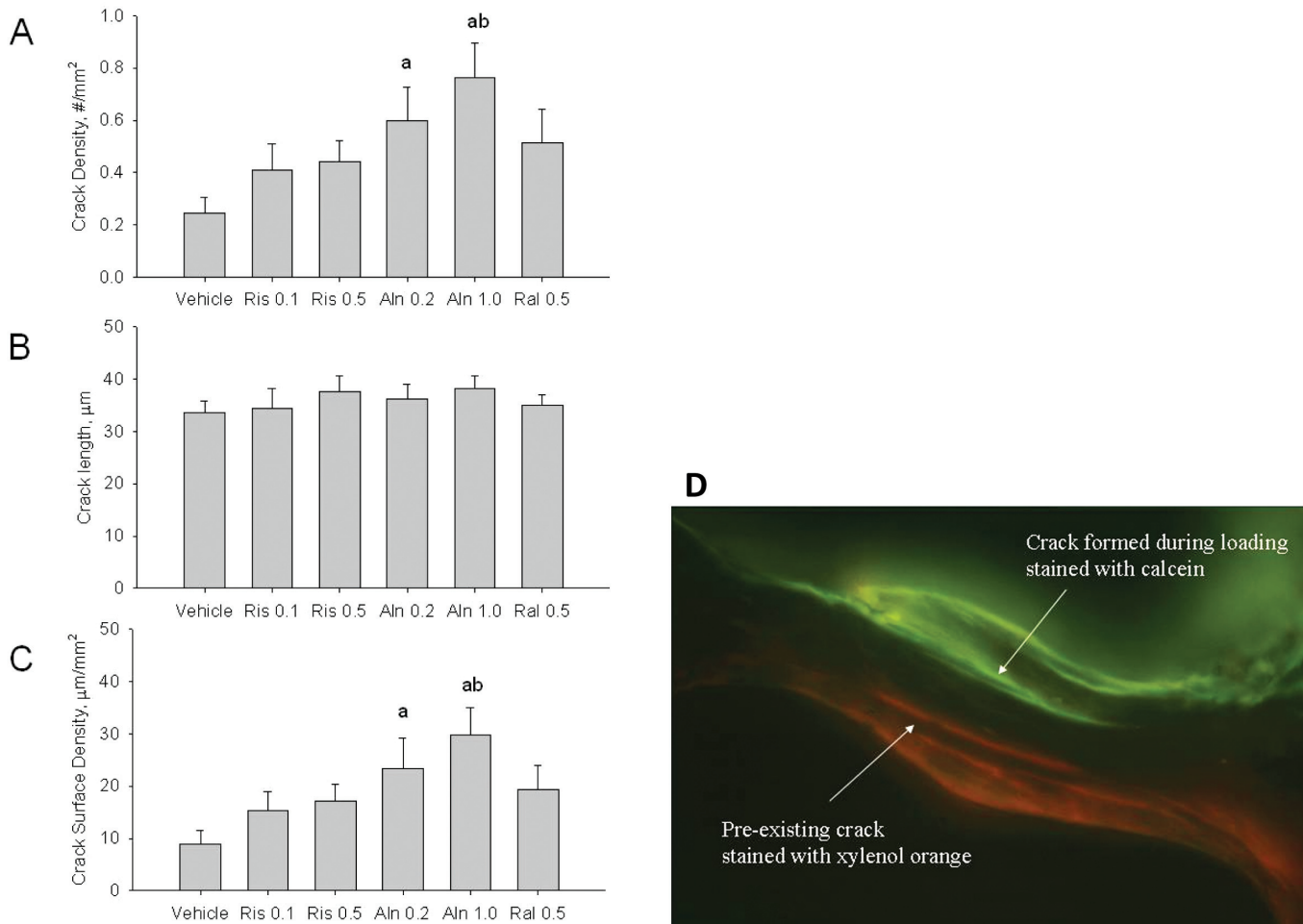


Figure 7. The lumbar vertebrae of dogs pre-treated for one year with one of several different anti-remodeling agents (the bisphosphonates alendronate [ALN, 0.2 or 1.0 mg/kg/day] or risedronate [RIS, 0.1 or 0.5 mg/kg/day], or the selective estrogen receptor modulator (SERM) raloxifene [RAL, 0.5 mg/kg/day] were loaded in compression for 100,000 cycles at 5 Hz between 100-300% body weight. Vertebrae were stained en bloc in alizarin prior to loading. Following loading, the specimens were again stained en bloc in calcein to identify new microcracks created by the loading. The data showed that vertebrae from dogs treated with alendronate were significantly more likely to initiate new microcracks under loading than untreated dogs.

of microdamage resulted in a greater incidence of stress fractures in those groups taking the bisphosphonate. This increased incidence was not statistically significant, however, in part due to the high dropout rate and resulting lower power. Nevertheless, it was clear that interfering with the repair of damage was not going to improve the prognosis for developing a stress fracture.

Remodeling suppression increases microcrack accumulation

Why might this be? It was known from previous pre-clinical experiments⁴⁵⁻⁴⁷ that high doses of bisphosphonates used to reduce remodeling in non-osteoporotic beagle dogs causes 2.5-7 fold increases in damage accumulation in the rib and spine. Subse-

quent experiments showed that using lower, more clinically relevant doses, and even lower than clinical doses, also allowed significant damage accumulation⁴⁸ caused both by greater initiation and by reduced repair (Figure 7)^{49,50}. The accumulation of microdamage occurs in a nonlinear fashion and is inversely associated with activation frequency, a measure of bone remodeling activity defined by the probability that a new remodeling unit will be started at a given location (Figure 8). This in turn is associated with ~20% reduction in energy to fracture when normalized to bone mineral density (BMD)^{45,46,50,51} meaning that for a given BMD, the quality of the bone tissue was impaired. This seemed to suggest that microdamage, as most people expected, led inevitably to mechanical degradation of the bone, and that repair was essential to maintain the health and quality of the bone tissue.

However, continued suppression of bone remodeling over

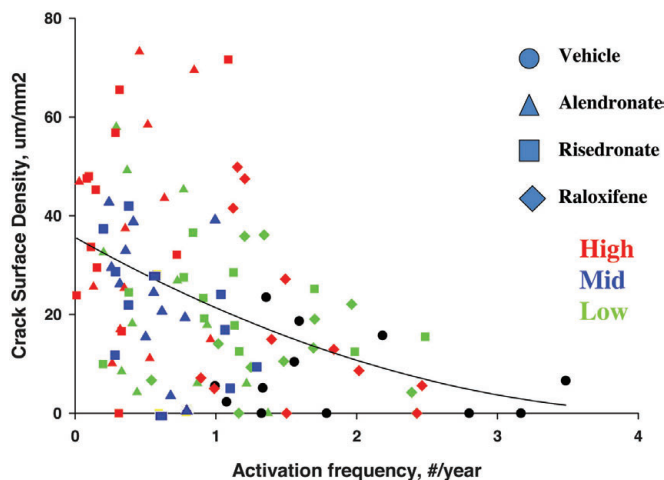


Figure 8. Microdamage will accumulate naturally if not repaired. The amount of damage that accumulates is nonlinearly related to the rate of bone remodeling, measured as activation frequency (Ac.f). This graph combines data from dogs treated for one year with saline vehicle, or alendronate, risedronate or raloxifene at high, clinical, or low doses to show the relationship between Ac.f and damage accumulation.

three years in this dog model did not result in significantly greater accumulation of microdamage compared to controls, yet toughness, the strain energy required to cause microcracking, continued to decline by a total of about 30% (Figure 9)^{51,52}. This suggested that microdamage accumulation is not responsible, or at least not totally responsible, for the reduction in mechanical properties. Moreover, using regression analyses, no relationship ($r^2=0.02$) could be found between microdamage and bone toughness^{53,54}, a result consistent with several other studies⁵⁵.

Subsequent studies have demonstrated that reduced bone remodeling allows the formation of additional collagen cross-links by non-enzymatic means, resulting in glycation and the accumulation of advanced glycation end-products (AGEs) in the bone tissue⁵⁶. The accumulation of AGEs is directly related to the rate of bone turnover, estimated by activation frequency, and appears to be an inevitable result of the failure to renew the tissue. Laboratory studies performed by Vashishth and his colleagues^{57,58} have clearly shown that bone glycation allows cracks in bone to grow more easily, therefore increasing the apparent microdamage burden measured as total crack surface density, and has the added effect of reducing the post-yield deformation of bone, making the bone tissue more brittle and more likely to fracture. *In vivo*, in the canine tibia, there is a significant non-linear reduction in post-yield energy to fracture (the area under the stress-strain curve after the yield point) associated with reduced remodeling and AGE accumulation⁵⁹, even though the bones are stronger and stiffer. Increased strength and stiffness of a bone without increased energy absorption necessarily implies a more brittle structure.

Although the growth of microcracks in bone, which will in-

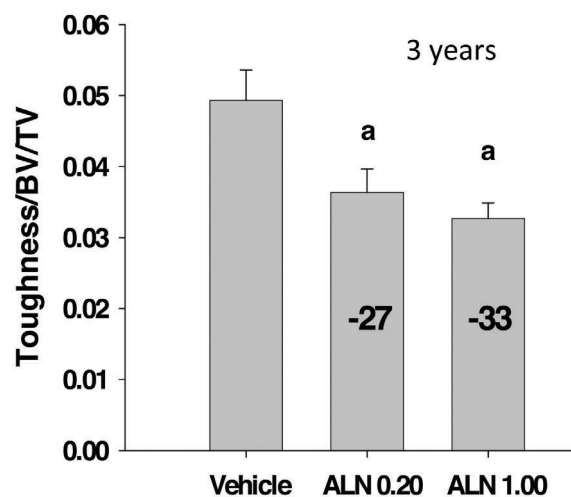
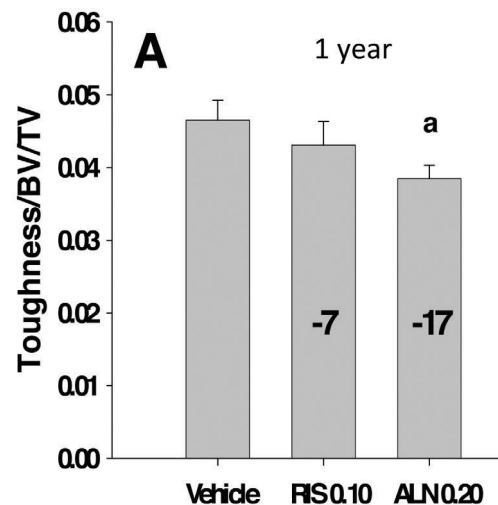


Figure 9. The modulus of toughness in vertebrae from dogs treated for one year with alendronate (ALN) or Risedronate (RIS) at the clinical dose declined significantly by 17% in the ALN treated group. Modulus of toughness in vertebrae from dogs following 3 years of treatment with ALN at either the clinical dose or a dose five times higher than that continued to decline by about 30% compared to that in untreated dogs. However there was no significant increase in microdamage accumulation between 1 and 3 years, suggesting that this mechanical decline was not related to damage accumulation. Also, even though there was significantly greater damage accumulation at the higher dose of ALN after three years of treatment⁵¹, there was no significant difference in toughness between the two doses, lending greater credence to the idea that damage accumulation was not responsible for the decline in toughness.

crease the apparent microdamage burden, is widely viewed as a negative effect on bone's mechanical properties (and is), it actually delays or prevents the ultimate failure of the bone by releasing energy that otherwise would lead to immediate bone fracture. Easier crack initiation in this case is an adaptation to prevent the early failure of more heavily glycosylated, and less ductile, bone. Thus, crack accumulation, whether caused by

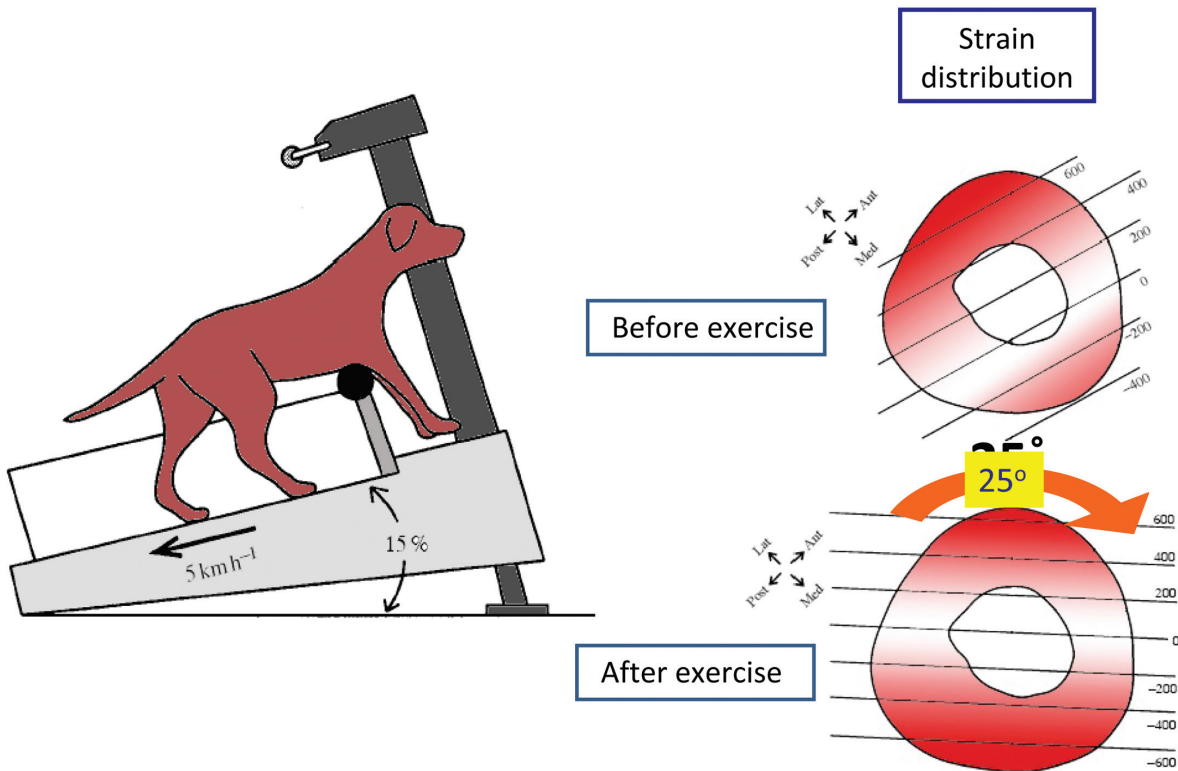


Figure 10. Strains were measured around the tibiae in dogs walked on an inclined treadmill to muscular fatigue. Following fatiguing exercise, the distribution of strain around the bone changed markedly, rotating by about 25° so that regions previously under low strain were under much greater strain following fatigue. (Adapted from Ref 65).

pharmaceutical treatments that reduce remodeling, or caused by overuse during athletic and military exercises, is an adaptive mechanism to dissipate energy and delay fracture. This is especially true if crack growth can be constrained by the heterogeneous microstructure of the bone, ie by interfaces such as cement lines that will allow the crack to dissipate energy, but prevent it from growing to critical size.

The role of muscle in energy dissipation and controlled crack growth

There are other mechanisms that the body uses to control crack growth and prevent bone fracture; this is not just a responsibility of bone structure. Muscles also serve this function by regulating and dissipating the energy that is imparted to the bone, in part through eccentric contraction⁶⁰⁻⁶² and in part by working synergistically to control loads⁶³. When a bone is bent, one surface is subject to compression and the opposite surface to tension. When muscles that span the tensile surface of a bone contract appropriately, they limit the magnitude of tension by adding compression to this surface, and reduce stress on the bone. Muscle forces are the greatest single forces placed on bones, and although we generally view muscles as creating loads and strains on bones, when they are properly functioning

they can actually relieve loads on bone and reduce bone strain, or strain rate^{64,65}. This is particularly true of tensile strain. Bone damage can be initiated more easily at lower strains by tensile forces than by compressive forces⁶⁶, and the nature of the microdamage tends to be in the form of more damaging linear microcracks than less mechanically severe diffuse damage¹¹.

Studies using dogs running on an inclined treadmill to fatigue showed that muscle fatigue was indeed associated with increased bone strains, although strain only increased by about 30%⁶⁵. Whether this is sufficient to generate microdamage in bone is not known. More importantly, however, muscular fatigue caused an alteration in the distribution of strain so that regions previously adapted to relatively low strains were suddenly subjected to strains of were many times higher than usual (Figure 10). Studies of soldiers undergoing basic training^{67,68} carrying backpacks on long forced marches and who are known to be at high risk for stress fractures verified that muscular fatigue increased tensile strain by more than 40%, both in the distal tibia and in the first metatarsal, both sites for increased risk of stress fracture (Table 2). Still other studies⁶⁹ have shown increased plantar pressures following fatiguing exercise, suggesting that metatarsal strains would be increased under such conditions (Figure 11).

More important is that strain rates, which may be more crit-

Phase	Strains ($\mu\epsilon$)		Strain Rates ($\mu\epsilon/\text{sec}$)	
	95 % Confidence Limits		95 % Confidence Limits	
	Tension	Compression	Tension	Compression
Pre run	394 (342-446)	672 (628-716)	4683 (4429-4937)	3820 (3687-3952)
Post run	533 (481-585)	572 (528-616)	5391 (5138-5645)	4217 (4084-4349)
Post march	558 (508-608)	513 (470-556)	5233 (4988-5477)	4615 (4488-4743)
P value				
Pre run vs. Post run	0.002	0.008	0.001	0.0004
Pre run vs. Post march	0.0002	0.0001	0.009	0.0001
Post run vs. Post march	0.766	0.14	0.633	0.0003

Table 2. Mean tibial axial strains and strain rates increase significantly after vigorous exercise.

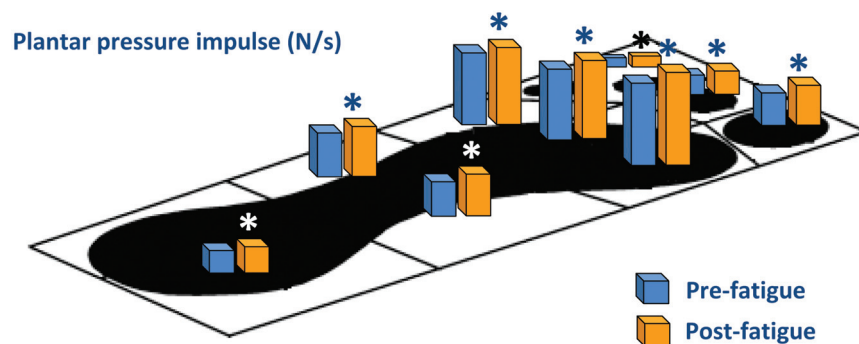


Figure 11. Foot pressures increase significantly at different locations on the sole of the foot following fatiguing exercise. (Adapted from Ref 69).

ical for the initiation of skeletal microdamage, increase by 10-20% following muscular fatigue⁶⁷. In a separate study⁷⁰ a period of fatiguing exercise in humans was associated with a significant increase in strain rate on the tibia in those younger than 35 years. It is known that muscle is less capable of dissipating energy following fatigue because the initiation of contraction does not begin as quickly and because the transfer of mechanical energy from concentric to eccentric contraction may be smaller (Figure 12)^{71,72}. Consequently, the muscles are unable to absorb and dissipate as much energy at heelstrike in a fatigued condition as they could when rested⁷³. Moreover, there is an acceleration of the lower limb joints during the swing phase of gait following muscular fatigue, which increases tibial accelerations by as much as 50%^{73,74} and causes greater impact forces at heelstrike. All of these features result in a 25% increase in ground reaction force, a fact likely to increase both strain and strain rate on bones of the lower limb.

Thus, the action of muscle is critical to preventing bone

fracture, at two different levels. The first is through its control over limb acceleration and deceleration, and the consequences that has on ground reaction force and the dissipation of that force at heelstrike. Secondly, however, muscles also control the formation and growth of cracks by contracting in synergistic patterns that regulate high levels of strain and high strain rates. These concerted actions may be as fundamental to bone's integrity as the mechanisms by which bone itself regulates its own damage formation and repair.

Conclusion

Our musculoskeletal system is a finely tuned integrated multi-organ system that functions to allow movement. But from an evolutionary and selective standpoint, its more important role is to prevent bone fracture which, in less civilized settings, can mean certain death (a very strong selective pressure indeed!). If bones were very stiff and didn't deform or bend at

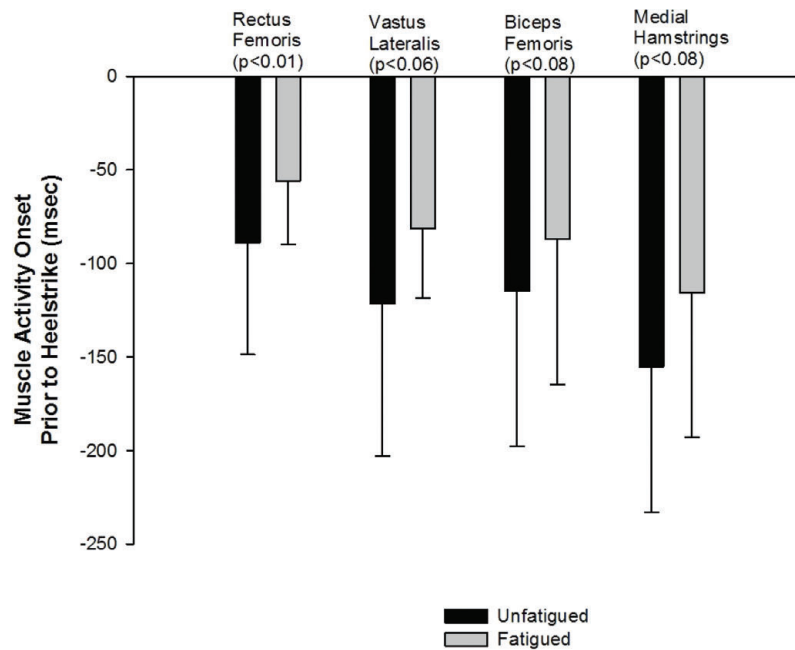


Figure 12. Time to initiate muscle activity in four muscle groups prior to and following fatigue. Times are in milliseconds (msec) prior to heel strike. This graph shows that there is a significant or nearly significant delay in the time to initiate muscle activity following muscular fatigue. This impairs the muscle's ability to slow the limb and damp energy prior to heel strike, increasing the potential for damaging loads on the lower limb. (Data from Ref 73).

all when muscles pulled on them, they would likely break very easily. At the same time, large and impulsive muscular forces impart energy to the bone that is manifest in high stresses and rapidly applied strains that can be damaging, and could cause bone failure through muscular contraction alone. So why don't bones break? The answer to this conundrum lies in the ability of the musculoskeletal system to dissipate energy at a variety of levels: muscles dissipate the energy that is imparted to bone; microdamage dissipates energy caused by stresses generated in part by forces applied to bone; and microstructural heterogeneity dissipates energy by slowing down and eventually "trapping" cracks within its structure. It's all about energy. Our application of high strain rates through the normal impulsive loading of our hindlimbs that is a requirement of bipedalism elicits adaptive responses over time within bone and to muscular response that effectively minimize damage, and prevent or delay fracture from fatigue-related processes.

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