JOURNAL OF BONE AND MINERAL RESEARCH
Volume 12, Number 1, 1997
Blackwell Science, Inc.

Perspective

Bone Microdamage and Skeletal Fragility in Osteoporotic and Stress Fractures

DAVID B. BURR,[1] MARK R. FORWOOD,[2] DAVID P. FYHRIE,[3] R. BRUCE MARTIN,[4] MITCHELL B. SCHAFFLER,[3] and CHARLES H. TURNER[5]

ABSTRACT

The accumulation of bone microdamage has been proposed as one factor that contributes to increased skeletal fragility with age and that may increase the risk for fracture in older women. This paper reviews the current status and understanding of microdamage physiology and its importance to skeletal fragility. Several questions are addressed: Does microdamage exist in vivo in bone? If it does, does it impair bone quality? Does microdamage accumulate with age, and is the accumulation of damage with age sufficient to cause a fracture? The nature of the damage repair mechanism is reviewed, and it is proposed that osteoporotic fracture may be a consequence of a positive feedback between damage accumulation and the increased remodeling space associated with repair. (J Bone Miner Res 1997;12:6–15)

INTRODUCTION

Osteoporosis often is defined by a bone fracture *subsequent to* the loss of bone mass.[1,2] The World Health Organization defines osteoporosis as bone mass 2.5 standard deviations (SD) below the mean for bone mineral density or bone mineral content in young adults.[3] However, low bone mass is not the only factor contributing to increased fracture incidence in the aging population, and the fractures that occur are not solely the *consequence of* low bone mass. Hui et al.[4] show that for a given bone mass, fracture risk increases with age. For instance, for a bone density of 0.70–0.79 g/cm, the risk of fracture in a group of 75-year-old women is about 70/1000 person-years, but only 10/1000 in 45-year-old women (Fig. 1). Each standard deviation decrease in bone mass (1 SD = 0.1 g/cm) increases the fracture risk by about 10 per 1000 person-years at age 75. This supports the concept that there is a component of bone fragility that is independent of bone mass.

No one knows entirely what factors besides reduced bone mass will predispose an individual to sustain a nontraumatic fracture, but several factors may act in combination to increase fracture risk. These factors can be divided into loading, structural, and material properties components. Loading factors include the incidence and mechanics of falls, which occur more frequently in the elderly.[5–11] Obviously, the more times an individual falls, particularly if that individual has a significantly lower bone mass than normal, the greater the risk of fracture.

Structural factors include changes in trabecular architecture and connectivity associated with reduced bone mass. As bone is lost, trabecular connectivity is decreased. Al-

[1]Departments of Anatomy and Orthopedic Surgery, Biomechanics and Biomaterials Research Center, Indiana University School of Medicine, Indianapolis, Indiana, U.S.A.
[2]Department of Anatomical Sciences, University of Queensland, Brisbane, Queensland, Australia.
[3]Bone and Joint Center, Henry Ford Hospital, Detroit, Michigan, U.S.A.
[4]Department of Orthopedic Surgery, University of California, Davis, California, U.S.A.
[5]Department of Orthopedic Surgery, Biomechanics and Biomaterials Research Center, Indiana University School of Medicine, Indianapolis, Indiana, U.S.A.

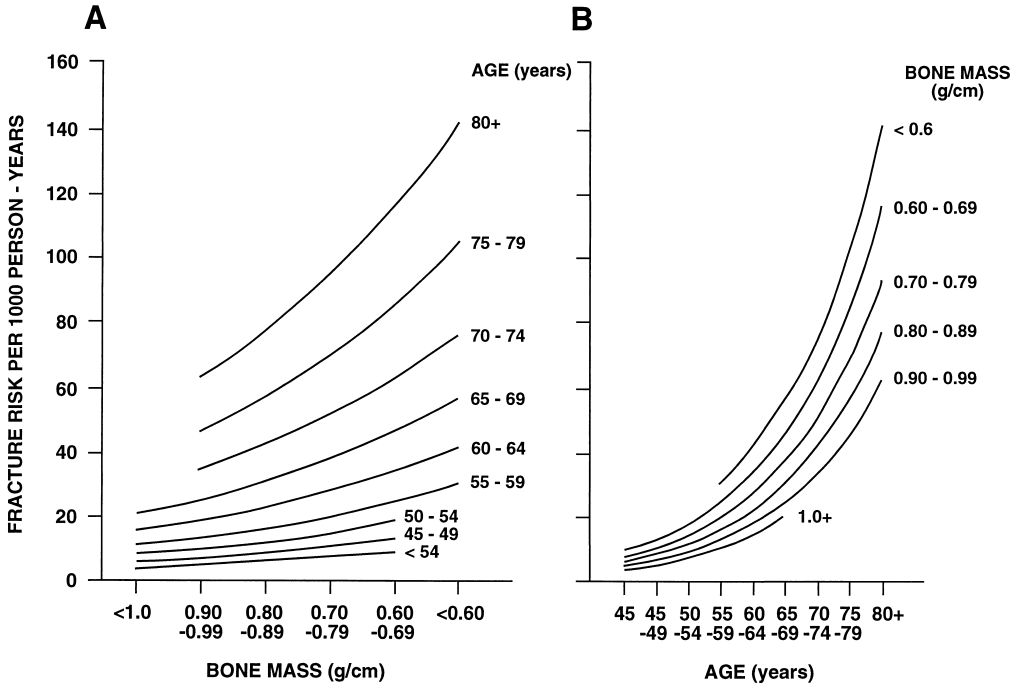

FIG. 1. For the same bone mass, the risk of fracture in older people is greater than that for younger ones, indicating that there are components to fracture risk that are independent of bone mass alone. Each increase of 0.1 g/cm equals one standard deviation. (Reproduced from *The Journal of Clinical Investigation*, 1988, **81:**1804–1809 by copyright permission of The American Society for Clinical Investigation.)

though connectivity is not independent of bone mass in nonpathological bone,[12,13] it is clearly important.[14]

Increased bone fragility with age could also be caused by a change in material properties of the tissue. This can be caused by the ways that bone matrix is deposited or mineralized or the accumulation of unrepaired microdamage that results from repeated small loads applied daily to the bone.[15,16] A large volume of work has been published in the last 5–10 years to determine the role, if any, played by microdamage in bone, but its role is still unclear. Understanding the degree to which microcracking occurs in vivo and the conditions under which microdamage accumulates in bone tissue are fundamental to the understanding of atraumatic osteoporotic fractures. This paper reviews some of that work and outlines the arguments for and against bone microdamage being a component of bone fragility independent of bone mass.

DOES MICRODAMAGE EXIST IN VIVO IN BONE?

Bone microdamage is generally defined as matrix failure detectable by light microscopy. By analogy to other materials, however, we know that damage must begin at the molecular level and have manifestations through all levels of the hierarchical structure of bone.

It is likely that damage initiates at the level of the collagen fiber or below. This is similar to the sequence of events found in fatigue of toughened composite and other nonbiological materials,[17,18] in which structural changes characterized by the formation of cracks and voids occur at the atomic or molecular levels.[19] In bone, this would correspond to collagen fiber-matrix debonding, disruption of the mineral-collagen aggregate, and collagen fiber failure. These small cracks and voids would accumulate until sufficient numbers exist to create very fine cracks observable only under high magnification ($>\times1000$) and eventually coalesce into dye-penetrable microcracks observable at low magnification ($<\times250$). (Alternatively, the cracks may change the stress state to produce more and larger cracks.) In the final stages of the process, dye-penetrable microcracks become cracks visible to the naked eye, and these finally become large, dynamically propagating macrocracks which quickly cause specimen failure.

To consider microdamage a significant component of bone's fragility, it first has to be real, not artifactual. Although engineers and material scientists familiar with damage in metals and composite materials generally accepted the idea that cyclic loads could create damage in bone, just as they do in other structural materials,[20] biologists were slower to accept the idea. There is still controversy about the reality of microdamage in bone.

In 1960, Frost[15] proposed a technique to distinguish the source of microdamage based on bulk staining of bone before the preparation of thin sections. This technique allows separation of artifactual damage from physiologic cracking because only cracks present in the bone before sectioning are stained. Thirty years later, Burr and Stafford[21] reported an experiment that clearly showed that

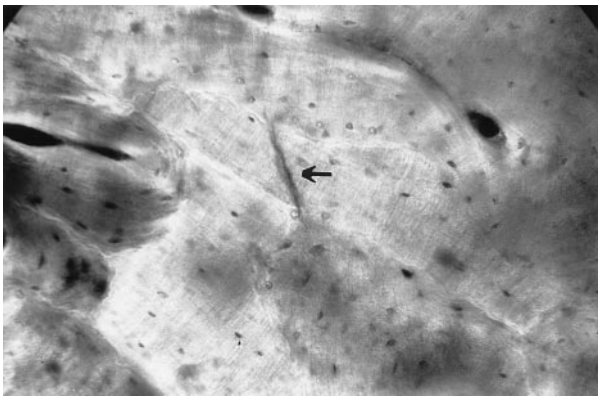

FIG. 2. Microcrack (arrow) in a rib section from a 60-year-old man. Stained en bloc with basic fuchsin. Original magnification ×62.5.

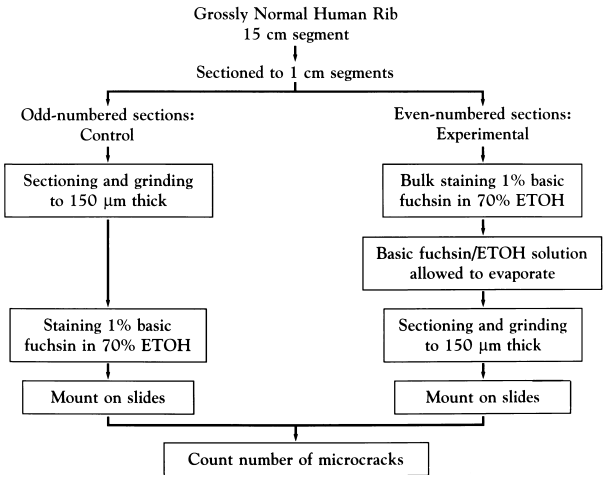

FIG. 3. Schematic outlining the experimental protocol to test the validity of the en bloc staining method. Control sections were cut before staining; experimental sections were stained en bloc before cutting. Only microcracks present in the bone at the time of death will be stained in the experimental sections, but both artifactual and nonartifactual cracks will be stained in the control sections.

Frost's en bloc staining technique is capable of separating artifactual cracking in bone from that caused by mechanical loading. They examined microcracks (Fig. 2) in 1-cm-long segments of human rib that were bulk stained either before preparation of a thin section (experimental) or stained after grinding to a thickness of 150 μm (control) (Fig. 3). Both experimental and control specimens had about the same number of total (stained and unstained) cracks (approximately 27 cracks/cm^2). The bulk staining technique therefore did not cause additional artifactual cracking through dehydration. Only about half of the cracks in the experimental sections were stained through the thickness of the section, whereas all of the cracks in the control specimens were stained, as would be expected if both existing and additional artifactual cracks were created by histological preparation (Table 1). Because the experimental sections were stained prior to histological preparation, stained cracks could not have been produced by sectioning and grinding. Chi-square analysis showed a significant difference ($p < 0.05$) in the number of stained versus unstained cracks, demonstrating that microdamage produced before processing (i.e., in vivo) can be separated from that caused by preparation of the sections.

Table 1. Microcrack Numerical Density*

Cracks	*Experimental*	*Control*
Stained cracks	14.25†	26.64
Stained + unstained cracks	28.50	27.40

*Per cm^2.
†$p < 0.05$.

Schaffler et al.[22] used a variation of this technique to allow visualization of bone microdamage at the ultrastructural level. Staining human ribs en bloc with lead-uranyl acetate, they found a good correspondence at the light microscopic level with damage levels reported previously by Frost[15] and Burr and Stafford.[21]

These techniques demonstrate the presence of microscopic cracks produced during life. Comparison of damage estimates from separate experiments[16,23] show that the techniques are reproducible. The failing of the techniques is that they undoubtedly underestimate the total number of cracks produced in vivo because, while all stained cracks must be present prior to preparation, all pre-existing cracks may not be stained. Nevertheless, these studies positively demonstrate the presence of microdamage produced in vivo, and provide a valid way to test hypotheses about the role that microdamage creation or its repair play in skeletal pathology. The techniques have now been used and verified by several independent groups,[24–28] proving that microdamage produced in vivo exists in bone.

DOES MICRODAMAGE AFFECT BONE QUALITY?

It has never been demonstrated unequivocally that the accumulation of microdamage in bone subsequent to cyclic loading leads to failure (defined by ASTM standards as a 30% loss of stiffness), although several studies imply that damage accumulation will impair mechanical properties.[24,29] The definitive experiments to prove that microcracks compromise bone quality have not been done. On the one hand, we know that cyclic loading of bone will degrade the elastic modulus of the tissue,[30–32] but measurements of crack density or length were not made in these experiments. On the other hand, we know that microcracks will accumulate in bone tissue subsequent to cyclic loading,[16,23,33] but measurements of modulus degradation were not made in these experiments.

An association between loss of stiffness and microdamage accumulation was suggested at about the same time by two groups working independently.[24,29] Forwood and

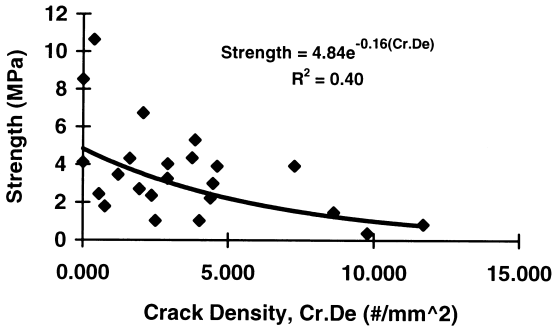

FIG. 4. The relationship between vertebral cancellous bone strength and the density of pre-existing (in vivo) microcracks (strength [MPa] = $4.84e^{-0.16\text{Cr.Dn}}$ [#/mm^2]; r^2 = 0.40). The negative exponential relationship between strength and crack density is consistent with the hypothesis that microcracks strongly affect vertebral cancellous bone strength.

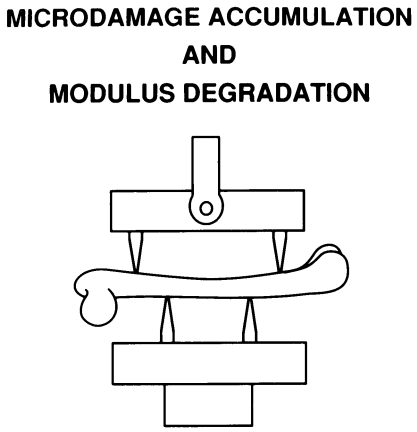

FIG. 5. Configuration for four-point bending tests of canine femora.

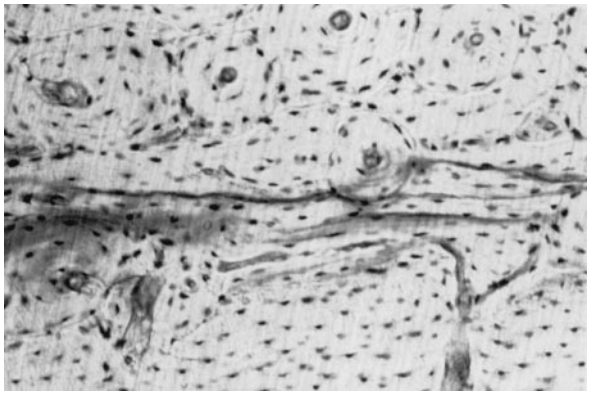

FIG. 6. Extensive microdamage was observed when there was >15% stiffness loss following cyclic four-point bending tests of canine femora. Stained en bloc with basic fuchsin. Original magnification ×60.

Parker found that the proportion of microdamage in rat tibiae increased significantly with an increase in angular deformation during cyclic torsional loading, and this in turn was associated with decreased torsional stiffness. In this experiment, microdamage was measured as the percent of the total number of sections in which damage was found, following Frost,[15] but the amount of damage within each section (e.g., Cr.Dn) was not quantified. This work implies a relationship between microdamage and loss of mechanical stiffness, but does not allow for a rigorous statistical test of these variables.

Schaffler et al.[29] found both a loss of stiffness and increased microcrack densities in cortical bone specimens cyclically loaded uniaxially in tension. They also demonstrated a strain rate dependency indicating that loading at high strain rates characteristic of more strenuous activities is more damaging to compact bone than loading at lower rates.

Apparent strength in compression, bone volume fraction (BV/TV), and in vivo (pre-existing) microcrack density (Cr.Dn) (DP Fyhrie et al., unpublished data) were measured for 23 cylindrical autopsy specimens of human vertebral cancellous bone, each from a different individual. Cr.Dn is a statistically significant predictor of strength for simple linear regression (strength = 4.99–0.40Cr.Dn, r^2 = 0.26, $p < 0.0005$), and a better predictor when nonlinear analysis is used (strength = $4.84e^{-0.16\text{Cr.Dn}}$, r^2 = 0.40; Fig. 4). Although bone volume fraction is the single best linear predictor of bone strength (strength = −1.44 + 29.90 BV/TV, r^2 = 0.76, $p < 0.0005$), Cr.Dn adds a marginally significant additional component to the prediction (strength = −0.52–0.14Cr.Dn + 27.3BV/TV, r^2 = 0.80, p[Cr.Dn] = 0.056; p[BV/TV] < 0.0005). These data suggest that the more pre-existing cracks in a vertebra, the lower its strength in compression. Cracks *do* predict strength, but not as well as BV/TV.

A recent experiment correlated elastic modulus and crack accumulation over time in an attempt to develop an experimental relation between microcrack numerical density (Cr.Dn) with bone stiffness.[34] We hypothesized a positive linear relationship between increased microdamage and the loss of stiffness. Femurs were removed bilaterally from 13 mature hounds (n = 25) and tested in four-point cyclic bending using an MTS 810 servohydraulic system (Fig. 5). All experiments were carried out under load control at an initial strain of 3000 microstrain at a frequency of 2 Hz using a haversine wave function while the bones were under constant saline irrigation at 37°C. Femurs were loaded until they had lost 5–43% of their elastic modulus (1.59×10^4 to 1.41×10^6 cycles). The mid-diaphysis was removed from the bone and stained en bloc.[35]

The density of dye-penetrable microcracks did not change over the first 15% of stiffness loss. However, with a loss of stiffness greater than 15%, a larger percentage of specimens showed focal areas of substantial microdamage (Fig. 6). These areas were so extensive they could not be quantified using conventional techniques for measuring Cr.Dn and Cr.Le.

These results indicate that the relationship between microdamage accumulation at the microscopic level and stiff-

ness loss is nonlinear and threshold-driven. Microdamage visible at the light microscopic level does not accumulate gradually with stiffness loss. Rather, damage is submicroscopic until a threshold is reached, at 15–25% stiffness loss when localized areas of diffuse damage become more frequent. Microdamage is not evenly distributed throughout the cortex, but is localized in pockets.

Bone can lose significant stiffness before microdamage becomes apparent. The implication of this is that the mechanical properties of bone can be significantly compromised even before substantial cracking is observed at the microscopic level. Therefore, the absence of visible microdamage is *not* an indication of the mechanical integrity of bone, underscoring the importance of performing mechanical tests on bone even if substantial damage is not visible at the light microscopic level. However, the accumulation of significant amounts of microdamage light microscopically visible at relatively low magnification probably is a valid indicator of compromised mechanical properties.

One reason for this may be that damage initiates at tissue levels beyond the resolution of the light microscope.[29] A diffuse area of lead-uranyl acetate staining can be observed emanating from the tip and edges of a microcrack when viewed using backscattered electron microscopy.[22] This suggests an area of ultrastructural damage, called the damage process zone, outside the crack itself in which the permeability to the heavy metal is changed. Similar observations were made following ex vivo crack propagation studies.[22]

The idea that damage initiates at the ultrastructural level prior to the appearance of microscopic cracks is supported by a recent study using standardized test specimens fatigued in unaxial loading until 15–30% stiffness loss had been achieved.[36] Although the incidence of dye-penetrable microcracks did not increase until very late in the fatigue process (at 30% modulus degradation), examination of basic fuchsin-stained sections of compact bone revealed that the area fraction occupied by focal patches of diffusely stained bone matrix increased in direct proportion to the degree of modulus degradation. The exact morphological nature of this diffuse staining remains unclear but appears to be a consequence of increased permeability of the fully mineralized bone matrix to stain. In some cases, small cracks can be seen in the center of the diffusely stained region.[35] These observations are consistent with the presence of a damage process zone, indicating damage at the ultrastructural level.

DOES MICRODAMAGE ACCUMULATE WITH AGE?

Osteoporotic fracture, whether in men or women, is associated with aging. Even if microdamage accumulation is associated with a reduction in mechanical properties of the bone tissue, it is unlikely to be a significant factor underlying osteoporotic fracture if it does not accumulate in the bone with age. Moreover, because the incidence of fracture in elderly women is higher than that in men, microdamage should accumulate more rapidly in women than men to be implicated as a biologically significant factor increasing skeletal fragility.

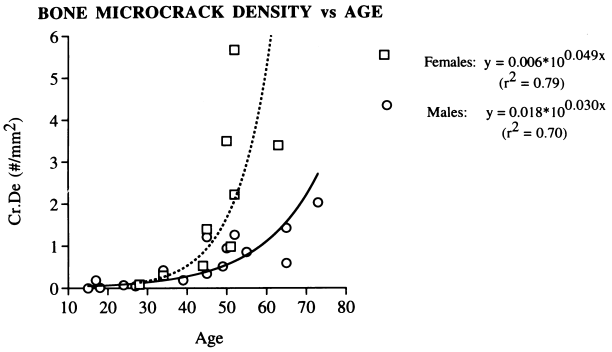

FIG. 7. There is an exponential increase in microdamage accumulation in the femoral cortex in both men and women after the age of 40 years. Damage accumulation occurs about twice as rapidly in women as in women.

Increased microdamage burden in older subjects has been reported in several bones and locations. Frost[15] first reported that microdamage appeared to accumulate in the human rib especially after the age of 40. Microcracks in the femoral head double in women between the ages of 46 and 78,[37] while overt microfractures, defined by the presence of trabecular callus, increase less dramatically ($r^2 = 0.14$; $p < 0.01$).[38] Exponential increases in damage occur in the femoral mid-diaphysis of both men and women, particularly after the age of 40 years (Fig. 7).[39] The increase in damage with age in women ($y = 0.006 \times 10^{0.049x}$; $r^2 = 0.79$) is more than 50% faster than that found in men ($y = 0.018 \times 10^{0.030x}$; $r^2 = 0.70$). These data are remarkably consistent with the rise in trabecular microfractures that occurs around the age of 40.[40] Similar age-associated increases in microdamage have been found in the femoral neck cortex in a small sample of men and women ranging in age from 18–75 years ($r^2 = 0.70$).[41]

Similarly, naturally occurring microcracks are common in human vertebral cancellous bone tissue.[26,42] Although Wenzel et al.[26] did not find a statistically significant association between crack density and chronological age in a small sample, the addition of disc pathology may predispose the vertebral cancellous bone to the accumulation of damage. In an ex vivo test, Hasegawa et al.[43] cyclically loaded functional spinal units (L1–L6) in which disc lesions had been created by nucleotomy. Following 100,000 load cycles at loads ranging between 100 and 300% of body weight, they observed significantly greater microcrack density in lesioned spines than in intact controls. Moreover, the damage was found predominantly in the region of the nucleotomized disk. For the spine, any pathology that reduces the stress modulating effect of the invertebral disks may predispose the vertebral cancellous bone to greater damage accumulation.

Generally, these data confirm that microcracks accumulate with age, probably in an exponential fashion, and are likely to increase more quickly in women than men after the age of 40. Accumulation in the spine may also be acceler-

ated by the presence of disc pathology. However, the role damage accumulation plays to increase fracture risk remains obscure.

IS THE ACCUMULATION OF DAMAGE SUFFICIENT TO CAUSE FRACTURE?

Microdamage occurs in bone, causes a degradation in elastic modulus of the tissue, and appears to accumulate with age. However, microdamage accumulation alone may not be able to account for the additional component of fragility associated with osteoporosis. If microdamage contributes to fracture risk, this may occur because (1) more damage is created in an osteopenic skeleton, (2) there is a failure to repair microdamage, or (3) there is a positive feedback between damage and the remodeling space associated with repair.

Is osteoporotic fracture a consequence of microdamage accumulation?

Mori et al. (unpublished data) examined microcrack accumulation in the nonosteoarthrotic femoral heads of young women (mean = 46 ± 6 years, n = 9) and older women either with (mean = 77 ± 11 years, n = 7) or without (mean = 78 ± 3.5 years, n = 12) femoral neck fractures. There was significantly less trabecular bone in the older women either with (16.8 ± 7.6%) or without (16.6 ± 4.4%) hip fracture than in younger women (24.7 ± 6.3%), and a two-fold increase in Cr.Dn in older women without a fracture than in younger women (0.39 ± 0.28/mm^2 vs. 0.16 ± 0.10/mm^2). However, by Fisher's LSD tests, there was not significantly more microdamage in older women who had sustained a fracture (0.37 ± 0.26/mm^2) than in those older women who had not.

Is osteoporotic fracture a consequence of the failure to repair damage?

If increased production of microdamage in nonosteoporotic bone cannot account for its fragility, is it possible that damage accumulates over time as a consequence of impairment in the repair mechanism? Bisphosphonates are compounds that, depending on dosage, can reduce bone turnover to nearly zero,[44,46] allowing virtually no repair of microdamage that may accumulate as the result of normal activity. Studies using bisphosphonates allow a test of the hypothesis that failure to repair microcracks can result in the accumulation of damage and eventual fracture.

Flora et al.[44,47] placed dogs on a daily intake of etidronate (EHDP, 0–10 mg/kg/day subcutaneously [sc]) or clodronate (0–25 mg/kg/day sc) for up to 12 months. Dogs receiving 0.5 mg/kg/day of EHDP fractured ribs spontaneously within 12 months. At higher doses, rib, spinous process, or pelvic fractures occurred between 9 and 12 months. The increased fracture rates in clodronate-treated animals were inversely proportional to the length of mineralizing surface (Fig. 8), suggesting that increased fragility was associated with reduced remodeling.[48]

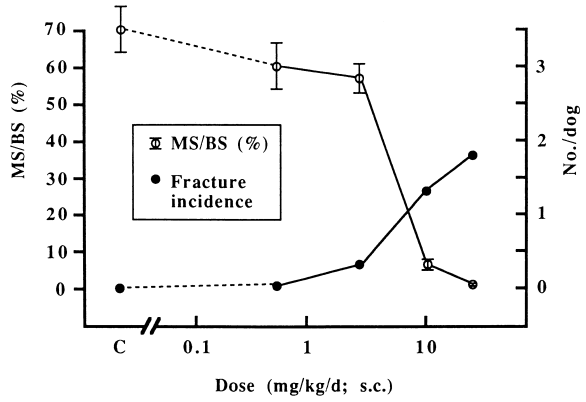

FIG. 8. There was an inverse relationship between mineralizing surface in cortical bone (MS/BS) and fracture incidence in dogs treated continuously with clodronate for 11 months. As dosage increases, remodeling is suppressed more severely, and fracture incidence rises. MS/BS was calculated at 5 months; fracture incidence represents fractures occurring by 11 months. (Reproduced from Burr DB 1993 Remodeling and the repair of fatigue microdamage. Calcif Tissue Int **53**(Suppl 1)**:**S75–S80 by copyright permission from Springer-Verlag, New York, NY, U.S.A.).

In this study, a treatment period of 9–12 months was required before the dogs presented with radiographic evidence of fracture. No changes in bone density or cortical area were correlated with treatment, so osteopenia was not implicated as a cause of fracture. However, both EHDP and clodronate can inhibit mineralization at higher doses, so it is unclear whether fractures were caused by accumulated microdamage or other factors.

In a later study, the effects on microdamage accumulation of another bisphosphonate, risedronate, were evaluated in dogs treated for 2 years.[45] Cortical and trabecular bone from the femoral neck of six female dogs from each of four dosage groups were analyzed using the en bloc staining technique. Activation frequency (Ac.f), the frequency with which new remodeling units are started, was significantly reduced by 80–90% in both cortical and trabecular bone. Microdamage accumulation did not occur, and no spontaneous fractures were reported in these dogs.

The hypothesis that impaired microcrack repair allows microdamage to accumulate can also be tested by examining the natural history of diseases that lower bone turnover. Cushing's disease (hyperadrenocorticism) lowers the bone formation rate,[49,50] reduces the activation frequency,[49,51–53] and is also associated with spontaneous fractures of the ribs and spine.[54] Norrdin et al.[55] induced hyperadrenocorticism in dogs by giving adult dogs either prednisone (1 mg/kg/day) or prednisone + calcium (1 g/day) orally for 6 months. At the end of the treatment period, they found that compressive strength of trabecular bone from the thoracic and lumbar vertebrae had decreased significantly, even though the bone volume was normal. Microdamage was increased in the treated dogs compared with placebo controls, but differences in microscopic damage among the groups were not statistically significant.

Another study irradiated dogs up to 68 Gy for 4 weeks to reduce bone turnover.[56] Radiation damages bone cell precursors and is associated with increased fracture rates in humans and dogs.[57,58] The irradiated dogs presented with spontaneous rib fractures, suggesting that the radiation increased fragility. Histological examination of the block of rib distal to the fracture revealed that Cr.Dn doubled and Cr.S.Dn tripled following treatment (DB Burr and RW Norrdin, unpublished data). Sample sizes were too small (2 controls, 4 irradiated) to evaluate adequately statistical significance. However, the results are similar to findings in humans with high doses of X-rays.[59]

These data provide conflicting views of the role that microdamage may play in the increased fragility of bone found in osteoporosis. They suggest that in some cases impaired repair of damage may contribute to increased fragility by compounding the weakening effects of reduced bone mass and connectivity. However, more work in this area is needed.

Is osteoporotic fracture a consequence of positive feedback between damage accumulation and damage repair?

Because neither damage accumulation nor inhibited repair alone has been shown conclusively to cause bone fragility, it may be possible that remodeling in response to cracks accelerates failure. It has been hypothesized that fatigue failure depends on an imbalance between damage production and damage repair.[51,60–62] Strain-related bone remodeling contributes significantly to the amounts, rates, and locations of bone formation and resorption. Recent evidence shows that microdamage may be one factor controlling the local stimulus for remodeling.

Repetitive loading in vivo of the forelimbs of eight skeletally mature dogs in three-point bending at 1500 microstrain for 10,000 cycles produced significant bone microdamage.[16] The dogs were sacrificed 1, 2, or 4 days after a single loading event, allowing time for the initiation of new remodeling events but insufficient time to completely eliminate damage. One goal of this experiment was to determine whether or not the observed frequency of association between resorption cavities and microcracks was significantly higher than expected from a purely random remodeling process. If higher, the argument that microcracks are one stimulus for remodeling would be strengthened. In this experiment, microcracks were associated with resorption spaces six times more often than expected by chance alone.[16,63] (The original analysis suggested that the relationship between resorption and cracks may have been even stronger, but the theoretical maximum number of osteons that can contain both a crack and a resorption space was underestimated so that the ratio of observed to expected cracked and resorbing osteons was overestimated.)

This experiment was compelling but did not demonstrate that microdamage caused resorption spaces rather than vice versa. It is possible that cracks had localized near existing resorption spaces, where stress concentrations exist, and did not actually initiate the new remodeling unit. This experiment was therefore not definitive.

A second experiment was performed to determine whether osteonal remodeling follows the accumulation of microcracks or whether microcracks simply accumulate at sites of pre-existing resorption.[23] Using the same dog model, repetitive three-point bending loads of 2500 microstrain were applied to the left forelimbs of 13 foxhounds for 10,000 cycles. The right forelimb was loaded in the same way 8 days later, and the dogs were sacrificed immediately after the second loading event. A second group of seven foxhounds was used as a nonloaded external surgical control (to control for the application of strain gauges to the left radius) and a nonloaded normal control (right radius). If osteonal remodeling follows the accumulation of microcracks, then both limbs should have an equal number of cracks. However, the limb that was loaded 8 days prior to sacrifice should have more resorption spaces and more cracks in association with resorption spaces. If cracks localize at sites of pre-existing resorption, then the numbers of cracks associated with resorption spaces should be the same in each limb.

This experiment showed equal numbers of microcracks in each radius, but significantly ($p < 0.025$) more resorption spaces and more association ($p < 0.005$) of cracks with resorption spaces in the limb loaded first than in the limb loaded immediately prior to sacrifice. A theoretical analysis showed that the number of cracks associated with resorption spaces in the limb loaded first was four times greater than expected by random remodeling processes alone. In other words, damage was being targeted for repair. This experiment provided direct proof that the significant increase in remodeling sites occurred subsequent to microdamage initiation. The results are inconsistent with the hypothesis that cracks localize at pre-existing resorption sites, and support a direct cause and effect association between damage and repair.

Remodeling begins with resorption, and each time bone repairs an increment of microdamage, it creates additional porosity, reducing bone mass. Stiffness and strength of the bone would be decreased exponentially.[64–66] Because there is less bone to sustain loading, strains on the remaining bone would increase, generating even more microdamage (Fig. 9). The additional microdamage would stimulate another sequence of local remodeling, bone loss, increased strain, generation of more microdamage, and so forth. Over time, this would lead to a gradual loss of bone, and a gradual increase in microdamage accumulation, until a fracture threshold is reached (Fig. 9).

Martin[67] simulated this positive feedback between increased porosity due to remodeling and the accumulation of fatigue damage in osteonal bone. He assumed that the activation frequency for new remodeling sites was proportional to the accumulated damage, i.e., a positive feedback between remodeling and damage initiation as suggested by Burr et al.[16] The model showed that, as strain magnitude or the number of load cycles per day increase, a critical threshold is reached at which porosity, strain, and damage begin to grow at a rapidly accelerating rate, and without limit. Although periosteal woven bone may strengthen the structure, it does not remove the instability. The model shows that porosity introduced by attempts to repair fatigue

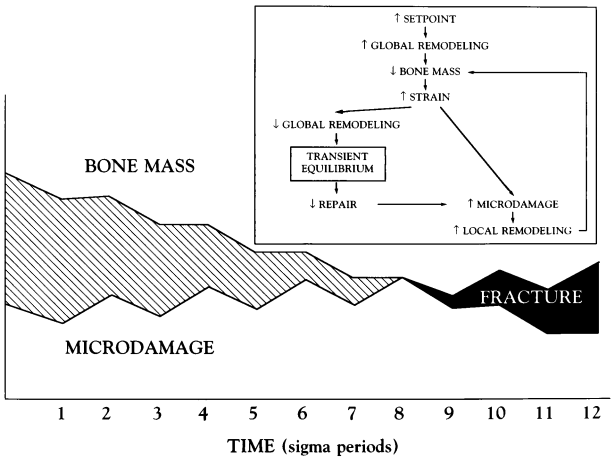

FIG. 9. Schematic demonstrating how a positive feedback between damage production and the increase in remodeling space associated with attempts to repair the damage may lead to fracture. With each remodeling cycle, bone mass is decreased a little bit more. This in turn increases mechanical strain on the remaining bone, causing a greater accumulation of damage that must be repaired. Over many remodeling periods, the gradual decline in bone mass and equally gradual accumulation of microdamage will lead to a greater fragility of the bone.

damage can contribute via a positive feedback mechanism to an unstable situation and eventual fracture. Varying the values of the parameters in the model showed that the system is inherently unstable if overloading of the bone persists. However, to be clinically predictive, the model must be supported by additional data relating fatigue damage, remodeling, and strain. Presently, the model is only a useful conceptual tool.

CONCLUSION

There is no definite answer yet to the question about whether microdamage in bone contributes to the variance of bone strength and fracture risk. Clearly, microdamage exists in vivo in bone and contributes to the degradation of bone's elastic properties during cyclic loading. Microdamage accumulates with age, consistent with the increased fracture risk in older women. Most data suggest, but not conclusively, that neither microdamage accumulation alone, nor the failure to repair damage, can fully explain the loss of strength or increased fracture risk of bone, but most tests have been performed on animal bone, or human bone with normal mass and mineral content. The relationship of damage accumulation and fatigue life in osteoporotic bone to that in normal bone following a period of long-term cyclic loading is unknown. It is possible that the relatively small increment of damage that may accumulate in bone only becomes significant when added to the bone-weakening effects of reduced bone mass. Both osteoporotic fractures and stress fractures may involve feedback between microdamage and the osteopenia caused by increased remodeling. In osteoporotic fracture, the increased remodeling is due to menopause; in stress fracture it may be caused by the attempt to repair damage or solely by the increased loading. In either case, remodeling produces at least a transient loss of bone, providing the positive feedback necessary for damage accumulation, loss of strength, and eventual catastrophic failure.

ACKNOWLEDGMENTS

The work reviewed in this paper was supported by several grants to the authors: NIH grants AR39708 (D.B.B.); AR41644 and AR42844 (R.B.M.); NIH AR41210 (M.B.S.); NIH AR40776 (D.P.F.); and an NH&MRC NH Fairley Fellowship (M.R.F.).

REFERENCES

1. Consensus Development Conference: Prophylaxis and Treatment of Osteoporosis 1991 Am J Med **90:**107–110.
2. Melton LJ, Wahner HW 1989 Defining osteoporosis. Calcif Tissue Int **45:**263–264.
3. World Health Organization 1994 Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a W.H.O. Study Group. World Health Organization, Geneva, Switzerland.
4. Hui S, Slemenda CW, Johnston CC 1988 Age and bone mass as predictors of fracture in a prospective study. J Clin Invest **81:**1804–1809.
5. Duthie EH Jr 1989 Falls. Med Clin N Am **73:**1321–1336.
6. Hayes WC, Piazza SJ, Zysset PK 1991 Biomechanics of fracture risk prediction of the hip and spine by quantitative computed tomography. Radiol Clin N Am **29:**1–18.
7. Nevitt MC, Cummings SR 1992 Falls and fractures in older women. Falls, Balance and Gait Disorders in the Elderly. Elsevier, Paris, France.
8. Nevitt MC, Cummings SR 1993 Type of fall and risk of hip and wrist fractures: The study of osteoporotic fractures. J Am Geriatr Soc **41:**1226–1234.
9. Hayes WC, Myers ER, Morris JN, Gerhart TN, Yett HS, Lipsitz LA 1993 Impact near the hip dominates fractures risk in elderly nursing home residents who fall. Calcif Tissue Int **52:**192–198.
10. Greenspan SL, Myers ER, Maitland LA, Resnick NM, Hayes WC 1994 Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. JAMA **271:**128–133.
11. Lord SR, Sambrook PN, Gilbert C, Kelly PJ, Nguyen T, Webster IW, Eisman JA 1994 Postural stability, falls and fractures in the elderly: Results from the Dubbo Osteoporosis Epidemiology Study. Med J Aust **160:**684–691.
12. Goldstein SA, Goulet R, McCubbrey D 1993 Measurement and significance of three-dimensional architecture to the mechanical integrity of trabecular bone. Calcif Tissue Int **53**(Suppl 1)**:**S127–S133.
13. Compston JE 1994 Connectivity of cancellous bone: Assessment and mechanical implications. Bone **15:**463–466.
14. Jensen KS, Mosekilde L, Mosekilde L 1990 A model of vertebral trabecular bone architecture and its mechanical properties. Bone **11:**417–423.
15. Frost HM 1960 Presence of microscopic cracks in vivo in bone. Bull Henry Ford Hosp **8:**25–35.
16. Burr DB, Martin RB, Schaffler MB, Radin EL 1985 Bone

remodeling in response to in vivo fatigue microdamage. J Biomech **18:**189–200.
17. Fuchs HO, Stephens RI 1980 Metal Fatigue in Engineering. John Wiley & Sons, New York, NY, U.S.A., p. 33.
18. Anderson TL 1991 Fracture Mechanics: Fundamentals and Applications. CRC Press, Boca Raton, FL, U.S.A., pp. 379–412.
19. Suresh S 1991 Fatigue of Materials. Cambridge University Press, New York, NY, U.S.A., pp. 457–498.
20. Carter DR, Hayes WC 1977 Compact bone fatigue damage: A microscopic examination. Clin Orthop Rel Res **127:**265–274.
21. Burr DB, Stafford T 1990 Validity of the bulk-staining technique to separate artifactual from in vivo bone microdamage. Clin Orthop Rel Res **260:**305–308.
22. Schaffler MB, Pitchford WC, Choi K, Riddle JM 1994 Examination of compact bone microdamage using back-scattered electron microscopy. Bone **15:**483–488.
23. Mori S, Burr DB 1993 Increased intracortical remodeling following fatigue damage. Bone **14:**103–109.
24. Forwood MR, Parker AW 1989 Microdamage in response to repetitive torsional loading in the rat tibia. Calcif Tissue Int **45:**47–53.
25. Norrdin RW, Robinson HT, Powers BE, Histand MB 1993 Evaluation of microdamage in canine trabecular bone. Trans Orthop Res Soc **18:**198.
26. Wenzel TE, Schaffler MB, Fyhrie DP 1994 In vivo trabecular microcracks in human vertebral bone. Trans Orthop Res Soc **19:**57.
27. Fyhrie DP, Schaffler MB 1994 Failure mechanisms in human vertebral cancellous bone. Bone **15:**105–109.
28. Villanueva AR, Longo JA III, Weiner G 1994 Staining and histomorphometry of microcracks in the human femoral head. Biotech Histochem **69:**81–88.
29. Schaffler MB, Radin EL, Burr DB 1989 Mechanical and morphological effects of strain rate on fatigue of compact bone. Bone **10:**207–214.
30. Carter DR, Hayes WC 1977 Compact bone fatigue damage–I. Residual strength and stiffness. J Biomech **10:**325–337.
31. Schaffler MB, Radin EL, Burr DB 1990 Long-term fatigue behavior of compact bone at low strain magnitude and rate. Bone **11:**321–326.
32. Pattin CA, Caler WE, Carter DR 1996 Cyclic mechanical property degradation during fatigue loading of cortical bone. J Biomech **29:**69–79.
33. Zioupos P, Currey JD 1994 The extent of microcracking and the morphology of microcracks in damaged bone. J Mater Sci **29:**978–986.
34. Burr DB, Turner CH, Naick P, Forwood MR, Pidaparti RMV 1995 Does microdamage accumulation affect the mechanical properties of bone? Trans Orthop Res Soc **20:**127.
35. Burr DB, Hooser M 1995 Alterations to the en bloc basic fuchsin staining protocol for the demonstration of microdamage produced in vivo. Bone **17:**431–433.
36. Schaffler MB, Boyce TM, Fyhrie DP 1996 Tissue and matrix failure modes in human compact bone during tensile fatigue. Trans Orthop Res Soc **21:**57.
37. Mori S, Isa S, Kanaya F, Sato S, Ibaraki K, Burr DB, Harruff R 1992 Microcrack distribution in human femoral heads. Proceedings of the 6th International Congress on Bone Morphometry, Lexington, KY, U.S.A., p. A24.
38. Wong SYP, Kariks J, Evans RA, Dunstan CR, Hills E 1985 The effect of age on bone composition and viability in the femoral head. J Bone Joint Surg **67A:**274–283.
39. Schaffler MB, Choi K, and Milgrom C 1995 Aging and bone matrix microdamage accumulation in human compact bone. Bone **17:**521–525.
40. Fazzalari NL, Vernon-Roberts B, Darracott J 1987 Osteoarthritis of the hip. Possible protective and causative roles of trabecular microfractures in the head of the femur. Clin Orthop Rel Res **216:**224–233.
41. Schaffler MB, Boyce TM, Lundin-Cannon KD, Milgrom C, Fyhrie DP 1995 Age-related architectural changes and microdamage accumulation in the human femoral neck cortex. Trans Orthop Res Soc **20:**549.
42. Wenzel TE, Schaffler MB, Fyhrie DP 1996 In vivo trabecular microcracks in human vertebral bone. Bone **19:**89–95.
43. Hasegawa K, Turner CH, Chen, J, Burr, DB 1995 Effect of disc lesion on microdamage accumulation in lumbar vertebrae under cyclic compression loading. Clin Orthop Rel Res **311:**190–198.
44. Flora L., Hassing GS, Parfitt AM, Villanueva AR 1980 Comparative skeletal effects of two diphosphonates in dogs. Metab Bone Dis Relat Res **2**(Suppl)**:**389–407.
45. Forwood MR, Burr DB, Eastman DF, Smith PN, Schwardt JD 1995 Risedronate treatment does not increase microdamage in the canine femoral neck. Bone **16:**643–650.
46. Balena R, Toolan BC, Shea M, Markatos A, Myers ER, Lee SC, Opas EE, Seedor JG, Klein H, Frankenfield D, Quartuccio H, Fioravanti C, Clair J, Brown E, Hayes WC, Rodan, GA 1993 The effects of 2-year treatment with the aminobisphosphonate alendronate on bone metabolism, bone histomorphometry, and bone strength in ovariectomized nonhuman primates. J Clin Invest **92:**2577–2586.
47. Flora L, Hassing GS, Cloyd GG, Bevan JA, Parfitt AM, Villanueva AR 1981 The long term skeletal effects of EHDP in dogs. Metab Bone Dis Relat Res **3:**289–300.
48. Burr DB 1993 Remodelling and the repair of fatigue microdamage. Calcif Tissue Int **53**(Suppl 1)**:**S75–S80.
49. Jett S, Wu, K, Duncan H, Frost HM 1970 Adrenalcorticosteroid and salicylate actions on human and canine haversian bone formation and resorption. Clin Orthop Rel Res **68:**301–315.
50. Meunier PJ, Dempster, DW, Edouard C, Chapuy MC, Arlot M, Charhon S 1984 Bone histomorphometry in corticosteroid-induced osteoporosis and Cushing's syndrome. Adv Exp Med Biol **171:**191–200.
51. Frost HM 1985 Bone microdamage: Factors that impair its repair. In: Uhthoff HK (ed.) Current Concepts of Bone Fragility. Springer-Verlag, Berlin, Germany, pp. 123–148.
52. Hahn TJ 1989 Steroid hormones and the skeleton. In: Tam CS, Heersche JNM, Murray TM (eds.) Metabolic Bone Disease: Cellular and Tissue Mechanisms. CRC Press, Boca Raton, FL, U.S.A.
53. Hahn TJ 1990 Steroid and drug-induced osteopenia. In: Favus MJ (ed.) Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. ASBMR, Kelseyville, CA, U.S.A., pp. 158–162.
54. Adinoff AD, Hollister JR 1983 Steroid-induced fractures and bone loss in patients with asthma. New Engl J Med **309:**265–268.
55. Norrdin RW, Robinson HT, Powers BE, Histand MB 1990 Evaluation of microdamage in canine trabecular bone in hyperadrenocorticism and radiation injury. Presented at the 22nd International Workshop on Hard Tissue Biology, Sun Valley, ID, U.S.A., August 1990.
56. Powers BE, Gillette EL, Beck ER, Norrdin RW 1990 Response of adult canine bone to irradiation. Proceedings of the Annual Meeting of the Radiation Research Society.
57. LaRue SM, Wrigley RH, Powers BE 1987 A review of the effects of radiation therapy on bone. Vet Radiol **28:**17–22.
58. Maeda M, Bryant MH, Yamagata M, Li G, Earle JD, Chao EYS 1988 Effects of irradiation on cortical bone and their time-related changes. J Bone Joint Surg **70A:**392–399.

59. Kolar J, Babicky A, Vrabec R 1965 The Physical Agents and Bone. Czechoslovak Academy of Sciences, Prague, Czechoslovakia.
60. Wainwright SA, Biggs WD, Currey JD, Gosline JM 1976 Mechanical Design in Organisms. Halsted Press, New York, NY, U.S.A.
61. Frost HM 1989 Transient-steady state phenomena in microdamage physiology: A proposed algorithm for lamellar bone. Calcif Tissue Res **44:**367–381.
62. Frost HM 1991 Some ABC's of skeletal pathophysiology. 5. Microdamage physiology. Calcif Tissue Int **49:**229–231.
63. Burr DB, Martin RB 1993 Calculating the probability that microcracks initiate resorption spaces. J Biomech **26:**613–616.
64. Carter DR, Hayes WC 1977 The compressive behavior of bone as a two phase porous structure. J Bone Joint Surg **59A:**954–962.
65. Rice JC, Cowin SC, Bowman JA 1988 On the dependence of the elasticity and strength of cancellous bone on apparent density. J Biomech **21:**155–168.
66. Schaffler MB, Burr DB 1988 Stiffness of compact bone: Effects of porosity and density. J Biomech **21:**13–16.
67. Martin RB 1995 Mathematical model for repair of fatigue damage and stress fracture in osteonal bone. J Orthop Res **13:**309–316.

Address reprint requests to:
David B. Burr, Ph.D.
Department of Anatomy, MS 259
Indiana University School of Medicine
635 Barnhill Drive
Indianapolis, IN 46202 U.S.A.

Received in original form January 29, 1996; in revised form June 24, 1996; accepted July 23, 1996.