Osteoporos Int (2003) 14 (Suppl 5): S73–S80
DOI 10.1007/s00198-003-1477-1

ORIGINAL ARTICLE

Role of bone turnover in microdamage

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Published online: 29 August 2003

Introduction

Turnover of cells and matrix occurs in a wide spectrum of organs and tissues and is essential to maintenance of tissue integrity. In bone, a major function of osteonal remodeling is to maintain tissue, wherein remodeling serves to remove and replace microscopic regions of compact bone that have reached the end of their functional life. Perhaps the best characterized circumstance in which bone reaches the end of its functional life is when it sustains microdamage due to fatigue. Left undetected and unrepaired, microdamage in bone leads to compromised mechanical properties and bone fragility. Recently, with wide clinical usage of drugs which turn off bone remodeling globally, a number of authors [1, 2] have raised concerns about whether inhibition of bone remodeling will predispose to the accumulation of matrix damage, leading to increased bone fragility. Accordingly, examination of factors that influence detection and repair of microdamage is fundamental to understanding skeletal health and disease.

Fatigue and microdamage in bone

Cyclic loading of bone, as in all materials, leads to failure incrementally through a process known as fatigue. In bone, this incremental failure process corresponds to the accumulation of microstructural level cracks or microdamage. Mechanically, the accumulation of microdamage is correlated to loss of material stiffness, or modulus reduction. Studies from both our laboratory and others show that bone fatigue and microdamage can occur at strain magnitudes comparable to those measured on living bones in the physiological loading environment during vigorous activity in animals and humans. At these modest strain magnitudes, the fatigue life to failure for compact bone is quite long—on the order of millions of loading cycles [3]. In life, this corresponds to approximately 5 to 10 years of use. However, significant amounts of fatigue damage occur *during* loading, damage that weakens the tissue and must be repaired to prevent fracture [3].

Microscopic cracking, or microdamage, in bone is the microstructural consequence of bone fatigue (Fig. 1). In 1960, Harold Frost [4] reported the earliest observations of microdamage in bone. Using human rib samples obtained at autopsy, he found small cracks, with a "linear" morphology, typically on the order of 30 to 100 μm in length. Frost posited that osteonal remodeling functions to remove and replace (repair) these microcracks. Such typical linear microcracks have received much study. They have been produced experimentally by fatigue loading bone in vivo and in vitro. However, linear microcracks appear to occur late in fatigue loading history of bones, after significant modulus degradation has occurred. Thus, there are other levels of matrix failure in bone, which occur early in the fatigue process and also strongly influence its fatigue behavior. Indeed, diffuse matrix damage (sublamellar-level cracking) recently has been shown to be a major characteristic of fatigue in bone [5]. Other types of matrix damage likely exist as well, as bone is a hierarchical, unhomogeneous material with extensive interfaces that potentially allow damage to form at many levels in this composite structure.

Microdamage and bone fragility

Before discussing the potential clinical significance of matrix microdamage, it is useful to review the basic aspects of mechanics that contribute to skeletal mechanical integrity, or the deficiencies therein that give rise to bone fragility. Fragility of bone can be defined in a clinically relevant, straightforward manner as the inability of the tissue to keep pace with normal mechanical demands. Much of the effort for defining bone fragility in aging and osteoporosis has focused on

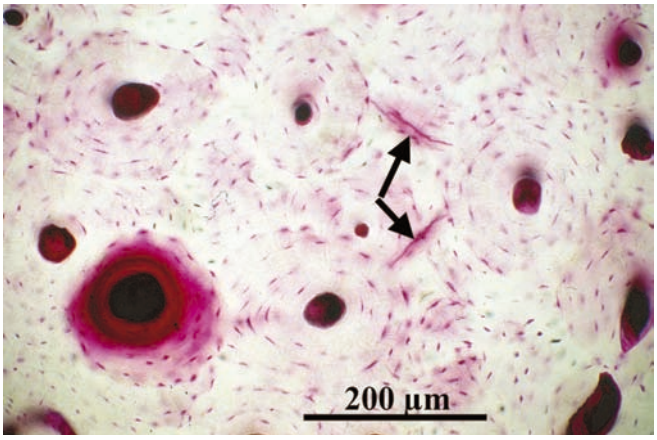

Fig. 1 Photomicrograph of a cross-section of basic fuchsin-stained, human femoral compact bone. *Arrows* show typical microcracks

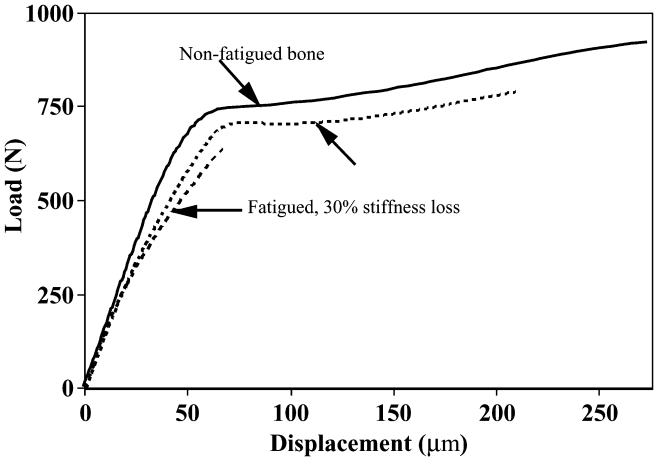

Fig. 2 Residual mechanical properties for human bone specimens at baseline and after fatigue loading. The global mechanical behavior of bone with a lower level of fatigue (15% stiffness loss) is similar to that in nondamaged bone, but with proportionate reductions of stiffness, strength and fracture resistance (work to fracture and postyield deformation). In contrast, bone specimens fatigued to higher fatigue levels showed losses of strength in proportion to stiffness loss, but degradations of work to fracture and postyield deformation were far greater than expected based on the stiffness changes in these specimens. Most striking, however, is that bone specimens fatigued to the higher level of fatigue showed effectively no postyield deformation; they fail immediately upon yield

determining whether bone is strong enough to bear normal loads, a logical extension of the fact that bone density (mass) and strength are well correlated. However, this approach presents an incomplete picture of the effectiveness with which bone resists fracture. Under mechanical loading, bone exhibits a region of elastic (recoverable) deformation, followed by a region of plastic (permanent) deformation; mechanistically, in this plastic or postyield deformation phase, the mineralized matrix cracks and collagen fibers tear, until the point of final complete fracture. Materials can be strong, stiff and tough (long plastic deformation after yield). Materials can also be strong and stiff, but very poor at resisting fracture, and fail in a brittle manner once their yield point has been reached. Examples of such material are glasses and ceramics. The key material properties that describe the fracture resistance of a material include work to fracture, postyield compliance and crack propagation parameters. Fracture resistances are independent of elastic properties or strength, and thus are not indexed at all in bone mass or density measurements. Accordingly, a global definition of bone fragility must take into account bone's fracture resistance as well as its strength determinants.

What are the consequences of different amounts of fatigue damage on the mechanical integrity of compact bone?

Studies show that the declines in fracture resistance for a given amount of fatigue-damaged bone exceed the losses of stiffness and strength, consistent with the consequences of fatigue in many synthetic composite materials as well. However, precise data defining the relationships between the amount of microdamage and degradation of specific mechanical properties do not exist.

It is well established in material sciences that microdamage content (quality and quantity) influences the residual (remaining) mechanical properties of a material. Indeed, in bone, as well as in other composite type materials, the mechanical definition of fatigue is based on stiffness loss. Stiffness loss correlates with loss of strength. However, as bone sustains fatigue and accumulates microdamage, the loss of fracture resistance can be disproportionately large. In the example shown in Fig. 2, low levels of fatigue induced ex vivo in human bone specimens result in proportionate reductions of strength and fracture resistance (work to fracture and postyield deformation); the overall mechanical behavior of bone with low levels of fatigue is similar to that in nondamaged bone. In contrast, bone specimens fatigued to higher fatigue level showed losses of strength in proportion to stiffness loss, but degradation of work to fracture and postyield deformation were far greater than expected based on the stiffness changes in these specimens. Most remarkably, however, is the striking absence of postyield deformation in bone specimens fatigued to the higher level of fatigue; they fail immediately upon yield. Thus, these data reveal that even small amounts of fatigue will compromise the functional-mechanical properties of bone, and show the potentially dramatic functional-mechanical consequences of fatigue in bone. These data also emphasize that the deleterious effects of matrix damage on the fracture resistance of bone may be more important than its effects on diminished stiffness and strength. Further studies are needed to define the threshold levels of microdamage in bone that can significantly impair fracture resistance.

Bone remodeling, microdamage repair and maintenance of tissue integrity

Frost [4, 6] first put the idea forth that remodeling targets microcracks in bone and is necessary to maintain the mechanical integrity of the skeleton. Since that time, considerable data have accrued to support this idea. Microcracks have been shown to be associated with intracortical resorption in overuse and stress fractures in human and dogs. Burr et al. [7] and Mori and Burr [8] showed experimentally that resorption spaces are associated with microcracks in canine compact bone. Bentolila et al. [9] found that when microdamage is produced in rat ulnae by fatigue loading, intracortical remodeling is stimulated in areas where microscopically visible damage occurs and where osteocyte morphology has been changed (Fig. 3). Rats loaded to the same strain magnitude, but which did not exhibit fatigue damage, did not exhibit intracortical remodeling. Since intracortical remodeling does not normally occur in rats, this is convincing evidence that fatigue is the initiating event for remodeling. Most compelling are the recent studies from Burr and coworkers [10, 11, 12]. They have found that in dogs treated with long-term bisphosphonates to suppress remodeling, there is a two- to threefold increase in bone microdamage content and a concomitant impairment of biomechanical properties. Thus, a range of studies during the last decade strongly supports Frost's microdamage-remodeling/repair hypothesis, showing both that microdamage results from normal mechanical use of the skeleton and that remodeling is necessary to prevent its accumulation.

What controls remodeling of microdamage in bone?

It is quite reasonable to presume that osteocytes, the only cells embedded in the bone matrix, would be affected by microdamage in the bone matrix and therefore play a key role in targeted bone remodeling. Osteocytes are extensively distributed throughout the bone matrix. Their canalicular processes completely infiltrate the matrix of bone. They have well-developed cytoskeletons; they are attached to their surrounding matrix through adhesion molecules and to their neighboring cells through gap junctions. Thus, they are strategically well situated to detect or to be affected by disruption of their surrounding matrix.

Several lines of indirect evidence support the hypothesis that osteocytes are needed to detect or respond to matrix-level injury. In several instances where osteocytes are absent from bone, fatigue failures will occur; well-known examples include radiation-induced death of osteocytes and allograft bone. Similar mechanisms also may play a role in bone fragility of avascular necrosis. Absence of osteocytes is associated with hip fracture. Parfitt [1] hypothesized that osteocyte death leads to fatigue microdamage accumulation in bone resulting from decreased ability in bone to detect matrix injury. These data are consistent with the ideas that osteocytes are needed to effect an appropriate biological response to matrix damage and are necessary to maintain the mechanical integrity of the skeleton. The involvement of osteocytes in bone fatigue and remodeling recently was directly shown by Verborgt et al. [13], who found that osteocytes undergo apoptosis (regulated cell death) in bone areas immediately surrounding bone microdamage. These areas of osteocyte apoptosis colocalize exactly with the areas of bone that subsequently undergo later resorption by osteoclasts.

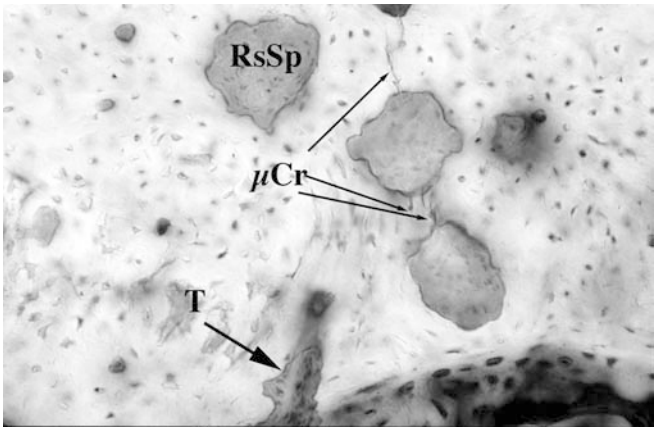

Fig. 3 Intracortical resorption spaces (*RsSp*) in association with fatigue microcracks (μCr) induced in vivo by cyclic loading of rat ulnae

Remodeling and microdamage: what happens when the normal homeostasis is altered?

There are considerable data to support the idea that an appropriate amount of bone remodeling is needed to effectively repair wear and tear microdamage in bone; that is, in healthy bone there is a "homeostatic balance" between wear and tear and intrinsic repair. The next question asks what happens to microdamage accumulation in bone when remodeling is not operating properly.

Can too much remodeling be a problem?

Schaffler, Radin and Burr [14] proposed that elevated intracortical remodeling can accelerate microdamage accumulation. They argued that increases in intracortical porosity, resulting from activation of intracortical remodeling, would have a dramatic effect on decreasing the stiffness of cortical bone. Continued loading of this focal region of osteoporotic bone will result in increased local stresses and strains, leading to rapid bone microdamage accumulation. Martin used a mathematical model to explore this concept in detail in the context of stress fracture development. Using a feedback model to

examine the effects of increasing porosity on the mechanical properties of compact bone, Martin [15] showed that there is a critical porosity, load interaction, microdamage accumulation threshold. Once the threshold for matrix damage is reached, through increased bone porosity and/or through increased local loading, bone becomes mechanically unstable and fails rapidly and catastrophically. Both the Schaffler hypothesis and Martin's model are consistent with a range of recent histopathological observations in early stress fracture. Accordingly, these data suggest that too much remodeling can accelerate bone microdamage accumulation.

Can too little remodeling be a problem?

The converse question, one that is more frequently discussed in context to aging-bone fragility and also to pharmacological treatment of metabolic bone disease, is whether too little bone remodeling leads to the accumulation of bone microdamage. The simple answer to this question is yes—too little remodeling leads to the build-up of bone microdamage. However, the reasons for this remain unresolved.

Analyses of the data pertaining to age-related accumulation of microdamage in bone are instructive in this regard. In 1995, we reported the first observations of increasing in vivo microdamage in aging bone [16]. Subsequent studies in a number of laboratories have shown that microdamage accumulation with aging occurs throughout the appendicular skeleton, in long bone diaphyses, in the cortex of the femoral neck and in the trabeculae of aging femoral heads. It has been argued that ineffective remodeling-repair of normal microdamage (in the aging skeleton) can explain the increasing microdamage content in bone. Alternatively, it has been posited that microdamage accumulation might be a "symptom" of matrix changes in the aging bone matrix (or in the drug-treated skeleton), which predisposes the bone to sustain microdamage.

Recent studies of bone from remodeling-suppressed animals reveal significant increases in bone microdamage in dogs treated with long-term bisphosphonates for 1 to 2 years, supporting the concept that ineffective remodeling-repair can lead to microdamage accumulation [10, 11, 12]. Moreover, the amount of microdamage accumulation was nominally proportional to the amount of remodeling suppression. Dogs treated with alendronate showed both greater remodeling suppression and greater microdamage increases than dogs treated with risedronate.

While at first glance these data suggest that inhibition of bone remodeling using bisphosphonates suppresses the repair of bone microdamage leading to its accumulation, there is a potential confounding factor to this interpretation. With remodeling suppression using bisphosphonates and the resulting low bone turnover, bone matrix mineral content increases at the microscopic level [17]. Such local changes in bone mineral composition are thought to cause bone to become more brittle and damageable [18], although a direct mechanical test of this hypothesis has not been done. Frost [6], Parfitt [1] and our group [16] observed that inadequacies of local remodeling processes in the aging skeleton can lead to a similar end point: bone becomes locally more fragile, and there are likely to be sites at which microdamage occurs. Whether, in fact, local mineral content, in the absence of adequate bone turnover, becomes sufficiently high so as to embrittle bone remains unknown.

Conclusion

In conclusion, existing data indicate that (1) microdamage accumulation impairs the mechanical integrity of bone, more so in terms of its ability to withstand fracture than in terms of reducing its strength, and (2) suppression of bone turnover causes microdamage to build up in vivo. Accordingly, we can ask the question of whether, from the standpoint of microdamage and mechanical integrity of bone, there are theoretical limits to the suppression of bone turnover? Logic dictates that there should be such a limit. However, in our current state of knowledge, we cannot yet define that limit. There remain several key deficiencies in our level of understanding of the processes involved. First, one key piece of needed information is a more complete understanding of how much matrix damage can occur before the mechanical integrity of bone is impaired at a clinically relevant level. Currently, we do not know how much microdamage in bone is too much. Implicit in this issue is the need to differentiate changes in mechanical integrity that are statistically significant in the experimental context from those that are significant and meaningful in the clinical context. Second is the need for more in vivo studies to measure microdamage accumulation in the living skeleton. This latter issue is problematic. Microdamage accumulation occurs in load-bearing bones, and it is not possible at this time to directly monitor matrix damage in patients. The same argument also holds for direct assessment of bone turnover in weight-bearing bones; we cannot do it with our current technologies and are therefore limited to extrapolations about long bone turnover based on direct studies of nonloaded bone biopsy sites, such as the iliac crest. Studies of bone samples from selected hip fractures may provide important insights into whether bisphosphonate-treated patients develop a high bone microdamage burden. Until the advent of new technologies to assess microdamage and bone remodeling in vivo in major load-bearing bones (for example, technologies that are based on functional-biological imaging of bone), the most critical data for microdamage accumulation and bone remodeling will need to come from additional long-term studies in large animals, which use various levels and modalities of remodeling suppression to modulate activation frequency. Such data

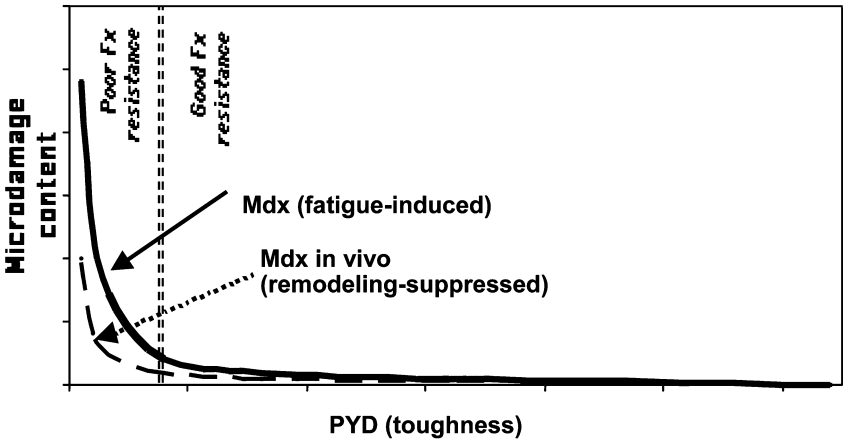

Fig. 4 Theoretical curve showing the expected relationship between microdamage content in bone and residual fracture resistance, as measured from postyield displacement, in fatigue-loaded (*Mdx*, fatigue-induced) bone. The inflection point of this curve is defined as the threshold level distinguishing mechanically good bone [good fracture (*Fx*) resistance] from mechanically impaired bone (poor Fx resistance). This curve provides a basis for estimating the mechanical consequence of in vivo microdamage accumulation, as has been observed with suppression of remodeling (*Mdx*, in vivo: remodeling-suppressed bone). *PYD* postyield depression

for microdamage accumulation in vivo, combined with complementary biomechanical data defining the threshold levels for in vivo bone microdamage accumulation that result in significantly impaired fracture resistance, will allow the development of predictive curves (Fig. 4) to estimate whether suppression of bone turnover will lead to bone fragility.

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Discussion

Dr. Currey: I'd like to ask what is the nature of the cracks that you're looking at? I think you show linear cracks in cross-sections. This would indicate to me what you're actually looking at are compressive cracks that go down in a long, straight line. Have you looked at sections at right angles, so the haversian systems are going up and down?

Dr. Burr: In these data, we've not looked at other orientations. In other specimens, we have looked longitudinally. In this case, the cracks basically run down the length of the haversian systems. In fact, they're fairly long, on the order of 200 μm to 300 μm on average.

Dr. Schaffler: Are they lines or planes?

Dr. Burr: They're planes.

Dr. Currey: Do you think they're compression or tension?

Dr. Schaffler: Neither. I think they're internal, interstitial shear in the material. If you apply a uniform load, it's not going to cause the same microstructural strains since the bone has material of different microscopic

stiffnesses. I think that for the linear cracks it gets to a point where either internal friction or whatever causes the damage to initiate gets there, and then material breaks like that internally. We've done a lot of studies on diffuse damage (shown in the confocal photomicrograph). The size order of those cracks is about the same as the crystal aggregates that were described by Green when he deorganified the surface of bone and looked at it with EM. Weiner and Price ground up pieces of bone and ran them through various molecular sieves and found similar results. They got small crystals on the normal crystal-like size, but also had a clustering of aggregates in the range of about 250 nm to 400 nm. That's the size order for those cracks. I think the cracks are a failure between the collagen and the mineral at that size order. But we really don't know what holds the bone together at that level—it's not quite ultrastructure and it's not quite microstructure.

Dr. Ferrari: You pointed out the extraordinary heterogeneity of number of cracks at a given age in a given bone. Which matters most then with regard to fragility, the initiation of cracks or the lack of repair? Maybe we should incorporate some very simple epidemiological data on patients, like the amount of exercise that the people from whom we got those bones were doing at a certain time, or markers of bone turnover to have a rough estimate of remodeling activity. Do we have any study where this heterogeneity has been observed, where we would have markers and epidemiological data to try to pin down what underlies this heterogeneity?

Dr. Burr: I don't know of any, but activity data will be terribly variable and will not tell you much. And I don't have much confidence in marker data. If you were able to look at damage using a bone sample from a biopsy for example, then my suggestion would be to look at turnover rate by labeling ahead of time and also measuring activation frequency. We have actually looked at the relationship between damage accumulation and fracture in femoral heads. We did an autopsy study a few years ago, in which we took femoral heads from women who had fractured the opposite side, i.e., femoral heads from women with a fracture, age-matched women who had not fractured and femoral heads from a younger sample of women. We found that both older groups had significantly more microdamage than the younger group. Within the older groups, the ones that had fractured and the ones that hadn't fractured didn't have any difference in microdamage accumulation. So the relationship between damage accumulation and fracture couldn't be explained based solely on whether there was a fracture present.

Dr. Bilezikian: At the doses of bisphosphonates that we currently use, is there any evidence in human studies for increase in microdamage?

Dr. Burr: We haven't done that study yet, but I would say this: Our study has been criticized because we use such high levels of bisphosphonates, but the amount of suppression that we got is no different than the amount of suppression that women have with lower doses of bisphosphonates. You get 90 to 95% suppression in the iliac crest. What we've shown is that the amount of damage you accumulate is very closely related simply to the amount of suppression that you get. So those studies haven't been done, but I wouldn't expect it to be very different.

Dr. Bouxsein: Do you think it's a function of just reducing turnover or does the actual mechanism of how that's done have an effect? For example, if bisphosphonates and SERMs had equal amount of turnover suppression, would you expect the same effect on microdamage accumulation or different effects because one is directly affecting osteoclast survival and the other presumably not?

Dr. Schaffler: My feeling is that it's strictly related to the amount of remodeling suppression, but we have just started looking at estrogen and SERMs, and there may be some differences.

Dr. Heaney: In the first of the Henry Ford symposium volumes, in a chapter by Lent Johnson, he notes with respect to stress fractures that the fracture occurs after the remodeling starts. So that's a confirmation of your observation.

Dr. Burr: Since that time, there has been at least one other instance in which biopsies have been done on stress fractures by Satosi Mori in Japan, and those pictures show that the remodeling is impressive.

Dr. Schaffler: Reviewing the postmortem data from race horses (if they get a stress fracture it's the end for a thoroughbred horse), Stover and coworkers found elevated remodeling at the contralateral limb at the same site even if they hadn't had the stress fracture occur.

Dr. Heaney: Dr. Burr, you have published a paper with high-dose etidronate in which you didn't find an increase in crack density, but you showed more recent data today. Can you integrate those two studies for me?

Dr. Burr: We used two different dosages of etidronate, 0.5 mg/kg /d and 5 mg/kg/d. The reason we chose these dosages was that we wanted to use a low dosage that wouldn't impair mineralization, and we wanted to use a higher dosage that Larry Flora and others, had found caused spontaneous fractures. We wanted to duplicate that and determine whether the incidence of spontaneous fractures was a microdamage-related or a mineralization phenomenon, and it turns out to be a mineralization phenomenon. In fact, you actually have less microdamage with the high dose of etidronate in those animals, presumably because the bone is more compliant, but they still fracture.

Dr. Heaney: They should be more ductile?

Dr. Burr: Yes, but they don't have much mineral in them.

Dr. Heaney: You can bend them, but that's not the same thing as fracture.

Dr. Burr: Well, high rates of fracture also occur in patients with osteomalacia.

Dr. Heaney: I'm not sure of that.

Dr. Burr: There are some data to suggest that that's true.

Dr. Jepsen: Regarding Dr. Burr's study, why did you attribute the decrease in toughness to microdamage?

Dr. Burr: We know that the reduced toughness is associated with microdamage, but we don't know that microdamage is the cause of the reduced toughness. It could also be the increase in the mean degree of mineralization of the tissue that makes it a bit more brittle. We have now shown that there is also an increased mean degree of mineralization in these dogs.

Dr. Jepsen: One of the things that kept coming up is that microdamage causes fragility, and it's really difficult to say that, because materials that show increased microdamage are also inherently brittle.

Dr. Burr: We did not make that statement in those papers. We never said that it was because of the microdamage. There's an association there, but we absolutely don't know that there's a cause-and-effect relationship.

Dr. Shmookler Reis: If you see an increase in microfracture density with age, it can mean any of three things. One is that the incidence of microfractures is higher in older people. The second is that the remodeling, which would cure them, is impaired. It doesn't have to be less efficient, just slower (it occurs with less frequency and so you can get a higher steady-state level of microfracture). And the third would be that there are some microfractures that are inaccessible to repair. Do we have any idea which of these occurs and is responsible for the difference with age? Is it possible the risk of fracture is considerably greater for either very long or conveniently clustered microfractures and that's what we really should be looking at for this?

Dr. Schaffler: All those factors you identified as potentially leading to damage accumulation with age are possibilities, and they probably all occur to some extent. We don't know which is predominant. We don't know if it's a detection error vis-à-vis the osteocytes or a failure to initiate remodeling. Certainly, there's evidence that older bone may have different damageability and that the damage could have the same mineralization issue that Karl and David were just discussing. In that argument, cracks could be perceived of as a symptom of a sick matrix. Then there's the issue of the loading conditions, which are different in the aging skeleton. It's not necessarily magnitude of load that causes damage, it's repetition of frequencies, and it's also loading rates. If you step off a curb unexpectedly, it's more damaging to your skeleton than if you step off the curb gradually. So it could be the frequency of those accidents that changes with age as well, but we don't have any insight. Eric Radin used to call that "micro-klutziness." It's a term that didn't catch on, but I think it has utility, and that "micro-klutziness" may increase with age as well. As far as the issue of crack number versus crack length interaction, David and I have basically summarized the data on what's known about how cracks interact in a quantitative way to weaken bone. Add to that a bit of data from Peter Ziopis and that summarizes 20 years of intensive research and data collection.

Dr. Jepsen: Typically, people count the number of cracks, so I think that's really going to be critical to some of these issues. I don't think these cracks would be weighted equally; a small crack versus a large crack, cracks in different orientations, and depending on where the crack is actually located within the matrix—are all of these going to have huge effects on the integrity of that tissue? That's not known. How do we count cracks? We just count the numbers. Currently, we don't really weight them.

Dr. Burr: They're weighted by length in some cases. Crack surface density is a combination of number and length, but we don't know how to weigh by orientation. There are lots of subtleties about the measurement techniques that we don't know how to handle.

Dr. Jepsen: The other thing is, a small crack in a brittle matrix is not going to behave the same way as a small crack in a ductile matrix.

Dr. Schaffler: Yes, one could even make the argument that it may be the volume of damage material that you should count (it isn't even the number of cracks) to understand function. It may be that we've approached this with standard histomorphometry tools the same as we've done for trabecular architecture and we've defined a counting paradigm that may not be the appropriate one for defining function.

Dr. Boivin: We have obtained essentially the same results as those reported by David Dempster in collaboration with Klaus Klaushofer. There is no difference between both states, and there is no significant difference with age in the control group. We compared our placebo group with our control group and after the placebo treatment, the degree of mineralization is the same as the control group. We have an increase in mineralization after bisphosphonate treatment if we compare with the placebo and if we compare with the control.

Dr. Turner: We know that reducing turnover has a lot of good effects and this has been reiterated a number of times. If you reduce bone turnover, you can disproportionately affect fracture rates in the spine at the very least. We may know from David's studies in dogs that if you reduce turnover down to 95% or down to 5% of what it was, that you may accumulate microdamage, increase mineralization or maybe create a brittleness issue. So there may be a safe level for reduction of turnover that will maybe repair all the microdamage and still afford antifracture efficacy. I was curious where Dr. Burr got the 50% number for "safe" suppression of remodeling?

Dr. Burr: The reason for the 50% number is because (at least in cortical bone), we found suppressions of 53 to 68%, and we still saw a threefold increase in damage. So I know it's not above 50%. That's why we suspect it's below 50%, but we don't know exactly what it is.

Dr. Bouxsein: Regarding the hypothesis that one of the things we would like to optimize is whole bone toughness, it seems that it is a parameter we're not even sure how to measure. Everything else we're talking about in toughness is on the material level, but what

happens when someone's fracture is a structural failure. Even with your very small decrease in ultimate strength, if it's enough, it is a catastrophic event. How do we bring our material level measurements of microdamage toughness to how they're going to impact whole bone strength or whole bone toughness? I think this is probably what's going to determine fracture risk in the end.

Dr. Jepsen: Just go back to some of the work that was done in the 1950s and 1960s and start breaking some bones and correlating material properties with those whole bone structures and it'll tell you.

Dr. Burr: I don't think that'll tell you. I think what you need to do is fatigue tests. If you're really talking about the toughness issues, then it's got to be a cyclic test.

Dr. Bouxsein: With the proximal femur, when you fall down you don't fracture in a fatigue mode, you fracture in the impact-loading mode.

Dr. Burr: Yes, but you may be predisposed to fracture from the impact. Thus, another interesting thing would be to look at the effect of damage accumulation on impact strength. It is important to try to define the percentage decrease in bone turnover that will be optimal in terms of preventing fracture. We guess that this may be between 30 and 50% suppression of activation frequency.

Dr. Ferrari: Whatever that number is, if it is as low as that, that is probably what we achieve in all the placebo arms of the current trials with just calcium, vitamin D. Yet we know the antifracture efficacy of this treatment is far from optimal. So there is a kind of a paradox coming out here.

Dr. Burr: I agree, we just don't know what the optimal amount of suppression might be for antifracture efficacy.