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13. ABSTRACT (Maximum 200 Words)

Having a narrow tibia relative to body mass has been shown to be a major predictor of stress fracture risk and fragility. The reason for this phenomenon is not understood. Based on studies of genetically distinct inbred mouse strains, we found a reciprocal relationship between bone mass and bone quality, such that slender bones are associated with more damageable bone tissue. *We postulate that a similar reciprocal relationship between bone mass and bone material properties exists in the human skeleton. The intriguing possibility that slender bones, like those we have demonstrated in animal models, may be composed of more damageable material than larger bones has not been considered.* To test this hypothesis, we propose to determine whether whole bone geometry is a predictor of tissue fragility in the tibia from young male donors. Tissue damageability will be assessed from biomechanical testing of compact bone samples and correlated with measures of bone slenderness. Specimens will be subjected to detailed analyses of bone microstructure, composition, and microdamage content. In the second set of experiments, these analyses will be repeated for female donors to test for gender differences in tissue fragility. Further, we will test whether fragility in cortical bone is a predictor of fragility in cancellous bone. Finally, we will conduct ultrasound measurements to identify an ultrasound parameter that is sensitive to the presence of damage and could be used for early diagnosis of stress fractures.

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Introduction

Having a narrow tibia relative to body mass has been shown to be a major predictor of stress fracture risk and fragility (Giladi et al, 1987; Milgrom et al, 1989; Beck et al, 1996). The reason for this phenomenon is not understood. Based on studies of genetically distinct inbred mouse strains, we found a reciprocal relationship between bone mass and bone quality, such that slender bones are associated with more damageable bone tissue (Jepsen et al, 2001). *We postulate that a similar reciprocal relationship between bone mass and bone material properties exists in the human skeleton. The intriguing possibility that slender bones, like those we have demonstrated in animal models, may be composed of more damageable material than larger bones has not been considered.* To test this hypothesis, we propose to determine whether whole bone geometry is a predictor of tissue fragility in the tibiae from young male donors. Tissue damageability will be assessed from biomechanical testing of compact bone samples and correlated with measures of bone slenderness. Specimens will be subjected to detailed analyses of bone microstructure, composition, and microdamage content. In the second set of experiments, these analyses will be repeated for female donors to test for gender differences in tissue fragility. Further, we will test whether fragility in cortical bone is a predictor of fragility in cancellous bone. Finally, we will conduct ultrasound measurements to identify an ultrasound parameter that is sensitive to the presence of damage and could be used for early, noninvasive diagnosis of stress fractures.

In addition to the primary focus of the grant outlined above, the parent grant was awarded a supplemental grant that was used to 1) purchase a microComputed Tomography system and 2) support a graduate student to investigate the effects of mechanical loading on bone morphology and tissue fragility in inbred mouse strains. This latter project has been completed in its entirety. In the past year, a supplemental subcontract was initiated with Louis Gerstenfeld, PhD of Boston University to examine variation among three inbred mouse strains in the expression of specific genes during growth and development of the femur.

Body

In the first year of this grant, we found that bone slenderness (a measure of bone size relative to body weight and bone length) varied significantly among males and females and that the tibiae of females were significantly more slender than the tibiae of males. Slenderness was initially defined as the tibial width normalized for length. In the second year of the grant, we switched to the formula proposed by Selker and Carter (1989), such that slenderness was defined as:

Slenderness = 1 / (Polar Moment of Inertia/medio-lateral width) / (Body weight * Tibial Length)

The inverse ratio was used so that a bone with a large slenderness value is one that is narrow for the height and weight of the individual. As shown in Figure 1, women have a significantly greater tibial slenderness value compared to males. This suggests that the female tibia is smaller (possibly underdesigned) relative to the body size of the individual compared to the male tibia. This suggests that the magnitude of loads engendered by the female skeleton may be greater than those engendered by the male skeleton during rigorous physical activity. These results may have important implications for understanding why female military recruits show 2-4 fold increase in stress fracture risk compared to males (Kowal, 1980; Friedl et al, 1992; Winfield et al, 1997).

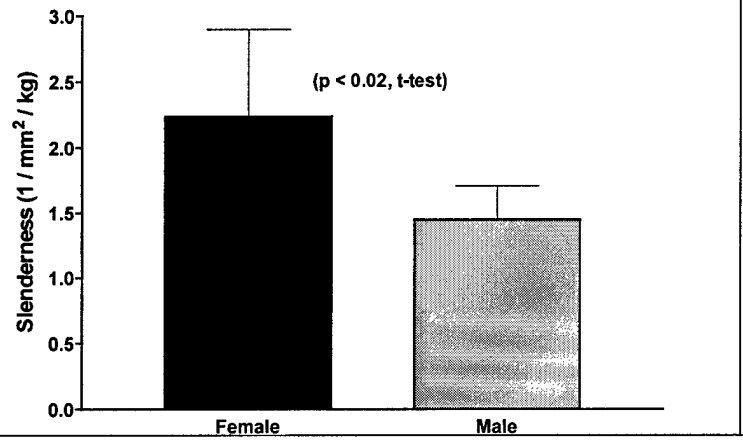


Figure 1. Tibial slenderness is greater for females (ages 22-46) compared to males (ages 17-46).

As noted in the critique of the first grant review, we were behind in the proposed mechanical testing experiments. In the second year of this grant, we developed a high through-put method of generating precisely machined bone samples from the diaphysis of the tibia. With this new machining method, we have nearly caught up with the proposed mechanical testing schedule. To date, we have completed the monotonic failure tests for 11 male and 6 female tibia and an additional 7 males and 3 females will be tested by this winter. All of the samples that were tested to failure in monotonic bending have been analyzed for density, ash content, and water content. The monotonic failure results were quite surprising. We expected to find large inter-individual differences in material properties that would accompany the large inter-individual variability in tibeal cross-sectional morphology. Further, because females and males showed significantly different slenderness values, we expected that the tissue-level modulus and strength of the females would be greater than that of the males to compensate for the smaller bone size. However, the monotonic and compositional data showed relatively little variation among individuals and there were no differences between males and females for any of the tissue-level material properties that were examined (for some of the properties, refer to Table 1). The average ash content of females was 61.3 $\pm$ 0.6% and for males the ash content was 60.9 $\pm$ 0.6%. The data was extremely tight and we do not expect that this will change when we complete the data set.

Table 1. Tissue-level mechanical properties of tibiae from females and males.

Gender	Modulus (GPa)	Yield Stress (MPa)	Max Stress (MPa)	Post-Yield Strain (mm/mm)	Total Energy (MPa)
Female	16.1 $\pm$ 1.21	101.5 $\pm$ 8.1	128.2 $\pm$ 6.4	0.027 $\pm$ 0.005	3.4 $\pm$ 0.6
Male	16.4 $\pm$ 1.5	102.6 $\pm$ 7.2	131.3 $\pm$ 6.5	0.027 $\pm$ 0.006	3.4 $\pm$ 1.0

To investigate the relationship between whole bone morphology and variation in the underlying material properties, we conducted linear regression analyses between slenderness and each of the underlying mechanical properties and compositional traits. We found significant correlations that appear to support our central hypothesis. We postulated that slender tibiae will show an increase in mineral content and that this would be associated with poor damageability (i.e., show increased amount of damage under similar load conditions). The linear regression analysis conducted between slenderness and ash content (Figure 2) revealed that, indeed, ash content increases with increasing slenderness for both males ($p<0.02$) and females (ns). The

overall regression for both males and females was borderline significant ($p<0.06$). It was quite surprising to see a significant positive slope given that the range in ash content was very small (<4% of the mean). This was entirely consistent with our original hypothesis.

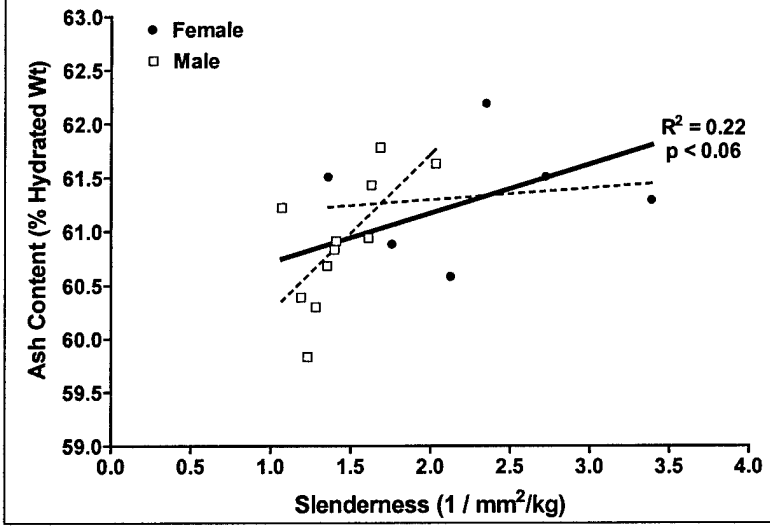


Figure 2. Ash content increases with tibial slenderness for both males and females.

There was only one tissue-level monotonic property that showed a significant correlation with tibial slenderness and that was maximum strength. As shown in Figure 3, strength decreased with slenderness ($p<0.02$, males and females). This suggests that there are material level differences among tibiae and these differences appear to correlate with the overall shape of the bone relative to body size. The decrease in strength with increased slenderness was opposite to what we would have expected given that ash content increased with slenderness and bone stiffness and strength generally increase with ash content (Currey, 1984). This was intriguing and suggested that there may be other changes in material composition or microstructure of the tibia that accompany the mineral content differences. We have begun the histological evaluation of these samples to test for differences in the degree of remodeled bone, porosity, osteon size, and osteon density.

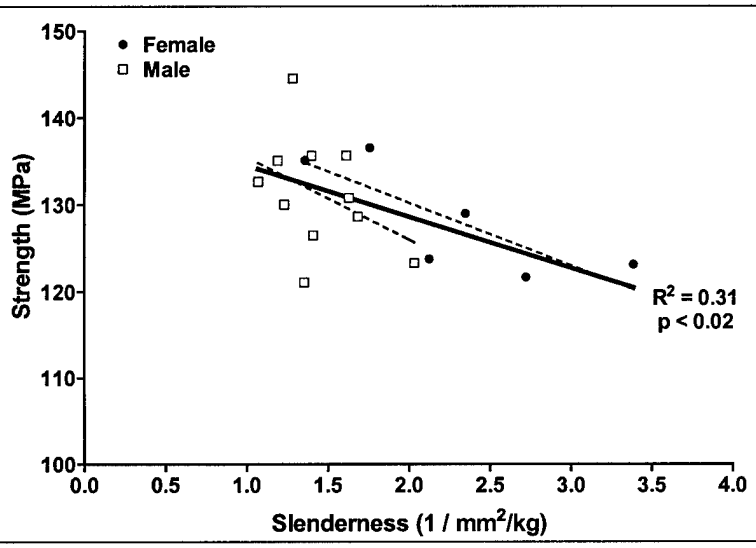


Figure 3. Tissue strength decreases with increasing bone slenderness.

We have begun the damage accumulation assays and have found some very exciting results. Given that the monotonic failure properties showed very small inter-individual variability, we felt it was necessary to change the damage accumulation from a fatigue test to a more sensitive assay. One problem with fatigue tests is that they are inherently noisy and it is difficult to detect subtle changes in tissue damageability. We made the strategic decision to use a cumulative damage accumulation assay, similar to what was done previously (Jepsen and Davy, 1997), since this assay provides a more sensitive measurement of variation in damage accumulation. The protocol we used is shown in Figure 4 and a typical damage curve is shown in Figure 5. Samples were subjected to diagnostic cycles and damage cycles, such that each damaging load cycle was sandwiched between two diagnostic load cycles. The load levels were based on the average displacement at yield which was determined from the monotonic failure tests. By progressively increasing the displacement level of the damage cycle, we induce a new amount of damage. Thus, for each damage cycle, the amount of damage will depend on the new load level plus the amount of prior damage induced (i.e., the damage history). We found previously that because bone is a viscoelastic material, part of the stiffness loss which occurs following a damaging event is actually recovered upon unloading. Thus, waiting 5 minutes after the damaging cycle allows transient effects to dissipate and allows us to obtain a more precise measure of the damage state (as reflected by stiffness degradation). Damage could be defined at any of the load cycles but was simplified in this preliminary analysis to be estimated from the last load cycle (this will provide the widest possible range of damage values). The damage estimate (D) was defined as:

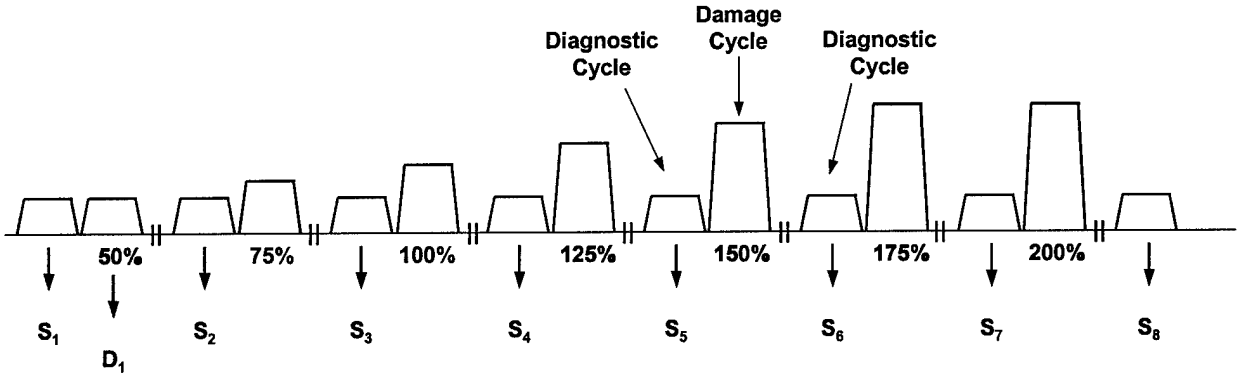
$$D = 1 - Stiffness_8 / Stiffness_0$$

where, $Stiffness_8$ is the initial tangent stiffness values for the 8th diagnostic load cycle and $Stiffness_0$ is average stiffness determined for the first two diagnostic cycles and the first damage cycle (see Figure 4). The damage estimate, D, varies between 0 (no damage) and 1 (rupture).

We will screen all of the tibiae using this protocol and then go back and test additional samples from the tibiae showing the least damageable and the most damageable behaviors. This will confirm that variation in tissue damageability observed in these damage tests is consistent with the damageability that will be seen under long term fatigue tests.

Using this new protocol, we found that the amount of damage incurred during the loading protocol increases with the slenderness of the bone (Figure 6). Thus, bones that are more slender show greater amount of damage compared to less slender bones. This supports our central hypothesis and suggests that individuals with more narrow tibia may actually have a different underlying bone quality that is less strong (monotonic results) and more damageable. These results have important implications for understanding why narrow tibia (small moment of inertia) is the primary indicator of stress fracture risk in the military. The data, thus far, imply that these individuals have a different bone quality that may damage more easily than individuals with larger tibiae. The increased damage that may be induced during extreme physical activity may lead to increased resorption (Johnson et al, 1963) and subsequently increased risk of developing a stress fracture. The data, to date, are very encouraging and imply that the human skeleton, like the mouse skeleton (Jepsen et al, 2001), has the capacity to modulate material properties in concert with whole bone morphology to accommodate mechanical demands imposed by weight-bearing. However, unlike the mouse skeleton, these effects in the human skeleton are more subtle and require precise testing protocols (like that shown in Figure 4) in order to discern these differences.

Figure 4. Schematic of loading protocol used to quantify tissue damageability.



Loading Protocol:

Diagnostic Cycle: **60 second trapezoidal waveform to 50% of yield displacement**

Damage Cycle: **60 second trapezoidal waveform to 50, 75, 100, 125, 175, 200% of yield displacement**

5 minute delay after end of each damage cycle and beginning of each diagnostic cycle.

Analysis:

Initial (undamaged) State = S_o = Average (S_1, D_1, S_2)

Damage Estimate = $D = 1 - S_i / S_o$

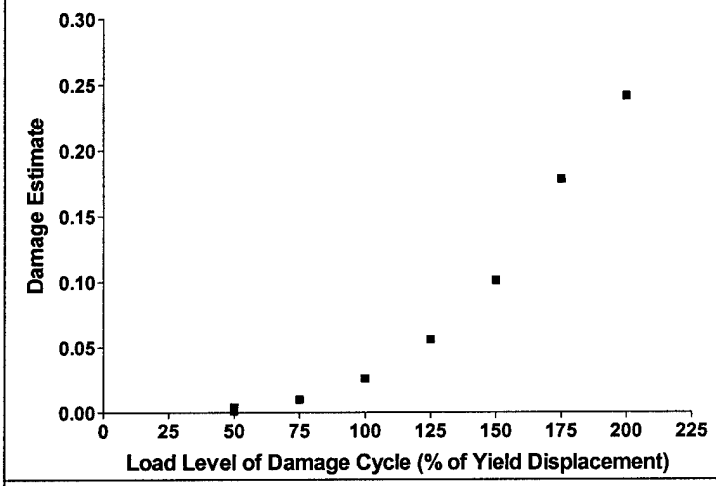


Figure 5. Example of the amount of damage, as estimated from stiffness degradation, as a function of the applied load level for the damaging cycle. The applied load level was expressed as a percentage of the average yield displacement determined from the monotonic failure tests.

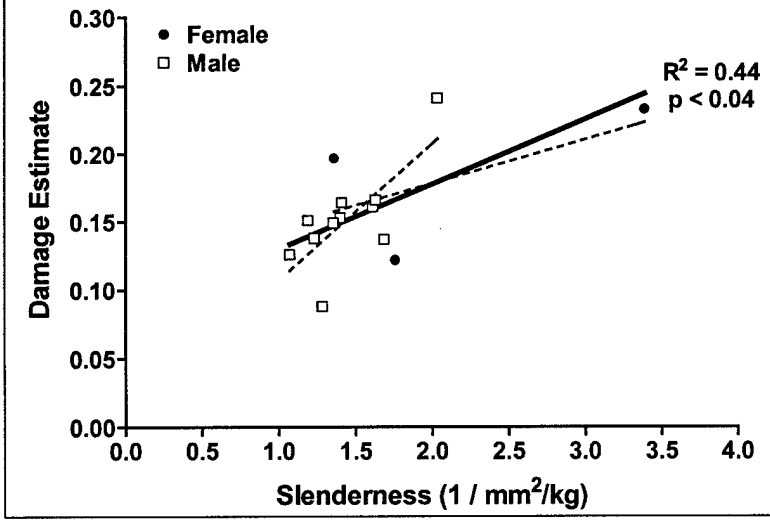


Figure 6. The amount of damage incurred during loading increases with overall slenderness of the tibia. This indicates that the more slender the bone, the more damageable it is.

Supplemental Funding (Subcontract to Boston University):

The goal of the subcontract with Boston University (supplemental funding) is to assess variation in gene expression during growth and development among three inbred mouse strains (A/J, C57BL/6J, C3H/HeJ). These three strains show significant variation in bone morphology (area, moment of inertia) as well as tissue composition (mineral content). Given that bone morphology and quality play a central role in stress fracture risk, it was important to better understand the biological control mechanisms involved in regulating these intrinsic bone traits. We spent the last 4 months generating the necessary pups for analysis. To date, pups for AJ, B6 and C3H mice have been generated for the 28 and 56 day time points. The femurs have been removed for in situ and mRNA analysis and will be shipped to Boston University shortly. The remaining time points (day 1, 4, 7, and 14) will be generated in the next 3 months. Thus, this project is moving along in a steady manner.

Key Research Accomplishments

1. Bone slenderness varies tremendously among individuals and between males and females. Females have tibia that are more narrow for their body size compared to males. We expect that a longitudinal study of bone size will show how bone size and body weight are related. We anticipate that after a certain age (~18 years), bone size does not increase proportional to body size and this may lead to significant variation in slenderness among individuals.

2. The primary outcome of the second year is that individuals with more slender bones appear to have different material properties. With increasing slenderness, the material is less strong and more damageable. This supports are central hypothesis. Further analysis will determine what microstructural or compositional variable is responsible for this relationship.

Reportable Outcomes

Bouxien, ML, Jepsen KJ. Etiology and biomechanics of hip and vertebral fractures. *Atlas of Osteoporosis,* Second Edition. Current Medicine, Inc., Eds. Eric S. Orwoll, Stanley G. Korenman, 2003.

Jepsen K. The aging cortex: to crack or not to crack. *Osteoporos Int.* 2003 Sep;14 Suppl 5:57-66. 2003.

Tommasini SM, Nasser P, Jepsen KJ. Gender differences in bone slenderness are not related to material properties. Submitted to the Orthopaedic Research Society, July, 2002.

Funding

None.

Conclusions

The results to date have provided new insight into the relationship between bone morphology and tissue mechanical properties. The investigations of the mouse skeleton revealed that genetic variations in bone morphology strongly influence tissue mechanical properties through variations in matrix composition. The data from the current year suggest that a similar relationship may also exist in the human skeleton. Thus, individuals who have smaller (more narrow) tibia for their body size may compensate for the smaller geometry through variation in material properties. One of the side effects of this compensation is altered damageability which may be revealed under extreme physical activity such as that experience during military training.

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Appendices

Appendix 1

Bouxien, ML, Jepsen KJ. Etiology and biomechanics of hip and vertebral fractures. *Atlas of Osteoporosis,* Second Edition. Current Medicine, Inc., Eds. Eric S. Orwoll, Stanley G. Korenman, 2003.

Appendix 2

Jepsen K. The aging cortex: to crack or not to crack. *Osteoporos Int.* 2003 Sep;14 Suppl 5:57-66. 2003.

Appendix 3

Tommasini SM, Nasser P, Jepsen KJ. Gender differences in bone slenderness are not related to material properties. Submitted to the Orthopaedic Research Society, July, 2002.

14

Etiology and Biomechanics of Hip and Vertebral Fractures

Mary L. Bouxsein and Karl J. Jepsen

Fractures are one of the most dramatic and devastating consequences of the aging of the human skeleton. In the United States alone, more than 1.5 million age-related fractures occur annually, including 300,000 hip and 500,000 vertebral fractures. Associated medical expenditures amount to nearly $14 billion annually. Moreover, on the basis of current demographic trends, which predict a dramatic increase in the number of individuals older than 70 years of age, the number of fractures is projected to double or triple in the next 50 years. Clearly, interventions for reducing the incidence of fractures are needed. To be most effective, these interventions must be based on a solid understanding of the cause of fractures. In the past, the predominant view was that age-related fractures were strictly a consequence of bone loss. This view was based on studies showing a dramatic increase in fracture incidence with age and a greater fracture rate in women than in men (*see* Chapter 1). However, recent evidence indicates that factors related not only to skeletal fragility but also to skeletal loading influence the risk of fracture.

This chapter reviews the cause of age-related fractures of the hip and spine, discusses basic concepts in bone biomechanics, presents age-related changes in bone properties, introduces a standard engineering concept used to evaluate structural failures, and applies this concept to skeletal fractures. Integrated into the discussion are concepts related to both skeletal loading and skeletal fragility.

Basic Bone Biomechanics

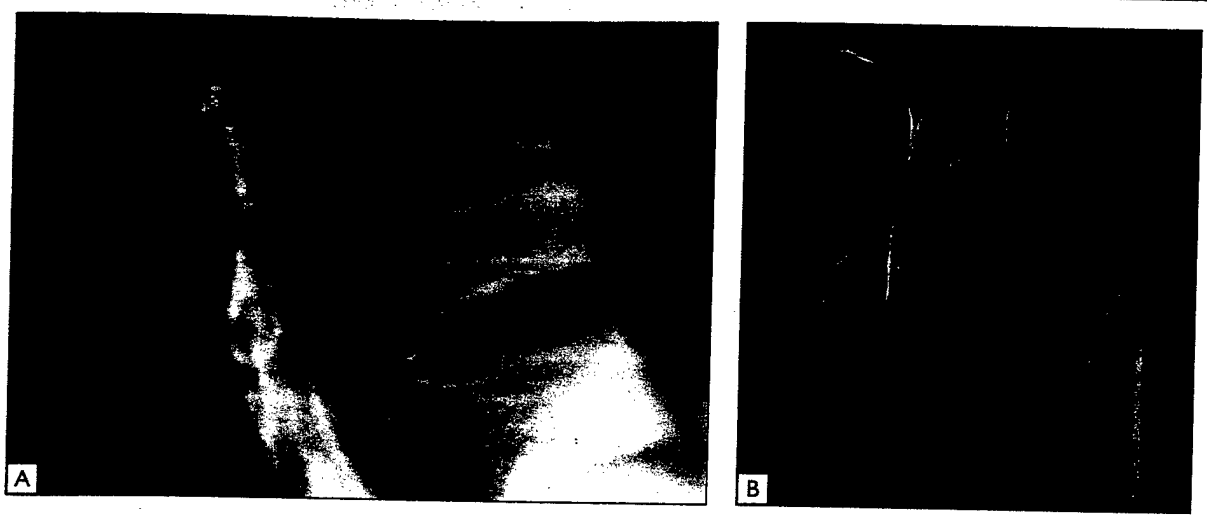


FIGURE 14-1. Definition of fracture. **A,** Vertebral compression fracture. **B,** Fracture of the femur. Although it is not entirely clear why bone fails, in general bone will fail when the applied load generates an internal stress that exceeds the strength of the underlying tissue. Alternatively, and equally important, failure can also occur when the energy or work imparted to the skeleton exceeds the energy-absorbing capacity or toughness of the underlying skeletal structure.

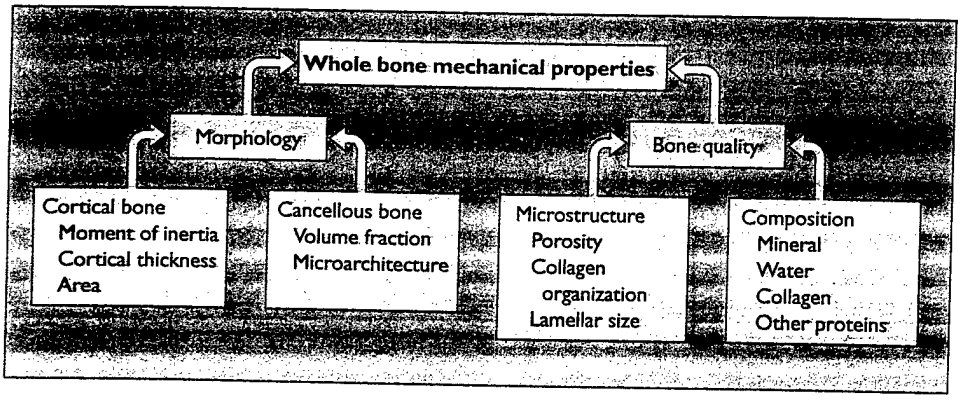


FIGURE 14-2. Relationship between mechanical properties of bone and skeletal traits. For all structures, whole bone mechanical properties, such as stiffness, failure load, and work-to-failure, depend on the size and shape (morphology) of the structure and the mechanical properties (quality) of the underlying tissue. *Bone quality* refers to a wide range of tissue-level mechanical properties, such as strength, modulus, toughness, and fatiguability. Thus, the failure of a skeletal structure depends on changes that occur to any of these underlying skeletal traits.

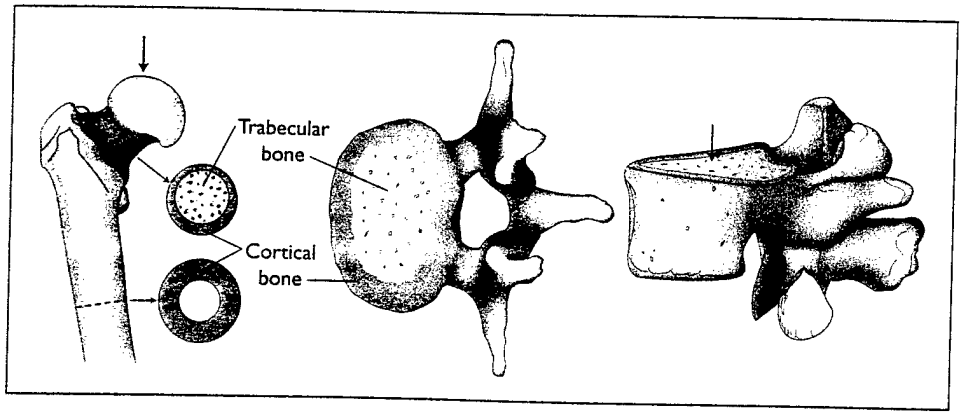
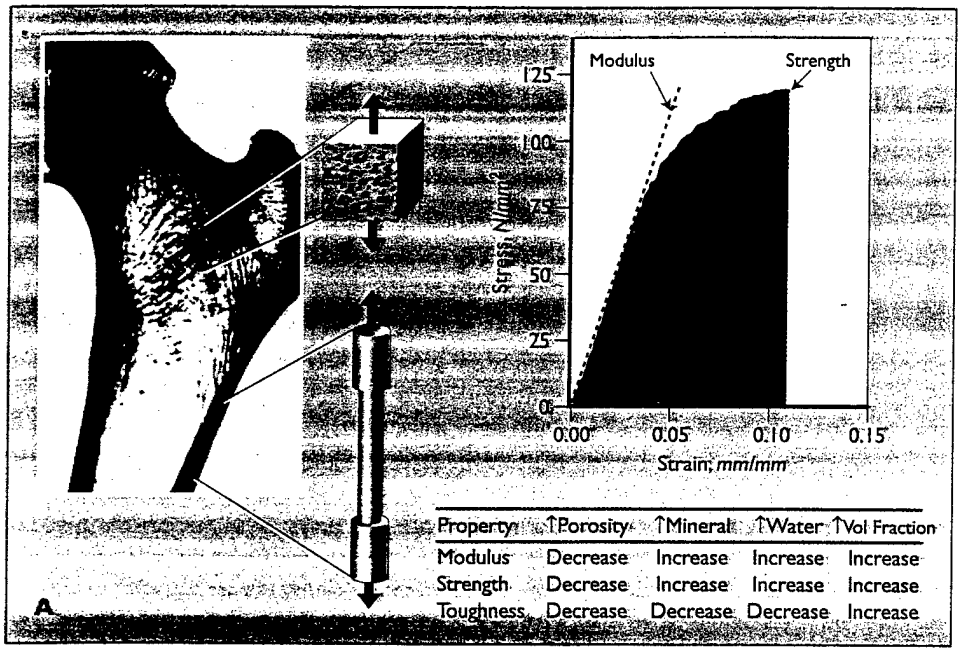


FIGURE 14-3. Effect of bone size and shape on its ability to resist failure. For the spine, which is subject largely to compressive loads during normal daily activities, a morphologic trait that plays an important role during loading is cross-sectional area. For the proximal femur, which is subject to a combination of compressive, bending, and torsional loads, the morphologic trait that acts to resist these loads is the moment of inertia. The moment of inertia, in contrast with area, which measures the amount of tissue, is a measure of the spatial distribution of tissue.



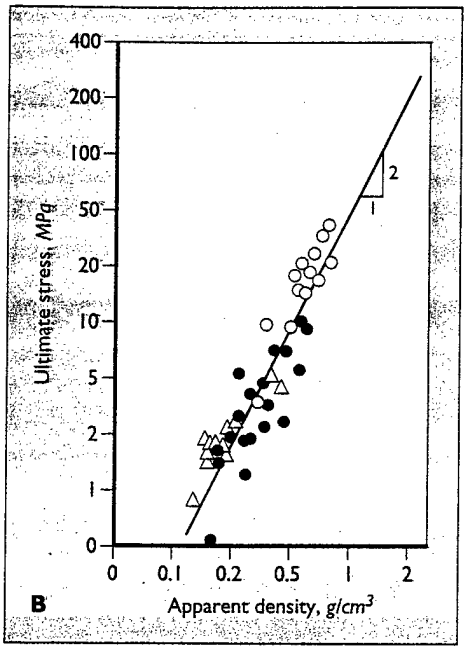


FIGURE 14-4. A, The mechanical properties of cortical and cancellous bone tissues can be determined by "machining" samples of each tissue type and subjecting these samples to a battery of standard mechanical tests. The test most commonly used is the monotonic test to failure. The stress (a measure of force intensity) and strain (a measure of relative displacement) data generated from the experiment are used to estimate the mechanical properties of the bone tissues, such as tissue stiffness (modulus), strength, and work-to-failure (toughness). These mechanical properties are defined by the composition and microstructure of the underlying matrix. Thus, variations in these matrix traits will result in alterations in each tissue mechanical property. **B,** The strong relationship between density and the mechanical behavior of trabecular bone. The relationship between these two variables is linear on a log-log scale and therefore can be described by a power law of the form $y = ax^b$. Several studies have shown that the exponent b is approximately 2. Therefore, small changes in density can result in dramatic changes in compressive strength. For example, a 25% decrease in apparent density, approximately equivalent to 20 to 25 years of age-related bone loss, would be predicted to cause an approximately 45% decrease in the compressive strength of trabecular bone. *(Adapted from* Carter and Hayes [2].)

Age-Related Changes in Bone

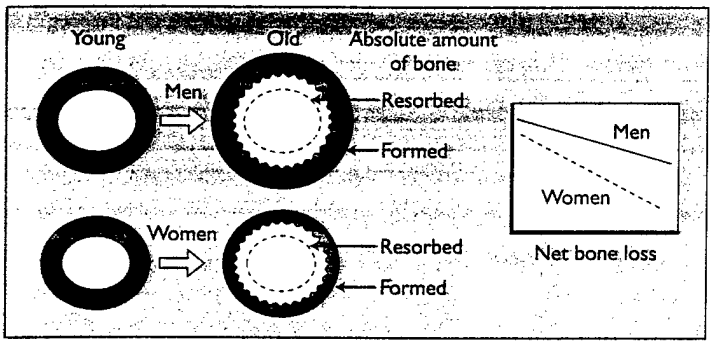
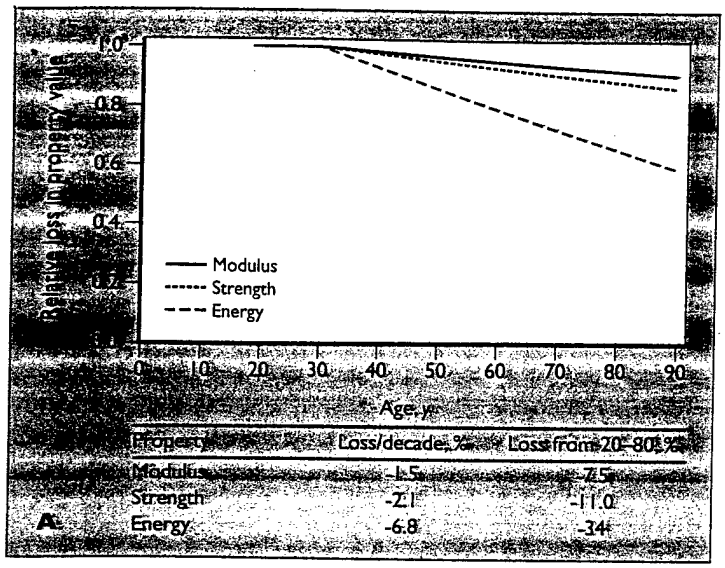


FIGURE 14-5. Age-related changes in the cross-sectional geometry of the femoral midshaft. In general, whereas both women and men undergo periosteal apposition with aging, the absolute amount of bone gained in men is greater than that in women [3]. These geometric adaptations increase the cross-sectional moment of inertia of the specimen and lead to an increased resistance to bending and torsional loads and probably help to offset the detrimental effects of an age-related increase in intracortical porosity, which tends to weaken the bone. Women with hip fractures have decreased cross-sectional area of the femoral neck and thinner cortices [4, 5], perhaps indicating that these individuals have a decreased ability to undergo this structural compensation with aging. Moreover, the amount of endosteal bone resorption with aging is relatively greater in women than in men. Taken together with lesser periosteal bone accumulation, this results in a greater weakening of diaphyseal bone strength in aging women. The structural differences between individuals with fractures and those who are fracture free, and between women and men, most probably have their origins in growth as well as aging, since to a larger extent it is during growth that adult bone morphology is determined [3]. *(Adapted from* Seeman [3].)



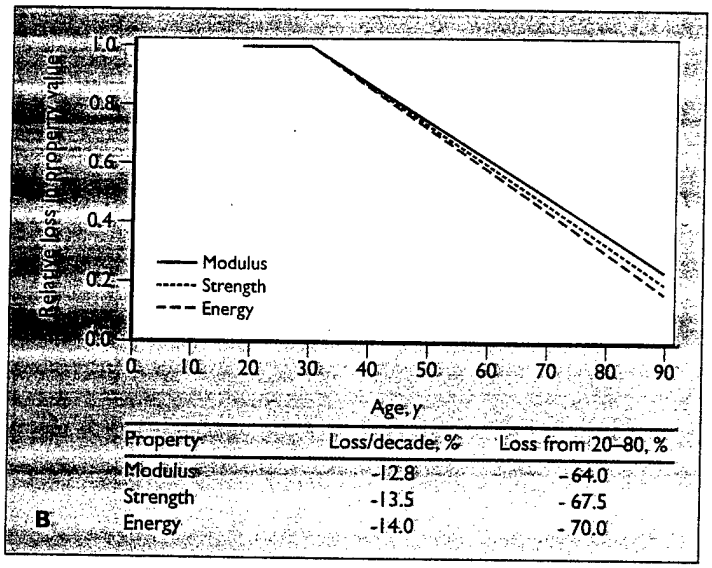
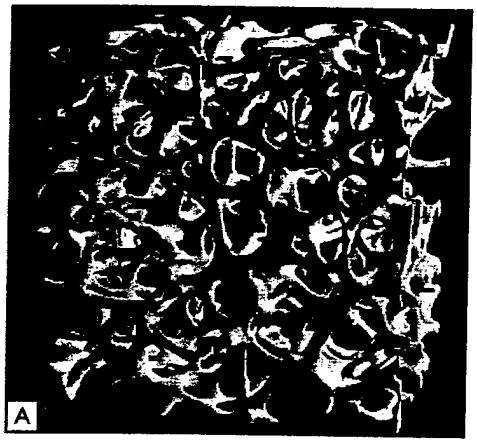


FIGURE 14-6. Age-related changes in the material properties of cancellous and cortical bone. **A,** Age-related changes in the stiffness, strength, and energy-to-failure of human femoral cortical bone in tension. These data indicate that the intrinsic mechanical properties of cortical bone decrease with age and that cortical bone therefore weakens. Importantly, the dramatic age-related reduction in energy-to-failure indicates that cortical bone becomes more brittle with age. Thus, in normal individuals, the stiffness and strength of cortical bone decrease by approximately 8% to 11% from 20 to 80 years of age, whereas the energy to failure declines 34% [6]. **B,** Age-related changes in the mechanical properties of human vertebral trabecular cancellous bone tissue. To study age-related changes in vertebral trabecular bone, Mosekilde *et al.* [7] collected cadaveric vertebrae from 42 persons aged 15 to 87 years. Trabecular bone specimens, oriented either parallel or perpendicular to the superior-inferior axis, were removed from the vertebral bodies and tested in compression. A strong relationship was seen between age and density, ultimate strength, elastic modulus, and the energy absorbed before failure. The density decreased approximately 9% per decade, whereas the mechanical properties decreased 12% to 15% per decade [7].



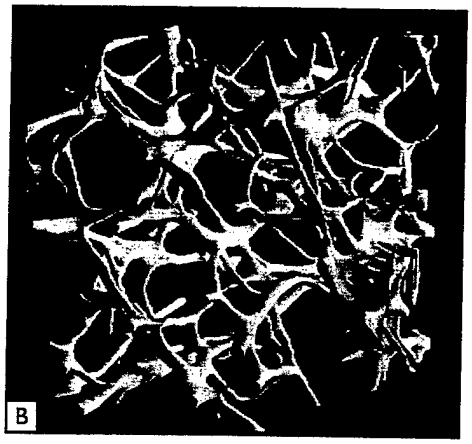


FIGURE 14-7. Dramatic age-related change in bone mass and architecture of vertebral trabecular bone. Trabecular bone strength depends not only on its density (Fig. 14-4B) but also on the arrangement and structure of the trabecular elements themselves. This trabecular architecture can be described by the number, orientation, spacing, thickness, and connectivity of trabeculae. This figure clearly shows that the changes in the architecture of trabecular bone accompany the age-related changes in bone density (42-year-old man [L2 level] [**A**] compared with 84-year-old woman [L2 level] [**B**]). The thickness and number of trabecular elements decrease, and the spacing between trabeculae increases, with a resulting decrease in density. In addition, there may be an accentuated loss of trabeculae that are oriented horizontally. It may be useful to picture the vertical trabeculae as columns that support compressive loads and to view the horizontal trabeculae as cross-struts that brace the columns. In this scenario, the thinning or loss of horizontal trabeculae would reduce the stability of the vertical trabecular "columns" and may lead to failure of the vertical trabeculae by buckling. The contribution of trabecular bone to overall bone strength varies with skeletal site. For example, by mass, the proportion of trabecular bone is approximately 60% to 90% at the vertebral body, 50% at the intertrochanteric region of the hip, 25% at the femoral neck, and less than 5% at the femoral and radial diaphyses [8]. *(Courtesy of* Dr. Ralph Müller, ETH, Zurich, Switzerland).

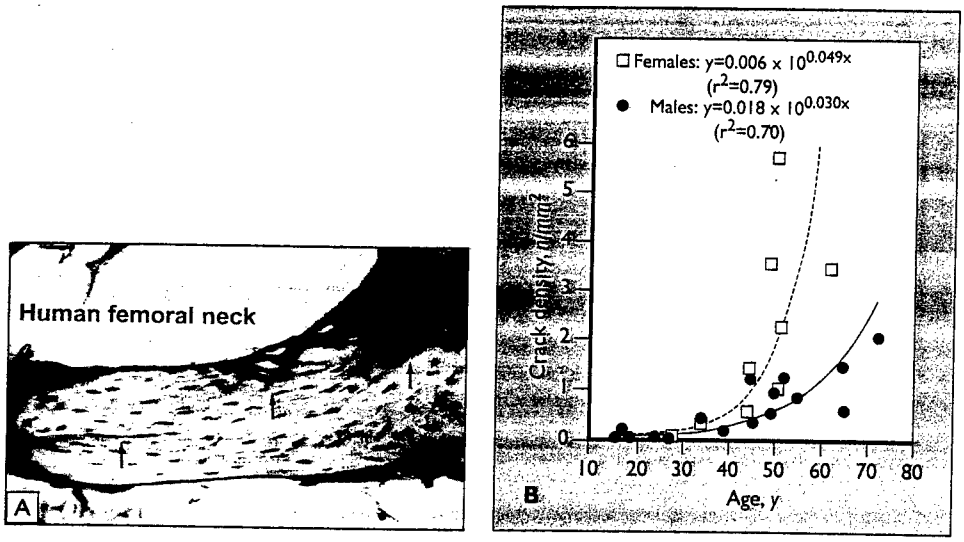
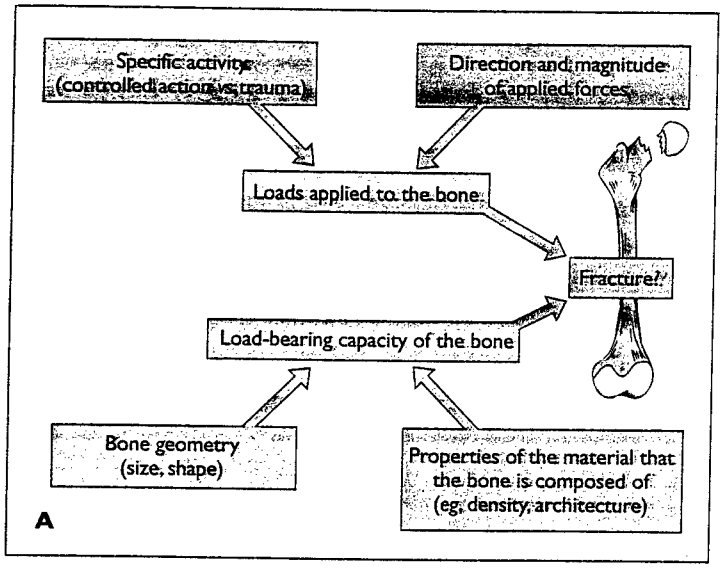


FIGURE 14-8. (see Color Plate) Age-related changes in microdamage accumulation in human cortical bone. Following repetitive loading, small cracks may develop in many materials. **A,** Small cracks in cortical and trabecular bone tissue, termed *microdamage*, have been identified using histologic techniques [9]. In excised bone specimens, an accumulation of microdamage leads to a decrease in the mechanical properties of the specimens. Microdamage has been observed in human cadaveric specimens from the femur and spine [10–12]. **B,** In one study, data from human cadaveric femurs suggest that the prevalence of microdamage increases dramatically with age, as measured by the concentration of microcracks in the femoral cortex [10]. This damage accumulation occurred about twice as rapidly in women as in men. Although it has been speculated that this may contribute to the higher fracture incidence in women than in men, there are no data to suggest a direct relationship between microdamage accumulation and fracture risk in humans [12].

Determinants of Fracture Risk and Introduction of the Factor of Risk



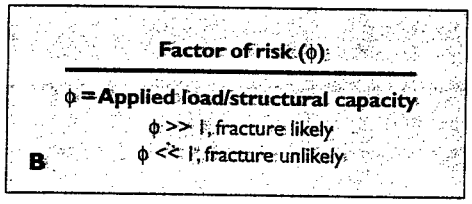


FIGURE 14-9. Factor of risk for fracture. **A,** Bone failure occurs when the load applied to a bone generates an internal stress that exceeds the strength of the underlying tissue. It is therefore obvious that skeletal loading is ultimately an important determinant of fracture risk. **B,** To express the related roles of skeletal loading and skeletal fragility, Hayes [13,14] introduced the concept of the factor of risk. The numerator of the factor of risk is the force applied to a bone during a given activity of interest, and the denominator is the structural capacity (or failure load) of the bone during that same activity. When this ratio is greater than 1 *(ie,* the force applied to the bone is much higher than the structural capacity of the bone), a fracture is predicted to occur. A high factor of risk may result from low bone mineral density and therefore very weak bones, or it may occur when high forces are applied to the skeleton, such as during a motor vehicle accident or a fall. For example, to implement the factor of risk concept for hip fractures, it is essential to 1) identify activities associated with a hip fracture, 2) determine the loads applied to the proximal femur during those activities, and 3) estimate the failure load of the proximal femur during those activities.

Biomechanics of Hip Fractures

MULTIPLE LOGISTIC REGRESSION ANALYSIS OF FACTORS ASSOCIATED WITH HIP FRACTURE IN COMMUNITY-DWELLING MEN AND WOMEN WHO FELL

Factor	Adjusted Odds Ratio	(95% Confidence Interval)	P Value
Fall to the side	5.7	(2.3–14)	<0.001
Femoral neck bone mineral density*	2.7	(1.6–4.6)	<0.001
Potential energy of fall†	2.8	(1.5–5.2)	<0.001
Body mass index*	2.2	(1.2–3.8)	0.003

*Calculated for a decrease of 1 standard deviation.
†Calculated for an increase of 1 standard deviation.

FIGURE 14-10. Investigation of the interactions between fall severity and bone mineral density as risk factors for hip fracture risk. Risk factors associated with hip fracture in community-dwelling men and women who fell [15]. This case-control study demonstrates that fall severity and bone mineral density are *independent* risk factors for hip fracture. In a case-control study of 149 community-dwelling men and women, 72 persons fell and sustained a hip fracture (case-patients) and 77 persons fell and did not sustain a hip fracture (controls). Multiple logistic regression analysis of the data showed that in the case-patients, characteristics related to fall severity, femoral bone mineral density (BMD), and body habitus were strong and independent risk factors for hip fracture. For example, persons who fell to the side were six times more likely to sustain a hip fracture than were persons who fell in any other direction. In agreement with other prospective studies of fracture risk [16–18] the risk of hip fracture increased nearly three times for every 1–standard deviation decrease in femoral BMD compared with the mean BMD, and approximately doubled for each standard deviation decrease in body mass index [19]. These findings emphasize the concept that some important determinants of hip fracture risk are not captured in a BMD measurement.

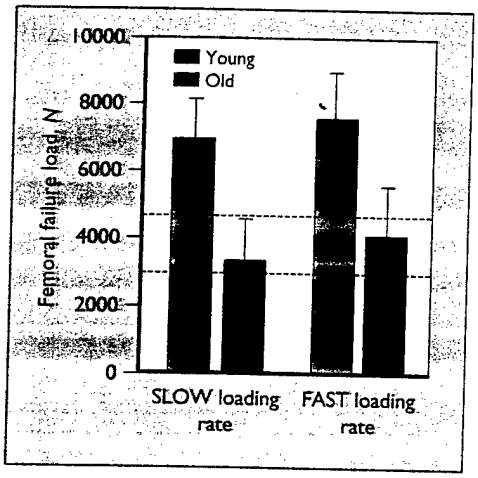


FIGURE 14-11. Influence of age and loading rate on the strength of human cadaveric femurs. Mean failure loads for cadaveric proximal femurs from young *(light shading)* and elderly *(dark shading)* donors. The femurs were mechanically tested to failure at slow (2 mm/sec) and fast (100 mm/sec) loading rates in a configuration designed to simulate a sideways fall with impact to the greater trochanter [20,21]. For both the slow and the fast loading rates, femurs from the young donor group were 80% to 100% stronger than femurs from elderly individuals. Femurs from both the young and the elderly group were approximately 20% to 30% stronger, and absorbed 20% to 30% more energy when tested at the fast loading rate than when tested at the slow loading rate. The two dashed horizontal lines represent the 95% confidence interval for the load that is predicted to be applied to the femur during a sideways fall from standing height. Thus, this cadaveric study indicates that most elderly individuals would be at high risk for hip fracture during a fall from standing height because the load applied to the femur is close to or exceeds the load required to break it. (*Adapted from* Courtney *et al.* [20,21].)

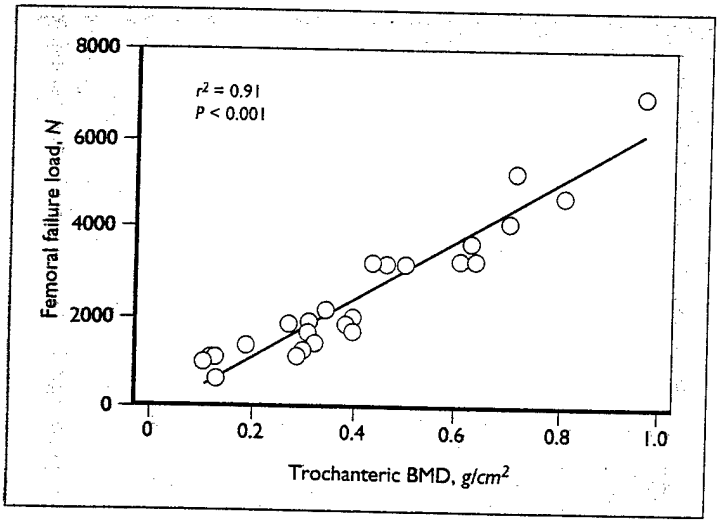


FIGURE 14-12. Relationship between bone mineral density and femoral strength. Trochanteric bone mineral density (BMD) and femoral failure load of cadaveric proximal femurs. There is a strong linear relationship between femoral BMD and the failure load of elderly cadaveric femurs tested in a configuration designed to simulate a fall to the side with impact to the greater trochanter. The load required to fracture the elderly proximal femur ranges from approximately 800 to 7000 N (or about 200 to 1700 pounds).

Biomechanics of Vertebral Fractures

RESULTS OF SURVEY OF PATIENTS WITH VERTEBRAL FRACTURE

Activity	Patients, %
Controlled (eg, lifting)	25
Fall	55
Slow onset/unknown	19

FIGURE 14-13. Circumstances associated with vertebral fracture. It has always been understood that only a small fraction of vertebral fractures are acutely symptomatic and cause the patient to seek medical assistance. However, only recently have large-scale clinical trials estimated the relative incidence of symptomatic and asymptomatic fractures. Results from the Fracture Intervention Trial (FIT), representing the experience of 2000 elderly women who had already sustained at least one vertebral fracture, now address this question [22]. Among approximately 1000 women assigned to receive placebo, new vertebral fractures occurred at an annual rate of 18%, as determined by periodic follow-up spine radiographs. By contrast, the annual incidence of clinically evident fractures was only 6%. Thus, patients are not aware of two of every three vertebral compression fractures at the time the fracture occurs. Consequently, understanding of the antecedent events that contribute to fracture must remain incomplete. In one study of consecutive patients reporting to an emergency department with vertebral fracture, patients underwent a structured interview within 1 week of the event to ascertain activities associated with fracture [23]. The prevalence of falls in these patients is surprisingly high. Thus, efforts aimed at preventing falls should be undertaken to prevent both hip and vertebral fracture.

PREDICTED COMPRESSIVE LOADS ON THE L2 AND T11 VERTEBRAE DURING VARIOUS ACTIVITIES

	Predicted Load on T11		Predicted Load on L2	
Activity	N	Body Weight, %	N	Body Weight, %
Relaxed standing	240	41	290	51
Rising from a chair, without use of hands	340	60	980	173
Standing, holding 8 kg of weight close to body	320	57	420	74
Standing, holding 8 kg of weight with arms extended	660	117	1302	230
Standing, trunk flexed 30°, arms extended	370	65	830	146
Standing, trunk flexed 30°, holding 8 kg of weight with arms extended	760	135	1830	323
Lift 15 kg of weight from floor, knees bent, arms straight down	593	104	1810	319

FIGURE 14-14. Predicted compressive loads on the second lumbar (L2) and 11th thoracic (T11) vertebrae during various activities. To further understand the factors that contribute to vertebral fracture risk, Wilson *et al.* [24] used a mathematical model of the spine to estimate the compressive loads on the thoracic and lumbar vertebrae during activities of daily living. For example, rising from a chair without the use of one's hands was predicted to generate a compressive load on the second lumbar vertebrae equal to 173% of one's body weight. The compressive load applied to the lumbar vertebrae during lifting approximately 30 lbs from the floor by bending at the waist is predicted to be three times an individual's body weight. The loads were computed for a woman who weighs 58 kg and is 162 cm tall [24]. N—newtons.

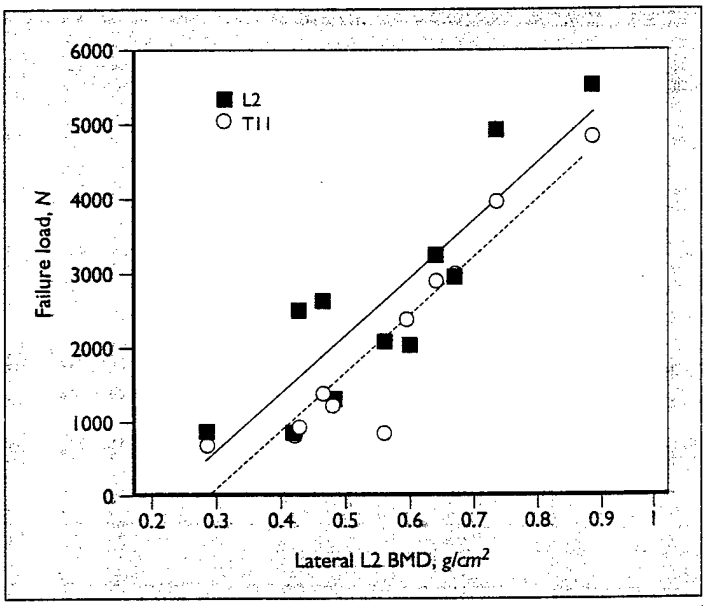


FIGURE 14-15. Linear relationship between lumbar spine bone mineral density (BMD) and compressive failure loads of the thoracic and lumbar vertebral bodies. Cadaveric spines from elderly donors (mean age, 72 years; range, 48–87) were subjected to compressive forces to determine their load-bearing capacity and to determine the relationship between lumbar BMD and the failure loads of both lumbar and thoracic vertebral bodies [25]. Vertebral bodies were obtained from the T10-T12 and L1-L3 regions of 25 elderly cadaveric spines (15 women, 10 men; 64 to 95 years of age). Bone mineral density was measured in each specimen with dual-energy x-ray absorptiometry (DEXA). Specimens were tested to failure in a forward-bending configuration to determine the failure load. There was a strong relationship between lumbar spine BMD and failure loads of T11 and L2 ($r = 0.94$, $P < 0.001$; and $r = 0.89$, $P < 0.001$; respectively). The failure loads ranged from approximately 800 to 5800 Newtons (*N*). These findings indicate that lumbar spine BMD, in general, is a reasonably good predictor of the load-bearing capacity of both thoracic and lumbar vertebral bodies, at least when analyzed over a fairly broad range of BMD values. However, it should be noted that the standard error of the estimate (*ie*, the error that could be expected when one is trying to predict the failure load of an individual vertebral body from a single BMD value) was substantial. Moreover, although suggestive, this type of study cannot address directly how *changes* in BMD would affect vertebral strength. (*Adapted from* Moro *et al.* [25].)

FACTOR OF RISK FOR VERTEBRAL FRACTURE ASSOCIATED WITH COMMON ACTIVITIES

Activity	Bone Mineral Density, g/cm^2						
	0.3	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
Get up from sitting	**1.5**	0.6	0.4	0.3	0.2	0.2	0.2
Lift 15 kg of weight with knees straight	**2.6**	**1.1**	**0.7**	0.5	0.4	0.3	0.3
Lift 30 kg of weight with knees straight	**3.7**	**1.5**	**1.0**	**0.7**	0.6	0.5	0.4
Lift 30 kg of weight with deep knee bend	**3.0**	**1.3**	**0.8**	0.6	0.5	0.4	0.3
Open window with 50 N of force	**1.1**	0.5	0.3	0.2	0.2	0.1	0.1
Open window with 100 N of force	**1.4**	0.6	0.4	0.3	0.2	0.2	0.2
Tie shoes while sitting down	**1.4**	0.6	0.4	0.3	0.2	0.2	0.2

FIGURE 14-16. Factor of risk for vertebral fracture associated with common activities, as a function of lumbar bone mineral density (BMD). The numerator of the factor of risk was determined from models of spine loading at L2 for an elderly woman of average height and weight. The denominator was determined from regression analysis between lateral lumbar BMD and the load-bearing capacity of the L2 vertebrae. The values for lateral BMD cover a wide range of densities, in particular very osteopenic individuals. The t-score (number of standard deviations from the mean value for BMD in young women) is approximately +1 for a BMD of 0.9 g/cm^2 and is –5 for a BMD of 0.4 g/cm^2. The factor of risk is predicted to be greater than or close to 1 for low BMD values (*shown in bold*). These results indicate that common activities of daily living, such as shoe tying or rising from a chair, can place persons in the lowest BMD categories at high risk for fracture. *(Adapted from* Myers and Wilson [26].)

Fracture Prevention

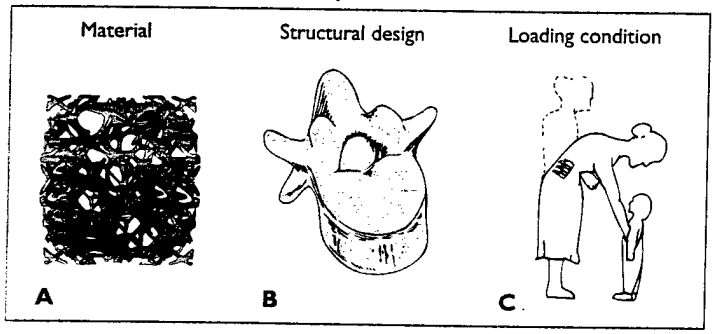


FIGURE 14-17. Factors that determine the amount of force a skeletal structure can withstand. In this figure, the vertebral body is used to demonstrate the characteristics of the spine that determine its capacity to resist mechanical loads. The ability of a structure to carry loads is determined by the intrinsic material that makes up the structure, the corresponding mechanical behavior of that matter, the way that the matter is arranged to form a skeletal structure, and the loading conditions to which the structure is subjected. In the spine, the vertebral bodies carry a large proportion of the compressive loading. The vertebral body consists primarily of trabecular bone (**A**). The structural design of the vertebral body is determined by the organization of this trabecular bone and by the size and shape of the vertebral body itself (**B**). Finally, the behavior of the structure is also determined by the loading conditions that arise from activities of daily living (**C**) or from traumatic loading situations *(eg,* falls or motor vehicle accidents). *(Adapted from* Myers and Wilson [26].)

FRACTURE PREVENTION STRATEGIES

- Maintain or increase bone strength
  - Exercise
  - Diet
  - Pharmacologic interventions
    - Antiresorptive (estrogen, SERMs, calcitonin, and bisphosphonates) and anabolic agents (fluoride, parathyroid hormone)
- Reduce the loads applied to bone
  - Decrease fall frequency
  - Decrease fall severity
  - Avoid lifting/bending activities
  - Use proper lifting techniques

FIGURE 14-18. Strategies for prevention of fractures. Based on the concept of the factor of risk, two complementary strategies could be used to reduce the risk of fracture: 1) improve bone strength *(ie,* improve the quantity and quality of bone) and 2) reduce the loads applied to the bone. The first approach requires attention to standard interventions, such as dietary adequacy, supplemental calcium and vitamin D use, regular frequent physical exercise, and various pharmacologic interventions (see Chapters 15 to 17). The second approach requires interventions aimed at reducing loads applied to bone via decreasing the risk of falling, decreasing the severity of falls that do occur, and minimizing damage caused by routine activities. Leg muscle weakness is an independent risk factor for falls and hip fracture; thus, a cautious program of progressive-resistance strength training is an attractive option. Although such a program does not consistently provide important gains in bone mineral density, it can lead to striking gains in muscle strength that are accompanied by improved performance of tasks, such as rising from a chair and walking [27]. SERM—selective estrogen receptor modulator.

REDUCTION IN HIP FRACTURE RISK WITH TROCHANTERIC PADDING

Type of Fracture	Hip-Protector Group, *n/1000 person-y*	Control Group, *n/1000 person-y*	Relative Hazard (95% Confidence Interval)
Hip fracture	21.3	46.0	0.4 (0.2–0.8)*
Pelvic fracture	3.3	8.2	0.4 (0.1–1.8)†
Other fractures of the legs or trunk	21.3	20.6	1.0 (0.5–2.0)†
Fracture of the arms	16.4	19.9	0.8 (0.4–1.7)†

**P = 0.008 for comparison between hip-protector group and control group.*
†P ≥ 0.05 for comparison between hip-protector group and control group.

FIGURE 14-19. Trochanteric padding reduces hip fracture risk. Wearing padding directly over the greater trochanter is an interesting strategy aimed at minimizing the force of a fall that is transmitted to the bone. To be effective, a padding system must attenuate forces under real-world impact conditions, must be worn by vulnerable patients, and must be able to reduce impact force below the level at which a fracture would be predicted to occur. Robinovitch *et al.* [28] performed testing of various trochanteric padding systems, demonstrating the ability of the pads to reduce the impact force applied to the femur during a sideways fall. In support of these laboratory findings, several prospective studies have demonstrated that use of trochanteric padding systems can dramatically reduce the risk of hip fracture in frail elderly adults [29–31]. The figure shows results from one study, in which 1800 ambulatory but frail elderly were randomly assigned either to a group that wore a hip protector or to a control group [30]. These individuals were followed for the incidence of falls and fractures of the hip and other sites. The rates of hip fracture in the hip protector and control groups, respectively, were 21.3 and 46.0 per 1000 person-years, representing a 54% reduction in hip fracture risk in the hip protector group. While these findings demonstrate the ability of hip protectors to reduce fracture risk among the frail elderly, compliance in wearing the pads was poor, highlighting an important challenge for clinical use of trochanteric padding devices.

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ORIGINAL ARTICLE

The aging cortex: to crack or not to crack

Karl J. Jepsen

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Introduction

This article presents a general overview of age-related changes in the cortex of the human skeleton. Existing data from the literature are examined in the context of how changes in bone structure and bone quality contribute to age-related increases in fracture risk. We postulate that fragility fractures are preventable. Novel targets for diagnosis and treatment will benefit directly by solving both the engineering problem ("Why does bone become brittle with age and disease?") and the biological problem ("Why does bone become brittle with age and disease?"). This review addresses primarily the engineering problem.

What defines whole-bone mechanical function?

Whole-bone mechanical function is defined by two bone trait categories: morphology (i.e., the amount and distribution of tissue) and material properties (i.e., bone quality). Alterations in whole bone function that lead to fracture risk can arise from changes in either of these trait categories. Given that fracture is a mechanical event, treatment strategies that aim to reduce fracture risk should be designed based, in part, upon the principles of mechanics.

Fragility fracture is defined as bone failure following an event (e.g., fall) that would otherwise not be traumatic for a healthy skeleton. Fragility fractures represent a broad class of fractures, and there are many different underlying factors that lead to each fracture-risk type. For example, fragility fractures are associated with mutations affecting collagen synthesis (e.g., osteogenesis imperfecta, or OI), mutations affecting bone resorption (e.g., osteopetrosis), low bone mass (osteoporosis), and aging.

Osteoporotic fracture risk is generally attributed to low bone mass [1], and this is a consequence of low-peak bone mass, excessive bone loss during menopause, or both. Bone mineral density (BMD), which provides a noninvasive measure of bone mass, identifies those currently at risk of fracture but it does not identify those who will be at risk of fracture in the future [2]. Age-related increases in fracture risk cannot be fully explained by BMD alone [3], and therefore the pathogenesis of age-related fragility fractures may include factors other than low bone mass. Thus, a prevention-based program must use multiple risk factors in addition to BMD to identify and treat at-risk individuals earlier in their life. There are many ways in which a bone can become fragile, and each way may require a different treatment strategy.

What is bone quality?

Bone quality is a generic term used to qualitatively describe the intrinsic (tissue-level) mechanical properties of bone. Although this term encompasses a large number of tissue mechanical properties (Table 1), it is often used in reference to bone stiffness and strength. These two particular properties are commonly used because the monotonic failure tests used to quantify these properties are more easily conducted than most other materials tests. To advance our understanding of how age contributes to fracture risk, we need to expand our concept of bone quality and determine how certain matrix changes affect a broader repertoire of whole-bone mechanical properties. In addition, we need to better understand how changes in tissue-level mechanical properties not only affect whole-bone strength but also whole-bone toughness.

Expanding our understanding of bone mechanical properties is important because it is not entirely clear which property or group of properties is responsible for bone fragility. Of the properties listed in Table 1, however, whole-bone strength and energy to failure are likely the most important determinants of fracture risk, and both should be measured when assessing the efficacy of any treatment regimen.

We do not fully understand how skeletal structures fail. For simple materials and structures, failure occurs

Table 1 List of commonly used tissue-level mechanical properties that are used to characterize bone behavior

Property	Test
Stiffness	Monotonic
Strength	Monotonic
Brittleness, ductility	Monotonic
Energy to failure	Monotonic
Fatigue strength	Cyclic
Residual strength	Cyclic
Creep strength	Creep
Energy release rate	Fracture toughness
Impact strength	Charpy impact test

Table 2 Strength values for human cortical bone

Condition	Strength value (MPa)	Reference
Mode = compression	205	[30]
Mode = tension	135	[30]
Mode = shear	70	[30]
Orientation = longitudinal (T)	135	[30]
Orientation = transverse (T)	53	[30]
Rate = 0.001%/s (tension)*	150	[31]
Rate = 1%/sec (tension)*	220	[31]
Fatigue strength (compression)[a]	89	[32]
Fatigue strength (tension)[a]	55	[32]
Creep[b]	63	[33]
Age: 35 year old (tension)	170	[6]
Age: 85 year old (tension)	144	[6]

*Values are for embalmed human bone
[a]Value reflects the stress required to get failure within 12,000 cycles for compression and 16,000 cycles for tension
[b]Value represents the approximate applied stress resulting in a time to failure of 1,000 seconds

when the load applied generates an internal stress that exceeds the strength of the material. As such, fracture risk should be related to bone strength. However, because bone is a damageable, viscoelastic composite material, it exhibits a very complex repertoire of mechanical properties. The strength of bone (Table 2) varies dramatically with loading mode, loading rate, loading direction, the number of load cycles, time, and age. As such, there is no single strength value that can be used as a predictor of fracture risk.

Given that bone has both complex material and morphological features, it may be more relevant to relate bone failure to the amount of energy that is imparted to the skeleton during a fall. If the bone is able to absorb the energy induced during a fall, then it will not break. However, if there is low bone mass or the matrix is compromised, then the structure will not be able to absorb this energy and it will break.

For a composite material like bone, failure is the end result of a damage accumulation process. Composite materials like bone accumulate microcracks during loading; with increased load magnitude, number of cycles, or time, these cracks will grow in number and size. Eventually, these microcracks will coalesce and form a fatal macrocrack. The propagation of this macrocrack through the bone structure represents the final event of failure. A healthy bone is able to delay the coalescence of microcracks and the formation of the macrocrack and can absorb a substantial amount of energy prior to failure.

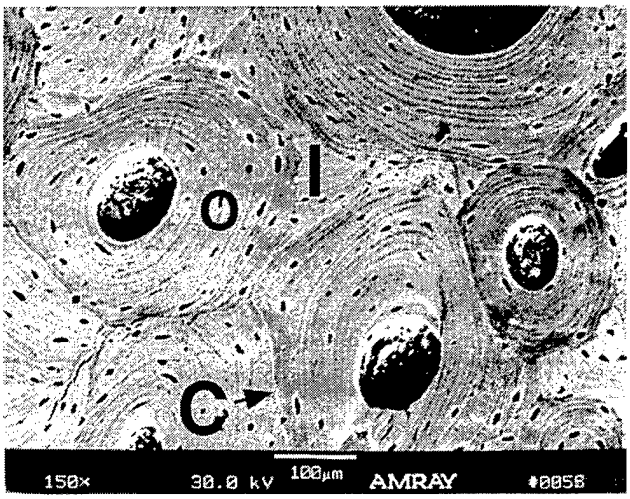

Fig. 1 Scanning electron micrograph of cross-section of human cortical bone (25-year-old male) showing osteons (*o*), cement line interfaces (*C*), interstitial tissue (*I*), and haversian canals

The ability to accumulate damage and prevent the damage from growing and coalescing is one of the key features that gives composite materials their toughness and superior fatigue resistance. For bone, cement lines and lamellar interfaces (Fig. 1) are critical microstructural features that act to stop or deter cracks. Thus, the damageability of bone depends on the ability of the microstructure to limit the growth (in size and number) of microscopic cracks. Normally, bone has an amazing capacity to deal with damage, such that microcracks generated during physiological conditions are small and isolated [4]. This allows time for biological processes to remove them with little, if any, compromise to tissue mechanical properties. However, certain constitutive changes can compromise this damageability, leading to premature formation and propagation of the fatal crack. For example, mutations affecting type I collagen synthesis have been shown to lead to altered tissue damageability [5]. In this case, bone fails in a brittle manner like chalk. It is important to note that brittle and ductile materials can exhibit similar stiffness and strength values. However, the energy required to break a brittle bone is substantially lower than the energy required to break a ductile or tough bone. Thus, bone fragility may depend on whether bone tissue is able to accumulate microcracks and deal with the presence of these cracks in a normal manner.

How do cortical bone tissue mechanical properties change with age?

Tissue-level mechanical properties of cortical bone are determined accurately by destructive material tests.

Samples of cortical bone are machined from cadaveric tissue to sizes and shapes that are specific to a particular mechanical test. These regular-shaped samples with known geometries are then subjected to specific loading regimens. Load and deformation are recorded and specific mechanical properties are calculated using standard formulas. Each mechanical test provides a unique glimpse into the behavior of bone. Importantly, no single mechanical property has been identified that fully characterizes the mechanical behavior of bone. Thus, multiple tests are needed to define the full repertoire of bone mechanical properties.

Ex vivo mechanical tests have characterized how the mechanical properties of bone change with age. In general, there is an age-related decrease in most mechanical properties (Table 3) and the magnitude of these changes is in agreement among most studies. It is important to note that not all properties degrade with age in the same way. Although the sample population varied among investigations, the changes reported here represent the mechanical properties of individuals between 20 and 102 years of age.

Tensile and compressive elastic moduli of bone change very little with age, showing decreases of only 0–2.2% per decade. These age-related regressions for tensile and compressive moduli are not significant. Shear modulus, however, shows a slightly larger age-related degradation of 4% per decade. Bone strength shows a slightly greater age-related degradation compared to tissue modulus such that the tensile, compressive, and shear strength of bone decrease 2–5% per decade. Thus, a person can expect femoral tensile modulus and strength to go from 15.2 GPa and 170 MPa at 35 years of age to approximately 13.7 GPa and 144 MPa at 85 years of age [6].

The mechanical properties related to failure mode show more dramatic changes with age compared to strength and stiffness. Work to failure, the critical stress intensity factor (Kc), fracture toughness (G_I and G_{II}), and energy absorption, decrease 7–12% per decade. These age-related changes in fracture toughness vary with skeletal site, with little changes observed for the femoral neck and significant changes observed for the femoral shaft [7]. Because bone samples are typically machined from individuals with no apparent skeletal abnormalities, these studies indicate that the "normal" aging process results in a significant increase in bone brittleness. Thus, the age-related changes in matrix composition and matrix organization affect bone toughness more dramatically than they affect bone stiffness and strength.

How do bone matrix properties change with age?

Because the mechanical properties of bone are a manifestation of matrix composition and microstructure, it is important to understand how age-related changes in matrix mineralization and organization affect the repertoire of bone mechanical properties (Table 4). In the aging human skeleton, there are structural changes that arise (Fig. 2) such as an increase in osteon density [8], a decrease in the average area of osteons [8], a decrease in the fraction of primary bone [8], an increase in overall porosity [8], a change in collagen orientation [9], and an increase in matrix microdamage [4]. The age-related increase in porosity is site specific such that the increased porosity begins near the endosteal surface and progresses toward the periosteal surface [10]. These porosity changes are also gender specific, with women showing increased porosity compared to men after the age of 70 [11].

Advancing age is also associated with compositional changes such as an increase in the amount of more highly mineralized bone [12]. an increase in overall mineralization or ash content [13], and an increase in pentosidine crosslinks (a marker of nonenzymatic glycation-induced crosslinks) [14]. Compared to age-matched controls, bone tissue from osteoporotic individuals shows overhydroxylation [15], a decrease in the level of

Table 3 Changes in cortical bone mechanical properties with age

Property	Age change (%/decade)	Reference
Tensile modulus	−1.5 (NS), 0	[11, 34]
Compressive modulus	−2.2 (NS)	[34]
Shear modulus	−4 (NS), −3.9	[34] Jepsen, KJ, Mt. Sinai School of Medicine. Unpublished data
Bending modulus	−2.3	[6, 14]
Tensile strength	−2.1, −5, −4	[34, 11]
Compressive strength	−2.5	[34]
Shear strength	−3.5	Jepsen, KJ. Mt. Sinai School of Medicine. Unpublished data
Bending strength	−3.7	[6]
Ultimate tensile strain	−5.1, −9	[11, 34]
Ultimate shear strain	0	Jepsen, KJ. Mt. Sinai School of Medicine. Unpublished data
Energy absorption (work)	−6.8, −12, −8.7	[6, 11, 34]
Impact energy	−300% between age 30 and 90	[13, 35]
Fatigue strength	56 year old, < 27 year old	[36]
Fracture toughness (Kc)	−4.1	[6]
J integral	−3	[6]

NS = not significant

stabilizing (pyrrole) crosslinks [16], and no change in pyridinoline crosslinks [16]. The biological determinant of mineralization is the rate of bone turnover. During rapid growth and periods of high turnover there is low mineralization (hypomineralization), whereas during aging and low remodeling there is high mineralization (hypermineralization). Thus, with aging, there is an increase in the amount of more highly mineralized bone that leads to an increase in overall mineralization. In addition, there is also an age-related increase in the fraction of tissue that becomes hypermineralized, and this tissue appears preferentially near ligamentous or tendinous insertion sites[17]. Thus, the aging skeleton becomes more porous, more highly mineralized, and there are specific changes in the organic matrix.

How do matrix level changes affect bone mechanical properties?

There is a tendency to attribute the changes in mechanical properties to specific changes in one or two underlying bone traits. One advantage of this reductionist approach is that identifying a small number of traits responsible for skeletal fragility provides rational targets for treatment strategies that may correct tissue fragility. In this regard, bone stiffness and strength have been attributed largely to mineralization and porosity. Similarly, postyield properties (e.g., toughness, brittleness) have been attributed to the organic phase that is mostly type I collagen. As such, improving matrix mineralization, porosity, and collagen content should have predictable effects on the skeleton. However, this reductionist approach may be too simplistic, as there are important relationships among these bone traits that need to be considered. For example, mineral content is associated with both increased stiffness and reduced toughness.

As noted previously, the aging skeleton is associated with multiple compositional and structural alterations. Importantly, the collective effect of these matrix alterations on the full repertoire of tissue and whole-bone mechanical properties is not well understood. Thus, multivariate approaches need to be used to understand how the combination of matrix alterations leads to mechanical property changes.

It has been postulated that certain matrix changes affect tissue-level and whole-bone mechanical properties by impairing the damage accumulation process. As noted previously, damage accumulation is central to the strength, toughness, brittleness, and fatigue resistance of bone. According to the Cook-Gordon failure mechanism [18], crack propagation may be halted, diverted, or uninterrupted by an interface, depending on the relative tensile and shear strengths of the interface and the opposing materials (Fig. 3). Thus, the damageability of

Table 4 Age-related changes in cortical bone matrix traits

Trait	Age-related change	Reference
Osteon density	Increase	[8]
Osteon size	Decrease	[8]
Porosity	Increase	[11]
Ash content	Increase	[13]
Pentosidine crosslinks	Increase	[14]
Microdamage	Increase	[4]

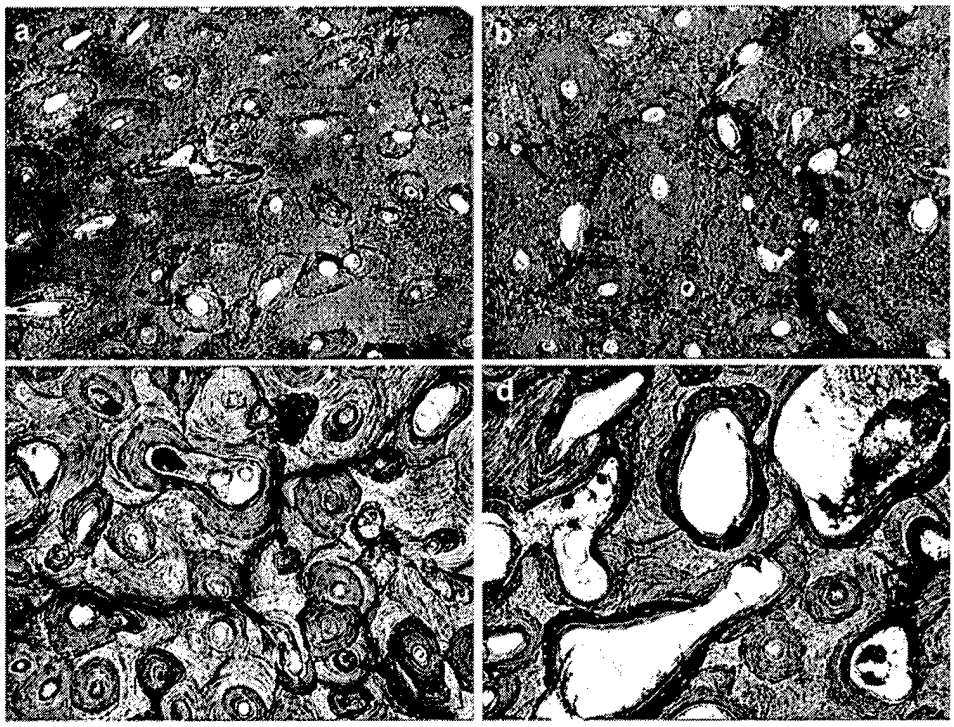

Fig. 2a–d Cross-sectional images of **a** 25-year-old male, **b** 34-year-old male, **c** and **d** 76-year-old male showing progressive changes in microstructure during aging

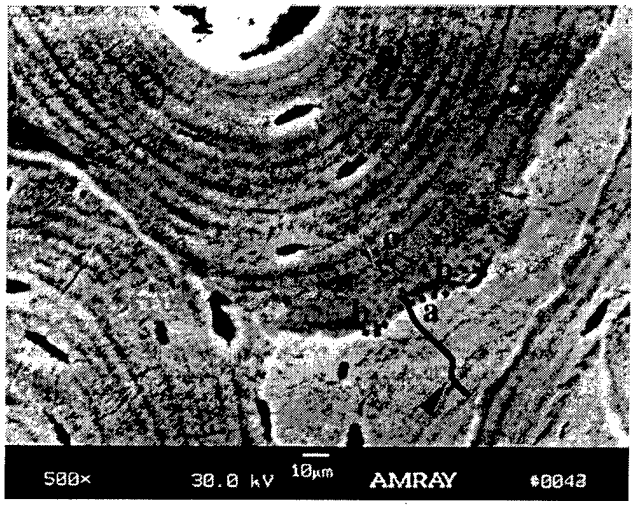

Fig. 3 A growing microcrack (*arrow*) in bone can be *a* stopped, *b* diverted, or *c* uninterrupted when encountering an internal interface such as a cement line

bone can be altered by a change in the number of interfaces (lamellae, cement lines) or a change in matrix composition (e.g., mineralization, collagen, proteoglycans, water, crosslinks) that affects the mechanical properties of osteons and interstitial tissue. This concept is supported by recent studies showing that the effectiveness of internal interfaces like cement lines degrade with age [6, 14, 19].

This damage-based paradigm represents a universal concept that explains how changes at the collagen-mineral level affect tissue-level mechanical properties. The age-related increase in osteon density, the number of cement-line interfaces, and the matrix-to-cement-line ratio indicate that there are plenty of interfaces in the aging cortex. Therefore, the decrease in fracture toughness and fatigue resistance with age appears to be a consequence of changes within the matrix that compromise the effectiveness of these interfaces at stopping or deterring cracks during loading.

The exact mechanism for this degraded effectiveness is not fully understood. One explanation is that age-related changes in the relative mechanical properties of the osteon and the interstitial tissue favor crack propagation rather than crack deterrence [19, 20]. With advancing age, an increase in the calcium content of interstitial periosteal lamellar bone leads to an age-related increase in stiffness and hardness of the interstitial tissue [21]. In contrast, the stiffness and hardness of the osteon stays relatively constant. Apparently, the presence of increased interstitial tissue mineralization and organic fraction changes interfere with the effectiveness of these interfaces.

Why does bone become brittle with age and disease?

Given that whole-bone mechanical function is determined by the combination of morphology and material properties, it is important to understand how age-related changes in bone morphology interact with age-related changes in the underlying material properties. With advancing age, most bones become bigger due to bone deposition on the periosteal surface. The persistent resorption of the cortex, which begins preferentially on the endosteal surface [10], results in an increase in the marrow space. Age-related increases in bone size have been observed for diaphyseal bone [22] as well as the femoral neck [23]. In men, the periosteal expansion is well balanced, with endosteal bone loss resulting in maintenance of cortical area and an increase in the moment of inertia. In women, the periosteal expansion is small at best, and the endosteal resorption is large, resulting in an age-related net loss in cortical area and moment of inertia. The increased moment of inertia observed for the male skeleton apparently compensates for the age-related decrease in material stiffness, arising from changes in matrix composition and microstructure, so that whole-bone strength stays constant [22]. In contrast, the loss of material strength and the lack of morphological compensation in the female skeleton leads to an age-related decrease in whole-bone stiffness and strength [22]. Thus, the increased incidence of fracture in women may be partly due to gender-specific differences in bone growth with advancing age.

Although we see that morphological changes compensate for decreases in material stiffness and strength, at least in the male skeleton, it is unclear whether these morphological changes also compensate for degradation of material toughness arising from alterations in tissue damageability. To understand why bone becomes brittle with age and disease, it will be necessary to shift our attention to understanding how these age-related changes in matrix composition and microstructure affect whole-bone toughness.

What are rational targets for treatment and therapy?

A major concern associated with the treatment of osteoporosis using pharmaceutical agents that suppress bone turnover is that there will be increased matrix mineralization. Given previous investigations, the increased mineral plus the reduced turnover would be expected to lead to increased accumulation of matrix microcracks; both factors will negatively affect tissue toughness. However, studies conducted using dogs have shown that clinical doses of bisphosphonates do not lead to increased microcrack accumulation or impaired mineralization, even after one to two years of treatment [24, 25, 26, 27, 28]. The magnitude of damage accumulation appeared to depend on drug dosage and increased matrix damage, and spontaneous bone fractures were generally only observed in dogs given doses that were 100 times greater than those used clinically. Interestingly, the data indicated that the spontaneous fractures associated with high drug doses were not a result of microcracks but a result of increased osteoid thickness

(and consequently reduced tissue strength) due to impaired mineralization.

As noted previously, aging is associated with changes in many bone traits, some large in magnitude and some small. It is not likely that one paradigm explains all forms of skeletal fragility. For osteoporosis, inhibiting osteoclastic resorption using bisphosphonates is a rational choice given that the principal risk factor is low bone mass [1]. Studies have shown that antiresorptive drugs decrease the incidence of hip and spine fractures indicating that this strategy works, at least in the short-term [29].

For age-related fragility fractures, the target for diagnosis and treatment is not as obvious. Age-related fragility fractures are not only a consequence of bone loss but also of altered matrix properties that degrade tissue toughness. Inhibiting resorption may help to alleviate the problems associated with increased porosity such as reduced material stiffness and strength. For the aging skeleton, where bone mass is only one of the factors contributing to fragility, treatment should have multiple targets, including matrix toughness.

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Discussion

Dr. Towler: How do you quantify the effectiveness of an interface?

Dr. Jepsen: The composites literature is more advanced than we are in the bone literature. In synthetic composites, you generally have a very stiff and strong fibril buttressed within a lower-stiffness matrix, like graphite and epoxy. So understanding how those interfaces and properties behave is a bit simpler than is the case for bone. In bone, it is much more difficult because you have the lamellar structure and, honestly, we don't fully understand if the lamellar interface is a true interface. We don't fully understand the microanatomy of bone yet. Moreover, although it may play a big role, we don't understand changes in interstitial tissue versus the surrounding matrix, and the effect of crack propagation and overall fragility. For example, with increased mineral content, as a crack starts in one area, it may propagate through to another area because the material that should resist its growth is too brittle.

Dr. Towler: Experimentally, how do you quantify the role of these potential interfaces?

Dr. Jepsen: We don't know the best method yet. Some people have used a fracture mechanics approach for this (i.e., the propagation of a macrofracture), whereas others have used a damage mechanics approach (i.e., the coalescence of microcracks).

Dr. Lindsay: Are we being oversimplistic in talking about bone? Should we be talking about which bone and where it is located and how it is loaded? Are we trying to address an unsolvable problem?

Dr. Dempster: Possibly, but some of these issues might be more amenable to study than others. I think that microarchitecture is one feature that we probably *can* study. That's why I think it is important to discuss how we can start measuring some of these variables noninvasively, because then we have the potential to study skeletal sites that are of clinical interest (i.e., the radius). Many of us have worked with transiliac bone biopsies. The problem there is we're not looking at a load-bearing site or fracture site. Whereas some features are likely correlated between skeletal sites, some may not be. I'd like to hear from Drs. Majumdar and Müller regarding a realistic timeline for in vivo assessments of microarchitecture.

Dr. Majumdar: The MRI technique we currently use measures structure at the wrist, the distal radius, and the calcaneus. Those sites are fairly well defined to date. Of course, you could always improve resolution and that's the hope, but at least today, one can get some initial characterization of the structure of those sites. The hip is the site that has been most difficult. In the last couple of years, imaging techniques for the hip have been improving but they are just not good enough. The advent of higher field-strength magnets will be useful. We are still trying to develop coils moving to the higher field strength, pushing for the NIH to do the three tesla imaging where it may be possible to image the proximal femur, particularly the trochanteric area. The resolution won't be like in histology, but you may be able to get some structural information. I've really given up on the vertebral body. The only spine region which I think would be possible to evaluate are the sacral vertebral bodies, but this would require use of an endorectal coil, so it is likely that it will not be possible to image the vertebral bodies. With regard to other body parts, we're also investigating the distal and proximal tibia, and the distal femur.

Dr. Müller: We have imaged pretty much the same sites with X-ray-based techniques. Of course, with X-ray-based techniques, your resolution and image quality are usually a little better than with MRI. But the limiting factor is not acquiring the image but doing so with a reasonable radiation dose. I think we still have much to learn from higher resolution systems on account of the in vivo studies that we've been doing. It may be important to have an approach that is very much hierarchical, for instance where you can look from the organ down to the cellular level at the same time using the same technology. Then you have some confidence that what you see is really happening. Some of the recent work that we've been doing is somehow discouraging. For some of that data, you really need the better resolution. We found that some of the features that are hard to assess without excellent resolution were very important for predicting mechanical behavior, i.e., thickness of specific elements. This has not been seen before, and we always thought we'd get away from having to assess trabecular thickness accurately. For those who are doing in vivo imaging, we always say "keep away from thickness measurements, because we cannot measure them right with 500-μm real resolution, 200-μm voxel sizes—it's impossible." However, it was exactly those features that were very important for prediction of bone strength. So I'm not so sure how much we can actually do in the in vivo system, but we'll learn and then maybe have some experience with animal studies where we can go down to about 20-μm resolution in vivo with longitudinal follow-up. I think we should use these animal data to point us towards what we should look at in humans.

Dr. Lindsay: How big an animal can you evaluate at that resolution?

Dr. Müller: We can acquire images with 20-μ resolution in a rat model. Actually, with the 20-μm system, we only do the proximal tibia.

Dr. Currey: Dr. Jepsen put forward the idea that the effectiveness of the interfaces decreases with aging. There we're talking about events taking place at the 10-μm level at most. The Cook-Gordon mechanism is when a crack goes towards a weak interface and the stress field in front of the crack is such that it pulls that interface apart and the crack gets diverted. I think we're going to need a terrific improvement in anything like μCT to look at that. However, it is clear that a different way of

looking at things is needed to see whether the weakening of interfacial effectiveness is a reality. When you're thinking about bone, remember what level are you thinking of. Are you thinking of the micron level? Are you thinking of the millimeter level, or what? And the answers are different and the questions are different at those different levels.

Dr. Majumdar: Clearly, the resolution you need and desire depends on the application. For example, if you are applying an imaging technique in a large number of women in a clinical trial, then you must weigh the practical aspects of what can be done with regard to image acquisition time versus increased image resolution. From that perspective, in vivo MRI will likely never answer questions at the micron and submicron level, i.e., looking at crack propagation or small little trabeculae which suddenly have been fused together in vivo.

Dr. Jepsen: I don't know that we actually have to use microdamage as a diagnostic tool. I don't think that's what we're really trying to see. What we're trying to see is if there is something in the matrix that is contributing to changes in its material behavior. Then that's what we really want to target, something that changes with aging, diet, exercise, etc.

Dr. Schaffler: How do we reconcile the mechanisms that govern fragility in cancellous bone from those that govern it in the diaphysis?

Dr. Jepsen: In putting this material together, I was amazed to see that there are investigators who look at bone-tissue properties and those who look at bone-structural properties, but they don't really come together too much. I think that's where we really should start integrating some of these ideas.

Dr. Lundy: We've heard that in cortical bone you need remodeling in order to remove microdamage. How does one measure that at each skeletal site? How do we take that into account with drugs like bisphosphonates or anabolic agents, where the remodeling is increasing or decreasing at different places?

Dr. Dempster: I think remodeling is crucial. You can certainly explain a lot of the efficacy of the antiresorptive agents with reduction in remodeling, involving a number of mechanisms that Dr. Heaney mentioned that are very reasonable. It's hard to test some of them, but some investigators have been able to do microfinite element analyses and show that the stress around the resorption cavity is very high. The trigger for a trabecular failure might well be a single resorption cavity. How we can assess it, though, is problematic. I think biochemical markers help us get there, but they provide integrated information on the remodeling rate of the entire skeleton, including both cancellous and cortical bone compartments. We don't really know what proportion of the markers comes from which compartment or which bone—so I think they give us a very global picture, but at least they are starting to give us some insight. Professor Currey has spent many pages in both of his books discussing why we remodel our skeletons. Removal of microdamage is presumably one purpose of remodeling, but we certainly do not need to remodel our skeletons to the extent that we do to achieve this purpose.

Dr. Shmookler Reis: I want to reflect back to Dr. Dempster's statement that microfinite element analysis of pQCT accounted for 75% of the variance in bone-failure load. Could you put that in context for us? Typically, I think, BMD or conventional pQCT can account for about 65% of the variance in whole-bone strength. Is this to any degree orthogonal, that is, do you get a larger effect from both of them? And what is it about this method that might add information that's not available from other techniques?

Dr. Bouxsein: This is a good question. However, until we can apply the technique in vivo, I am not sure that we can say whether it will provide information independent from BMD for either diagnosis or monitoring the response to treatment.

Dr. Shmookler Reis: Is it simply a better way of deriving architectural information from pQCT?

Dr. Weinans: Yes, basically you derive the effects of architecture or geometry, and the better your resolution, the better you can do that.

Dr. Shmookler Reis: Then I am astonished that you get so little more by knowing about the architecture than you already have by knowing just the BMD.

Dr. Weinans: You have to consider that these data were from a whole-bone test, and therefore the influence of architecture may not be tremendously high. However, if you do a similar analysis on little blocks of cancellous bone, and correlate volume fraction with strength or stiffness, you typically get correlations of at least 65–70%. If you then derive the architecture using microfinite element models, you get correlations of 95%. You explain really a lot then, and the only things which are unknown are at the tissue level, such as microdamage and mineralization.

Dr. Shmookler Reis: But that doesn't leave much for microdamage, does it?

Dr. Weinans: That's right, it doesn't leave much for microdamage, at least with regard to predicting failure properties of normal bone. These relationships may be specific disease, it might be just at the tissue level; so for that one typical example, you might be far off.

Dr. Schaffler: I would like to respond to Dr. Shmookler's comment that architecture adds so little once you know bone mass. We need to open the discussion of what is meant by bone architecture. We're dealing with a series of histomorphometrically designed or derived indices, which are descriptors of some average architecture. They are certainly not what an engineer or an architect would describe as an architect; we're not actually measuring the structure. We are getting some statistical mean value based on histomorphometry, which is an extrapolation of stereological theory. Our descriptors of architecture may be limited because we're calling this architecture like it has a real meaning, which it doesn't. These parameters are arbitrarily defined within a statistical envelope. So I think if we're going to ask the question of how to better use architecture, we

need to actually think about what we mean by "architecture." All of the current architectural features are very highly correlated to bone mass and they are intercorrelated among themselves, so it's not surprising that they don't add much to the prediction of bone strength. There are other quantitative descriptors of structure, such as spatial frequency analysis, that may be more appropriate.

Dr. Weinans: Clinically, we use DXA as a diagnostic tool, which it is not. All the fractures happen in people who then don't have the diagnosis. There has to be something different in that population that makes them more likely to fracture. The question is, do any of the issues that we've talked about in terms of architecture, are they capable of getting us closer to that population at highest risk for fracture, so we don't have to treat a thousand people to prevent one fracture?

Dr. Dempster: Bone mineral density is pretty good for predicting fracture risk in general. However, to get better predictions, you may need to measure architectural and structural variables at the specific sites of fracture, such as vertebra, hip, or radius.

Dr. Lindsay: Previously, I asked whether we could consider bone as an organ or must we consider individual skeletal sites? So you're quite right that there are differences in the dynamics of fractures, but the underlying clinical problem is that we miss most of the fractures by using the tools that we are using today.

Dr. Weinans: I think anisotropy is a very critical issue. Dr. Dempster referred to the paper by Ciarelli et al (Ciarelli TE, Fyhrie DP, Schaffler MB, Goldstein SA (2000) Variations in three-dimensional cancellous bone architecture of the proximal femur in female hip fractures and in controls. *J Bone Miner Res* 15:32–40) and by Homminga and colleagues (Homminga J, McCreadie BR, Ciarelli TE, Weinans H, Goldstein SA, Huiskes R (2002) Cancellous bone mechanical properties from normals and patients with hip fractures differ on the structure level, not on the bone hard tissue level. *Bone* 30:759–764). These are, as far as I know, the first demonstration of a clear difference in architecture between fracture and nonfracture groups, which is independent of bone mass. Thus, once you know that anisotropy is important, you might actually be able to come up with a tool which doesn't need an extremely high resolution to measure it. But once we know what to look for, we might end up with diagnostic methods that actually could do that in a much simpler way than just pushing the resolution all the time.

Dr. Lindsay: I agree. What's important is the distinction between fracture and nonfracture cases, not so much the correlation with bone strength, because bone strength is just a surrogate for fracture.

Dr. Schaffler: I think that's why it's so important we get cadaver material and really try to define what to look for. This was a very nice example of that.

Dr. Beck: One of the problems with the histomorphometry work, elegant and sophisticated that it is, is that most of the load is actually borne by the cortex, which is not generally measured to any great extent using histomorphometric techniques. Several things occur with aging, one of which is that bones expand with age. The expansion with age has several effects, one of which is that BMD is reduced, even if the mass didn't change. So much of the interpretation of BMD change as mass loss is fundamentally wrong. We think expansion is also evidence of a homeostatic mechanism to maintain bending strength as bones age; as bones get bigger in diameter, the mass is further from the center of mass, it doesn't need as much bone material to maintain the same strength. This unidirectional progression with age makes the bone gradually evolve to a condition where it may be locally unstable due to thin cortices in a relatively large diameter.

Dr. Heaney: Does the periosteal expansion come first with the endosteal resorption following it, rather than the periosteal expansion being adaptive?

Dr. Beck: Since long bones are mainly subjected to bending stress, remodeling tends to be favored at sites within the bone where the strains are lowest (i.e., closest to the center of mass). Remodeling produces a transitory increase in the mechanical strain on the periosteal surface and causes bone to be added to that surface. Although it is mostly an appropriate adaptive response, this progression is unidirectional towards a thinner, larger-diameter bone, and may ultimately create an unstable mechanical situation if it progresses too far.

Dr. Turner: I want to bring up the example of raloxifene. This is a weak antiresorptive that reduces spine fractures but doesn't reduce hip fractures. It doesn't build bone mass very much, at least not nearly in proportion to the reduction in spine fractures. The proposed mechanisms are that this is working on a focal resorption in the trabecular bone in the vertebral body, a site that is rich in trabecular bone and where the trabecular bone contributes strongly to its mechanical behavior. I disagree with Dr. Beck in this regard, because in the spine, it is the trabecular bone rather than cortical bone that is important. If we accept that the strength of the hip is built around cortical bone and the spine is around trabecular bone, we can somewhat explain the raloxifene conundrum. If it is true that these focal resorption sites are what are most important in architecture, and is also where the antiresorptive drugs are working, I haven't heard a single architectural measure by any technique that actually measures or quantitates this particular aspect.

Dr. Dempster: The only measure that you can do is "eroded surface," and it is not very reliable. Again, the problem is the biopsy is done in the iliac crest, which is not a weight-bearing site. Even with bisphosphonates, it's hard to show a reduction in eroded surface. So we don't have the evidence for this measurement, but it might be because we're looking at the wrong site, or there is too much variability in the measurement.

Dr. Turner: But it's not only eroded surface, it's eroded surface right in the middle of the trabeculum, which would be the most damaging and very focal.

Dr. Dempster: I agree. It may be possible to get information on the location of resorption cavities on the trabeculae using histomorphometry.

Dr. Turner: But has this been well studied by anybody?

Dr. Dempster: No.

Dr. Bouxsein: With regard to architectural features, we often report only the mean trabecular thickness or separation. However, the new 3D evaluation techniques afford an assessment of the *distribution* of trabecular thicknesses. Thus, it may be instructive to look at features of the distribution, such as the median, skewness, and how they change with age and treatment. For instance, does the proportion of very low trabecular thickness values (i.e., that are about to be perforated) decline with treatment? These types of data should be available since investigators are using 3D techniques to measure biopsies. Maybe we just haven't looked at the characteristics in the right way yet.

Dr. Müller: I agree with you. In addition, we have found that locally derived measurements and not looking at averages may be very important predictors of bone mechanical behavior.

GENDER DIFFERENCES IN BONE SLENDERNESS ARE NOT RELATED TO MATERIAL PROPERTIES

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Introduction: Stress fractures are a major problem among elite runners and military recruits [1]. Having a narrow tibia relative to body mass has been shown to be a major predictor of stress fracture risk and fragility in both men and women [2]. However, the reasons why individuals with more slender bones for their body size are at increased risk of stress fracture are not fully understood.

Strain gauge studies of animals [3] and humans [4] suggest that bone adapts to maintain an in vivo strain level of 2000με or less under normal and vigorous activity levels. Based on the idea that bone adapts to maintain this microstrain level, it is reasonable to question whether tibiae with lower polar moment of inertia are being subject to greater in vivo strains than expected, or does an alternative compensatory mechanism for smaller bone size relative to body weight maintain in vivo strain levels at 2000με? Based on studies of genetically distinct inbred mouse strains, mice with slender bones had increased mineral content [5]. Although increased mineral content may have compensated for smaller morphology by increasing tissue stiffness and strength, this mineral had the adverse effect of increased bone brittleness and tissue damageability under fatigue loading. Data from the inbred mice suggest that bone morphology and quality may be biologically coupled to satisfy mechanical demands imposed by weight bearing. To determine whether this concept also exists in the human skeleton we assessed the biomechanical properties of tibia from young adults to determine whether individuals with slender bones also show compensatory increases in tissue stiffness and strength.

Methods: Female (n=7) and male (n=13) human tibiae from donors ages 17 to 46 with no known orthopaedic pathologic conditions were acquired from the Musculoskeletal Transplant Foundation. The donor body weight and height were obtained from the source. Tibia width was measured in the antero-posterior (AP) and medial-lateral (ML) directions at 10% intervals from 30% to 70% of the total tibia length.

Bone morphology was determined from 3-mm thick mid-diaphyseal cross-sections at 30%, 50%, and 70% of the total tibia length. A thresholded image of each cross-section was obtained using a digital camera and image analysis software was used to quantify cortical area (CtAr), the moments of inertia about the AP (I_{AP}) and ML (I_{ML}) axes, and the polar moment of inertia ($J_0 = I_{AP}+I_{ML}$). A slenderness index (S) was quantified by normalizing the cross-sectional polar moment of inertia for height and weight and is defined as the inverse ratio of the section modulus (J_0/width) to tibia length and body weight:

$$S = 1/[(J_0/(\text{ML width}))/(L*BW)], \quad (1)$$

where L = tibia length (cm) and BW = body weight (kg). The section modulus has been shown to scale to body mass [6]. The inverse ratio was used so that a tibia with a large slenderness is one that is thinner or narrower for the weight and height of an individual. A small slenderness value reflects a stocky tibia.

To assess material properties, a total of 4 cortical bone samples with dimensions of 2.5mm x 5mm x 55mm were machined from the diaphysis of each bone and loaded to failure by 4-point bending in a 37°C PBS solution with added calcium [7]. Load and deflection were converted to stress and strain using the following equations which take yielding into consideration:

$$\sigma = 2[2M + \phi dM/d\phi]/bh^2 \quad (2)$$

$$\varepsilon = h\phi/2a = \tfrac{1}{2}\, h\Delta[(L-a)/(2a^3/3 - a^2L + L^3/3)], \quad (3)$$

where σ and ε are the stress and strain at the outer surface of the beam, M = applied moment, b = specimen width, h = specimen height, a = ½ the span between the upper 2 load points = 9mm, L = ½ the length of the specimen = 21mm, and φ = angle of inclination = a/ρ. The angle of inclination was written in terms of the measured deflection (Δ) by estimating the curvature (ρ) using standard beam equations. Mechanical properties measured were modulus, strength, total energy, and post-yield strain as a measure of brittleness. Differences in morphologic and mechanical properties were determined using a student's t-test.

Results: Geometric measures (Table 1) revealed that while men and women in this study had similar ages and similar body weights, women were significantly shorter than men leading to shorter tibiae. Female bones had nearly 30% less cortical area and 50% lower J_0 compared to males. Females also had significantly thinner bones than males in both the AP and ML directions. Slenderness calculations (Fig. 1) revealed that women had significantly more slender bones compared to men relative to body weight and stature. Regardless of the parameter used to correct J_0 (length, cortical area, weight, and width), female tibiae were still roughly 50% smaller for their given body size compared to males.

To date, 5 female and 5 male bones have been examined for mechanical properties. Bones were selected at both extremes of the measured J_0 values. Biomechanical data (Table 2) revealed no significant differences in modulus between genders. There were also no significant differences between male and female tibia specimens in measures of tissue strength, post-yield strain, and total energy.

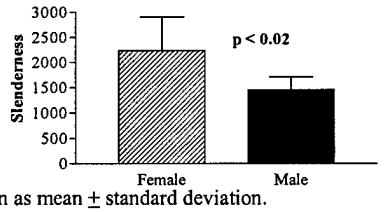
Discussion: The primary finding of this study is that inter-gender differences in morphology of young adult bone do not correlate with tissue level material properties. If a compensatory relationship between slenderness and mineral content existed, slender bones would be expected to have increased stiffness and decreased post-yield strain (i.e., more brittle) and this was not observed. Based on comparison between males and females, the data suggests that the compensatory relationship between morphology and mineral content seen in the mouse skeleton may not exist in the human skeleton. This may explain the higher incidence of stress fractures among women [8] whose tibia, even after normalization for body weight and height, were significantly more narrow and had thinner cortices compared to males [2]. However, we have yet to look at intra-gender variation in material properties and damageability in fatigue loading. In conclusion, individuals with smaller tibia J_0 relative to body weight may fall outside the paradigm that bone adapts to maintain a peak in vivo strain level of 2000με. Thus, our data is consistent with the idea that individuals with tibia that have smaller J_0 relative to body weight may be experiencing higher in vivo strains [2].

Table 1. Gender differences in age, body size, and cross-sectional morphology.

Trait	*Female* (n=7)	*Male* (n=13)
Age [yr.]	37.4 ± 8.5	33.2 ± 10.5
Body Weight [kg]	79.6 ± 26.5	80.2 ± 17.6
Body Height [cm]	164.0 ± 6.5*	177.8 ± 4.0*
Tibia Length [cm]	33.5 ± 3.3*	38.3 ± 2.0*
CtAr [cm^2]	2.5 ± 0.5*	3.5 ± 0.4*
AP Width [cm]	2.6 ± 0.3*	3.1 ± 0.2*
ML Width [cm]	2.0 ± 0.2*	2.4 ± 0.2*
I_{ML} [cm^4]	0.8 ± 0.3*	1.7 ± 0.4*
J_0 [cm^4]	2.5 ± 1.0*	5.1 ± 1.1*

* Significantly different ($p < 0.01$).
Data shown as mean ± standard deviation.

Figure 1. Gender differences in tibia slenderness.



Data shown as mean ± standard deviation.

Table 2. Gender differences in mechanical properties.

	Female (n=5)	*Male* (n=5)
E [GPa]	15.8 ± 1.0	15.4 ± 1.5
Strength [N]	158.1 ± 7.4	155 ± 12.4
Total Energy [MPa]	3.5 ± 0.7	3.4 ± 1.3
Post-Yield Strain	0.027 ± 0.005	0.026 ± 0.008

Data shown as mean ± standard deviation.

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