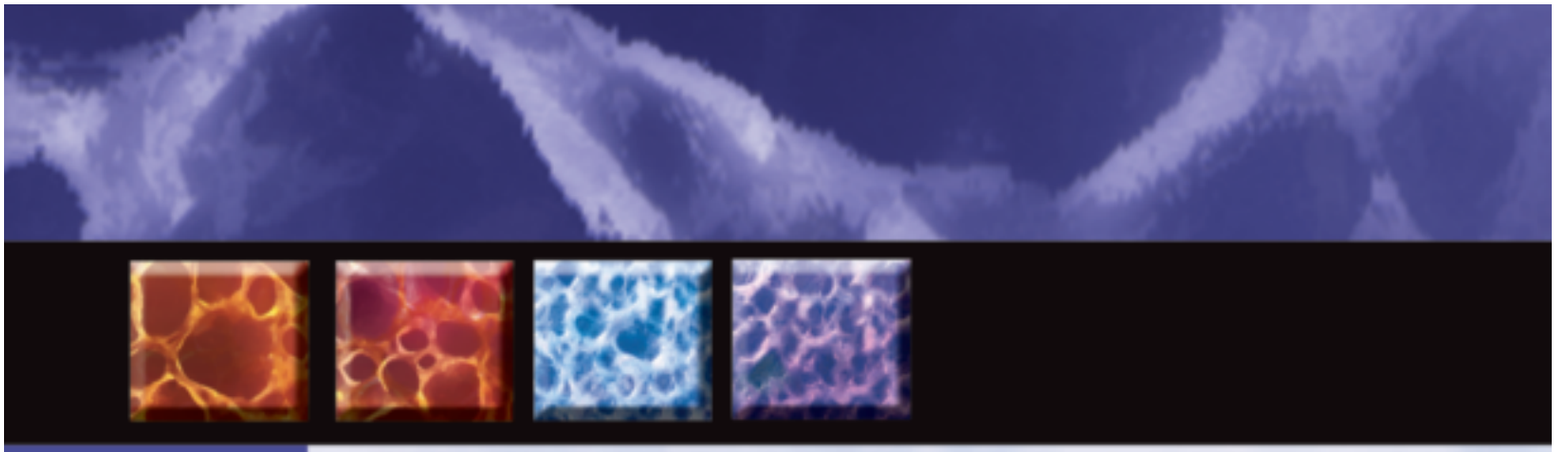

DETERMINANTS OF BONE STRENGTH AND IMPACT OF ANTIRESORPTIVE THERAPY

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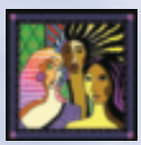

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Endocrinologists, orthopedists, primary care clinicians, geriatricians, obstetrician/gynecologists, nurse practitioners, physician assistants, and healthcare professionals with an interest in bone health.

EDUCATIONAL OBJECTIVES

Upon completion of this program, the participant should be able to:

- Relate current advances in the understanding of the composition of bone and its physiology
- Describe the components of bone strength and their link to fracture risk reduction
- Relate the current available data surrounding the impact of antiresorptive therapy on bone strength

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DETERMINANTS OF BONE STRENGTH AND IMPACT OF ANTIRESORPTIVE THERAPY

INTRODUCTION

A clear understanding of the cellular, molecular, and biomechanical mechanisms involved in bone fragility provides a basis for evaluating increased fracture risk for elderly individuals and those with osteoporosis. Such an understanding also facilitates the development of therapies that decrease fracture risk. Although structural deterioration leading to fracture is one biomechanical problem, there is no single property that describes bone strength comprehensively. Factors that may be important include the ability to resist deformation (elastic modulus or stiffness), the ability to absorb energy (toughness), accommodation of repetitive loading (fatigue strength), and inhibition of crack progression (fracture toughness). These properties permit bone to resist bending or breaking when loaded and allow flexing to absorb energy, thus supporting posture and body movements. The multiple factors contributing to bone strength derive from bone's complex geometry, the composite structure of its matrix, and cellular activity.[1,2]

Osteoporosis is a common skeletal disorder characterized by compromised bone strength and increased fracture risk.[3] The incidence of osteoporosis is high and is rising with increasing life expectancy. A 50-year-old white woman has 16% and 32% risks of hip and vertebral fractures, respectively, in her remaining lifetime.[4] It is a common misperception that osteoporosis is always the result of bone loss. Osteoporosis also may develop in individuals who did not reach optimal peak bone mass before entering adulthood.[5] All the features that determine bone quality and strength are impacted by osteoporosis and are important targets for intervention. This publication will review factors that contribute to bone strength and how they are affected by osteoporosis and antiresorptive therapy.

ASPECTS OF BONE STRENGTH

Several factors contribute to the strength of bone and its ability to resist fracture. These include bone geometry, turnover, mineralization, microarchitecture, crystal size, and collagen cross-links.

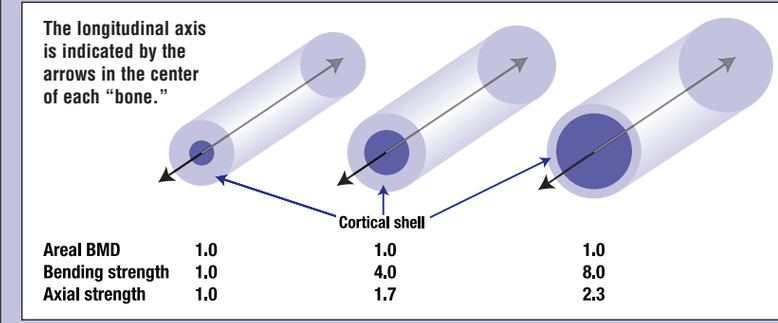
Geometry

The geometry of bone affects the distribution of mass and, consequently, the ability of bone to resist bending and torsion. The size of bone appears to have an effect on its overall fragility. In fact, bone size may affect fracture risk more than does bone mineral density (BMD). Vertebral bones have been found to be smaller in women with spinal fractures than in healthy women, and women with spinal fractures were also found to have smaller bones than were matched controls with the same areal BMD.[4]

Sex and age differences in bone strength are related to bone size—width as well as length, rather than to apparent BMD (a density calculation based on the entire bone area). Vertebral bodies in young men are both wider and taller than in age-matched women,[2] but apparent BMD is the same for young women and young men. Volumetric apparent BMD is also independent of age in children. Thus, greater bone strength in older than in younger children and in young men than in young women is provided at least in part by larger bones.[2] Bone length and width are correlated, but cortical thickness is not closely related to bone length. Both overall size and cortical thickness are related to bone strength, with diameter predicting up to 55% of the variation in bone strength.[2,6] Increased shaft diameter, even without increased BMD, places the cortical shell at a greater distance from the longitudinal axis **(Figure 1)**.[7] The increased circumference of larger bones has the effect that a given load will be more widely distributed and resistance to bending and torsion will be greater than in a smaller-diameter bone with equivalent BMD.[2]

FIGURE 1

Bone strength is determined by width and length



Areal BMD	1.0	1.0	1.0
Bending strength	1.0	4.0	8.0
Axial strength	1.0	1.7	2.3

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Turnover

Throughout life, skeletal integrity is maintained via a remodeling process involving bone resorption and formation **(Figure 2)**.[8] The basic multicellular unit that carries out bone remodeling is composed of osteoclasts and osteoblasts. At the beginning of the remodeling cycle, osteoclast precursor cells, recruited to the bone surface, fuse and begin to resorb bone matrix, creating resorption cavities. This process occurs over a period of approximately 3 weeks. The osteoclasts are then replaced by osteoblasts that secrete unmineralized matrix into the resorption cavity. This secondary phase takes place over a 3-month period.[8] As the remodeling process continues, the matrix mineralizes in a rapid phase, primary mineralization, followed by a slower phase, secondary mineralization **(Figure 3)**.[8] An efficient bone-remodeling process culminates in new bone completely filling the resorption cavity and the surface being fully restored.[4,7] The total time for the bone remodelling process is variable.

The balance of osteoclastic and osteoblastic activities within a remodeling unit is determined by multiple factors. Apoptosis, the process of regulated cell death, appears to play an important role in this balance, in part by regulating the balance of cell types in the remodeling unit. When there is a negative balance in the remodeling process, less bone is formed than is removed. The balance most likely begins to shift in young adulthood. In women, menopause has been shown to be associated with elevated turnover and increased bone loss. Acceleration of bone loss during perimenopause is independent of chronologic age and is linked to the decline in estrogen production characteristic of this transition. Reduced estrogen levels lead to a decreased lifespan of bone-forming osteoblasts and an increased lifespan of osteoclasts. At menopause, bone remodeling is doubled over that for young women, and it is tripled by 13 years postmenopause. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients.[9]

In men, aging is associated with reduced bone formation and thinning of trabeculae, but there is no midlife acceleration in remodeling or resultant enhanced loss of connectivity corresponding to that in postmenopausal women.[2,4] Despite the fact that there is no universal equivalent of menopause in men, it should be noted that androgen levels might be expected to impact this process strongly in both men and women. Androgens induce osteoblast differentiation.[10] Weinstein et al reported that loss of gonadal steroids increases osteoblast apoptosis.[11] It has been noted that testosterone deficiency in men is analogous to estrogen deficiency in women, since both decrease BMD.[12]

Increased bone turnover due to estrogen deficiency produces greater numbers of resorption cavities and deeper lacunae on the surface of cancellous bone. This results in a net loss of trabecular connectivity, deterioration in trabecular architecture, and reduced bone strength. Resorption cavities act as "stress risers" (points of weakness)[3]; an increase in the depth of these cavities may contribute more to trabecular perforation and predisposition to fracture than reduced trabecular structure and strength overall.[13] The presence of deeper resorption cavities, along with a negative balance in bone turnover, is associated with higher rates of trabecular bone loss in women with osteoporosis than in normal elderly women.[4,14] Results of recent clinical studies indicate that the level of bone remodeling activity is not only a predictor of future changes in bone mass but also a determinant of future fracture risk, independent of bone mass.[6,15]

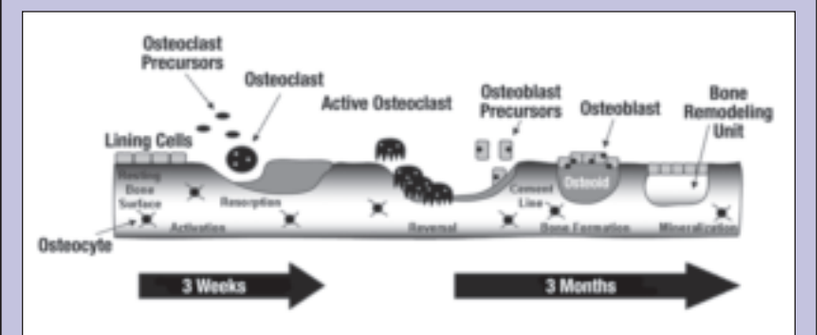
Mineralization

Bone mineralization depends on the remodeling activities of osteoclasts and osteoblasts as well as on the pace of remodeling. New bone laid down during the remodeling stage is relatively undermineralized. If remodeling is rapid, full mineralization cannot take place, because resorption resumes before this process is complete.[7] The degree of bone mineralization has an important influence on its strength. Up to a point, higher mineralization of cancellous bone results in greater stiffness and compressive strength. Further increases in mineralization (>60% ash content [the amount of solid residue remaining when bone is burned or oxidized by chemical means]) may make the bone more brittle, less able to absorb impact forces, and more susceptible to fracture.[16,17]

Conversely, decreased bone mineralization is also associated with increased fracture risk. Comparison of the degree of matrix mineralization in femoral neck biopsies taken from patients with intracapsular hip fracture versus age- and sex-matched postmortem controls indicated that the level of mineralization was lower in the fracture patients than in the controls (P=.001). The lower mineralization density in cancellous bone of patients with fractures was not regionally dependent.[17] Somewhat different results were reported by Ciarelli and colleagues, who studied human iliac cancellous bone mineralization in biopsies from healthy controls and patients with vertebral fracture. Mean levels of mineralization were not significantly different between the 2 groups. In controls, however, the mineralization estimates had a Gaussian distribution, whereas in patients with fractures, it had a bimodal distribution, with peaks at the extremes of the normal range.[18] This result suggests that the fracture population is not homogeneous and that elevated fracture risk may be correlated with either low or high bone mineralization.

FIGURE 2

Basic multicellular unit involved in normal bone remodeling



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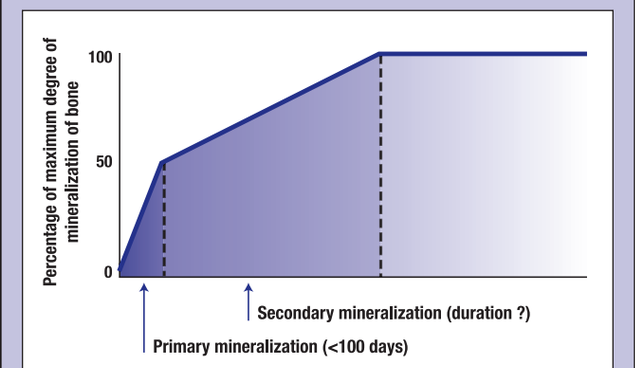
Microarchitecture

The microarchitecture of bone, comprising trabecular orientation, thickness, spacing, and extent of trabecular interconnection, as well as cortical thickness and integrity, is a particularly important determinant of

FIGURE 3

Steps in bone mineralization



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strength. Trabeculae that are widely scattered, thick, and poorly connected are less structurally competent than an equivalent amount of bone consisting of thin, numerous, and well-connected trabeculae.[4] Increased bone resorption is likely to result in an increased trabecular perforation and disconnections in the trabecular network **(Figure 4)**.[19] These changes may result in only minor changes in bone density, but they could produce major alterations in mechanical behavior.[7]

Results of one study indicated that disconnected trabeculae were not repaired by remodeling and may account for up to 21% of bone loss in older individuals.[20] The amount of trabecular bone lost with aging in men is equivalent to or only slightly smaller than that in women. In men, however, the loss is primarily due to trabecular thinning, whereas in women, bone loss occurs as trabeculae become disconnected, resulting in a more profound decrease in strength.[2] As with overall bone loss, reduced trabecular connectivity is accelerated by estrogen deficiency following ovariectomy or natural menopause.[2,6]

Changes in the mechanical behavior of bone that result from trabecular loss by thinning rather than from a reduced number of trabeculae were modeled by Silva and Gibson using finite element analysis. Loss of individual trabeculae had a greater effect on bone strength than did the same amount of bone mass reduction by trabecular thinning. A 10% loss in bone mass attributable solely to a reduction in trabecular thickness predicted a 20% loss of bone strength, and the equivalent reduction due to a decline in the number of trabeculae predicted a 63% decline in bone strength. In aged bone with both trabecular thinning and a reduced number of trabeculae, strength was only 23% of the value for intact, young adult bone.[21]

In the absence of differences in total bone volume, altered trabecular structure is associated with inferior mechanical performance. In the study by Ciarelli and colleagues, samples of cancellous bone from controls had significantly higher bone volume fraction, trabecular number, and connectivity than did samples from subjects who had sustained hip fracture. No difference was seen, however, in trabecular thickness. Control bone also was stiffer (required greater force to bend or buckle, higher modulus) and stronger (required greater force to break, higher ultimate stress resistance) than did that from patients with fractures. The patient samples had greater anisotropy (ie, contained axis of preferred orientation) in the spatial arrangement of trabeculae than did control specimens, with proportionately fewer trabecular elements transverse to the primary load axis. This suggests that for constant bone volume, reduced cross-bracing makes trabeculae susceptible to buckling along the primary load axis and less able to resist transverse loads.[22]

Crystal Size

Bone tissue is principally composed of inorganic apatite crystals that mineralize a matrix built of collagen type I fibers. In addition to the degree of mineralization, bone strength is also influenced by crystal size and orientation, the physical properties of the matrix, and the relative proportions of crystals and matrix.[4] The mineral crystals in mature bone are thin, irregularly shaped plates of hydroxyapatite; the average lengths and widths are 500 and 250 Å, respectively, and thicknesses are 20 to 30 Å. The crystals are arranged in parallel layers within and throughout the collagen fiber bundle and form a staggered array with a periodicity of 640 Å. Crystal area is associated significantly with the elastic properties of bone.[23]

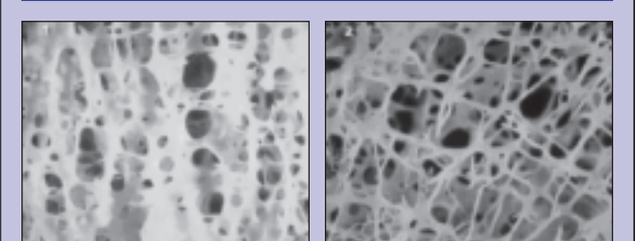
Mechanical properties of bone are related to the distribution of crystal sizes. In younger animals, which have strong bones, the mixture contains a relatively large number of small (recently formed) crystals as well as larger crystals.[24] In bones of older animals and those with osteoporosis, the crystal size distribution is narrower, and a larger proportion of crystals are large. Bones containing a preponderance of larger crystals may be more brittle (less resistant to load) and, therefore, fracture more easily.[24]

Collagen

Collagen comprises 90% of the organic portion of bone matrix, and the posttranslational modifications of this matrix impact both mechanical and structural properties.[25] A particularly distinctive characteristic of type I collagen present in mineralized tissues is the chemistry of its cross-links.[4] The more cross-links that are present in the collagen molecules, the more resistant to extraction they will be. Oxlund et al demonstrated the greater extractability of bone collagen from individuals with osteoporosis is consistent with the observation that collagen cross-links are reduced in osteoporosis. This change would lead to lower material strength of bone trabeculae in individuals with osteoporosis, even if the amount of trabecular bone were the same as in healthy controls.[26] The reduction in cross-links in osteoporotic bone is associated with altered activity pat-

FIGURE 4

Change in trabecular architecture in osteoporosis



Panel 1: normal bone **Panel 2: osteoporotic bone**

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terns of lysine hydroxylase, an enzyme that varies widely among types of collagen and governs the nature of the cross-links.[25]

ASSESSING FRACTURE RISK AND TREATMENT EFFECTS

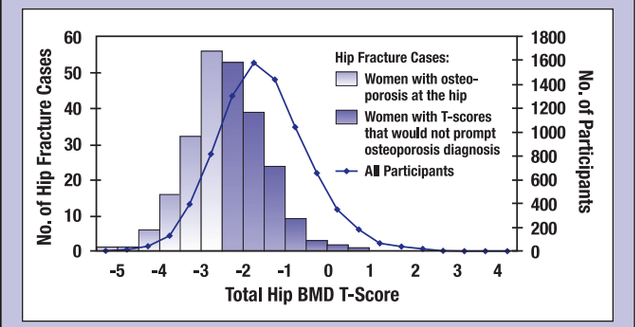
There is a strong inverse relationship between fracture risk and BMD in untreated patients. However, this metric does not account for other effects of age, such as propensity to fall. Currently, only changes in BMD and bone turnover can be measured easily and noninvasively as part of routine clinical practice. Other parameters related to bone quality require either specialized imaging or more complex assays or may only be applicable to biopsy or cadaver specimens.[3,8] Measurement of areal BMD with dual-energy X-ray absorptiometry is currently the most recognized tool for assessment of fracture risk and the efficacy of antiresorptive therapy, at least across study populations if not in individual patients.[8,27,28]

There are a number of difficulties, however, in applying standards based solely on areal BMD measurements to assess fracture risk or therapeutic outcomes. As noted above, bone quality is multifactorial, and areal BMD measurement reflects only one aspect: the quantity of mineral per unit area. It does not capture the specific attributes of 3-dimensional bone geometry, cortical and cancellous density, trabecular architecture, intrinsic properties of bone matrix, or size and orientation of hydroxyapatite crystals.[1,7] Further, it does not capture nonskeletal fracture risk factors, such as propensity to fall.[29] BMD should not be relied on as the sole indicator of present and future fracture risk. A low BMD should be regarded as only one of several factors contributing to fracture risk.[28,30,31] Fractures also occur in patients with BMD within the normal range[32] **(Figure 5)**.[33]

Increasingly, the risk of fracture is being addressed as an absolute risk comprising several factors, including age, life expectancy, and current relative risk (which takes BMD into account). Because no treatment is prescribed for life and various risk factors change as time passes, several organizations have proposed that fracture risk should be considered as absolute risk over a particular interval, eg, 10 years. Although Kanis and colleagues have proposed an algorithm for 10-year fracture probability, they also caution that the interactions of risk factors such as corticosteroid use and prior fragility fracture have yet to be explored and integrated into a final algorithm.[29]

FIGURE 5

Total hip BMD scores for women with hip fractures (n=243) and all participants (N=8065) in the Study of Osteoporotic Fractures



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Although the risk of fracture roughly doubles for every standard deviation below the mean healthy young adult BMD, the converse of this does not hold for the effects of antiresorptive treatment.[4] A meta-analysis of 11 randomized, placebo-controlled clinical trials showed that antiresorptive therapy increases bone density in both early postmenopausal women and those with established osteoporosis while reducing the rate of vertebral fracture over 2 to 3 years of treatment. These substantial reductions in nonvertebral fracture risk were evident among postmenopausal women without prevalent fractures and who had BMD values well below the World Health Organization threshold for osteoporosis.[34]

Watts and colleagues analyzed pooled data from 3 large clinical studies (Vertebral Efficacy with Risedronate Therapy North America, Multinational Clinical Studies, and the Hip Intervention Program) that all used the same methodology to assess the effect of treatment on nonvertebral fracture incidence. They found an estimated 32% reduction in nonvertebral fracture incidence with risedronate treatment versus placebo ($P<.001$) across all levels of change in BMD at both the lumbar spine and the femoral neck. Changes in lumbar spine and femoral neck BMD explained only 12% and 7%, respectively, of the reduction in nonvertebral fracture incidence.[35]

Thus, changes in BMD with antiresorptive therapies account for only a small fraction (4% to 28%) of the reduction in fracture risk, and greater increases in BMD do not necessarily predict greater decreases in fracture risk.[8,36-38] In addition, reductions in fracture risk in treated patients substantially outpace increases in BMD, suggesting other effects of antiresorptive therapy.[8,39]

Assessment of bone turnover biomarkers provides an alternate means to evaluate the effects of treatment. Indices of bone formation include bone-specific alkaline phosphates and osteocalcin. Pyridinolines, deoxypyridinolines, and type I collagen telopeptides (N-terminal telopeptide cross-linked collagen type I and C-terminal telopeptide cross-linked collagen type I) are markers of bone resorption.[5] Controversy exists regarding whether elevated levels of bone turnover markers can be used to evaluate baseline fracture risk.[3] Changes in bone turnover, however, can predict reductions in vertebral fracture risk with antiresorptive therapy, and this relationship reinforces the conclusion that the effectiveness of these agents extends to aspects of bone structure independent of BMD.[8]

Bone turnover is assessed in vivo by measuring changes in levels of markers of bone remodeling. Changes in markers may be apparent days to months before BMD changes become apparent. Results of clinical trials have been inconsistent and as a result, the use of markers in routine clinical practice remains controversial. Bauer et al performed a post hoc analysis of data from the Fracture Intervention Trial (FIT) comparing alendronate treatment with placebo. The analysis demonstrated a reduced risk of nonvertebral fracture in which the reduction size increased with pretreatment tertiles of bone turnover markers. However, reduction in vertebral fracture risk with bisphosphonate treatment has been found to be independent of pretreatment rates of bone turnover.[40]

Another FIT data analysis by Bauer and colleagues found that alendronate-treated women who achieved a 30% reduction in bone-specific

alkaline phosphatase, a marker of bone turnover, had a lower overall risk of nonvertebral fractures compared with those with reductions <30%.[41] In a risedronate treatment study, Eastell et al found that greater decreases in bone resorption markers were associated with greater decreases in both vertebral and nonvertebral fractures. They also found, as with BMD, bone turnover explains only part of the overall reduction in fracture risk. In that study, the relationship between markers of bone turnover and vertebral fracture risk was nonlinear and appears to have a "plateau effect" in that reductions in bone resorption of more than 35% to 60% yield no additional decrease in vertebral fracture risk.[42] However, neither Bauer nor Eastell found evidence of such a plateau effect for nonvertebral fracture.

Noninvasive, high-resolution imaging methods, such as magnetic resonance imaging (MRI) and computed tomography, through their ability to image the 3-dimensional microarchitecture of trabecular bone, may offer a more comprehensive assessment of bone strength. Ultrasound critical angle reflectometry may provide information regarding bone elasticity, a correlate of bone strength independent of BMD. The use of ultrasound systems for assessing the skeleton has gained momentum. The benefits of using ultrasound are not to subject patients to ionizing radiation, portability, and cost. However, whether clinical decisions should be based on ultrasound results alone or whether it should be used as a prescreening test for dual-energy X-ray absorptiometry remain to be determined. Although these advances may offer insight into the pathophysiology of bone degeneration and elucidate therapeutic mechanisms, their cost and complexity are currently prohibitive for routine use.[8] Therefore, for the present time, the most effective overall measure of the ability of any resorptive therapy to increase bone strength remains its ability to decrease the occurrence of fractures.[3]

FACTORS THAT INCREASE BONE STRENGTH AND DECREASE FRACTURE RISK

Several factors aside from pharmacologic treatment are considered important to maintain bone strength and reduce fracture risk. Physical activity, calcium, and vitamin D are essential for bone development in childhood and adolescence, and in later years may help slow the decline in bone strength. Intake of calcium and vitamin D modulates age-related increases in parathyroid hormone and bone resorption, and clinical trials have demonstrated that adequate dietary or supplemental calcium reduces the risk of vertebral and other bone fractures.[5]

Calcium and Vitamin D

A meta-analysis of 15 clinical trials that included 1806 patients indicated that calcium supplementation increases bone density and decreases fracture risk. The pooled difference in percentage change from baseline was 2.05% for total body bone density (P=.03), 1.66% for the lumbar spine at 2 years (P<.01), 1.64% for the hip (P<.01), and 1.91% for the distal radius (P=.02). These results support the conclusions that calcium supplementation has a positive effect on bone density and that it may also decrease the risk for fractures slightly.[43]

A study of 9605 community-dwelling elderly individuals demonstrated that a combination of vitamin D (400 IU/d) and calcium (1000 mg/d) supplementation may prevent fractures. Participants who took calcium and vitamin D supplements experienced an overall 16% reduction in fracture risk (P<.025).[44] In 389 men and women ≥65 years of age who also were living in the community, a slightly higher dose of vitamin D (700 IU/d) added to calcium (500 mg/d) moderately reduced bone loss in the femoral neck, spine, and total body over 3 years. This regimen also significantly reduced the incidence of nonvertebral fractures compared with placebo (P=.002).[45] Another study of 583 elderly women found that combined administration of calcium (1200 mg/d) and vitamin D (800 IU/d) reduced the risk of hip fracture, although not significantly (P=.07).[46]

However, a recent report from the Women's Health Initiative (WHI) suggests that supplementation with calcium and vitamin D offers only limited protection against fracture. Specifically, among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density. Use of these supplements, however, did not significantly reduce hip fracture. In a subgroup analysis, researchers found that women who were most compliant taking the supplements experienced a significant 29% decrease in hip fracture and women 60 years and older had a significant 21% reduction in broken hips.[47]

These results are surprising, and several possibilities have been suggested to account for them. Among the possibilities is poor compliance with study medication over the duration of follow-up (7 years).[47] Also, a recently reported meta-analysis suggests that doses of 700 to 800 IU, nearly twice the 400 IU received by the participants in the WHI trial, are necessary to prevent fractures.[48] However, 2 studies from the United Kingdom argue against the latter possibility. In these trials, supplementation with vitamin D3 (800 IU/d) and calcium (1000 mg/d), alone or in combination, did not reduce the risk of fractures in elderly patients.[49,50] Alternatively, a small but significant difference may not have been observed because a lower than expected incidence of hip fractures among the study population decreased the power of the study.[47]

Leading researchers, however, still support the use of calcium and vitamin D but suggest that the use of these supplements alone may not be adequate for protection against osteoporosis.

Physical Activity

Physical activity promotes bone acquisition and maintenance throughout adulthood. Experimental studies involving animal models of immobilization-induced bone loss demonstrate up to a 60% reduction from baseline in bone mass.[51] Prolonged immobilization of hospital patients with stroke or spinal cord injury can lead to a 7-fold increase in fracture risk, principally due to bone loss via osteoclastic resorption.[52]

Small but significant increases in BMD have been observed in postmenopausal women participating in aerobic exercise programs and resistance training.[53,54] A meta-analysis of 18 randomized, controlled trials concluded that aerobic, weight-bearing, and resistance exercise were all effective in increasing spine BMD. Walking was observed to benefit BMD of both the spine and the hip, and aerobics also increased wrist BMD.[55] It should be noted that the benefits of exercise are likely due to factors other than changes in BMD, despite the small increases in BMD resulting from participation in exercise. For example, an association between exercise and reduced falls also has been reported. In a study of women between 65 and 75 years of age, those who exercised regularly had significantly more improvement (P<.05) in dynamic balance and knee extension strength, both independent risk factors for falling, and more improvement in static balance, than did nonexercising controls.[56]

Pharmacotherapy

Several pharmacologic agents are available for treating osteoporosis, including the antiresorptive drugs and the anabolic agent teriparatide. Antiresorptive compounds, including calcitonin, estrogen, the selective estrogen receptor modulator raloxifene, and particularly the bisphosphonates alendronate, risedronate, and ibandronate, are the therapeutic agents used most often for the treatment of osteoporosis.[3] Therefore, this review focuses primarily on these agents.

Antiresorptive Therapies

The aims of antiresorptive treatment are to restore bone density by reducing turnover while maintaining the ability to repair microdamage to bone and to increase bone strength.[57] Antiresorptive therapy affects multiple aspects of bone strength. Treatment may decrease fracture risk by reducing bone turnover, stabilizing or increasing BMD, improving or preserving microarchitecture, decreasing the number or size of resorption sites, increasing mineralization, and preserving collagen cross-links.[3]

The Qualitative Evaluation of Salmon Calcitonin Therapy (QUEST) evaluated changes in trabecular microarchitecture using MRI in 91 postmenopausal women with osteoporosis.[58] Participants were randomized to receive salmon calcitonin or placebo nasal spray for 2 years. Although differences in BMD between the 2 groups were not significant, those receiving calcitonin demonstrated significant preservation of trabecular bone microarchitecture in the wrist compared with those in the placebo group, who experienced significant deterioration.[58]

These findings are consistent with the significant reduction in new vertebral fractures over 5 years observed in postmenopausal women taking salmon calcitonin nasal spray (200 IU/d) compared with those receiving placebo.[59] A significant decrease in nonvertebral fractures was observed at the 100 IU dose ($P<.05$), but the number of nonvertebral fractures that occurred in the study population was too small to make meaningful statistical analyses.[59]

Estrogens and raloxifene suppress bone remodeling to the premenopausal range in postmenopausal women.[57] Unfortunately, although the large WHI demonstrated a significant antifracture benefit, significant health risks with the administration of conjugated equine estrogen alone or in combination were documented. The discovery of these risks has led to substantial reduction in the use of hormone therapy by postmenopausal women and an increase in the use of alternative treatments.[60]

The Multiple Outcomes of Raloxifene Evaluation study evaluated the effectiveness of raloxifene in reducing vertebral fracture risk in women with osteoporosis who had been postmenopausal for at least 2 years. During 3 years' follow-up, treatment with 60 mg/day raloxifene decreased vertebral fracture risk by 30% and 50%, respectively, for women with and without prior vertebral fractures. Similar to calcitonin, raloxifene has not been shown to be effective in preventing nonvertebral fractures or hip fractures.[61]

Impact of Bisphosphonate Therapy on Aspects of Bone Strength

The factors contributing to bone strength and its ability to resist fracture, including bone geometry, turnover, mineralization, microarchitecture, crystal sizes, and collagen, are described above. The following section discusses the effects of bisphosphonate therapy on these parameters.

Geometry and Turnover. The effect, if any, of bisphosphonate therapy on bone geometry is at present uncertain.[3]

Bisphosphonates decrease bone remodeling by reducing osteoclast activity, inhibiting osteoclast recruitment, and inducing osteoclast apoptosis.[57] This allows more time for secondary mineralization to proceed to completion in the existing bone tissue.

The bisphosphonate ibandronate was approved by the U.S. Food and Drug Administration in 2005 for the treatment of osteoporosis; there are not yet extensive clinical data regarding its effects on variables related to bone strength. In one 3-year trial, however, ibandronate was observed to cause significant, sustained reductions in biochemical markers of bone turnover ($P<.0001$), improvements in spine and hip BMD, and a reduction in vertebral fracture risk.[62] In this study, no significant difference in nonvertebral fracture risk was observed. It is important to note that more data are needed to determine the effect of ibandronate on nonvertebral fractures as the study was not designed to assess this question as a primary end point.

Mineralization. Nonpharmacologic interventions have beneficial effects on bone mineralization. In the placebo arm of a 2-year study of postmenopausal women, Boivin and colleagues observed a 5% increase in mean bone mineralization ($P<.05$) among patients who received supplemental calcium and vitamin D but no active pharmacologic treatment.[63]

Bisphosphonate therapy also has significant positive effects on bone mineralization. In a small study (N=55) of postmenopausal women with osteoporosis, risedronate treatment resulted in a reduction in bone turnover. The basic bone multicellular unit balance improved in women treated with risedronate and decreased in those who received placebo.[64] Similarly, in another study, treatment of postmenopausal women with alendronate for 2 to 3 years was associated with significantly higher bone mineralization than was placebo.[65] Most recently, a 3-year trial compared risedronate and placebo in the trabecular bone of paired transiliac biopsies taken at baseline and after 3 years of treatment. Results indicated significant increases from baseline mineralization with active therapy.[16]

The possibility that long-term bisphosphonate therapy might result in hypermineralization and deleterious effects on bone strength was addressed in a longitudinal study of women who received 5 or 10 mg alendronate or placebo. Mineralization density, as assessed by quantitative backscattered electron imaging, was no higher in the patients who had received 10 years of alendronate than in those who had received only 5 years of treatment.[66] Safety data did not suggest any association between prolonged treatment and excessive fracture risk.[67]

Microarchitecture. Deterioration in the architecture of both cancellous and cortical bone is a hallmark of osteoporosis; effective treatments for this disease should, minimally, prevent further deterioration in bone microarchitecture and, optimally, improve it.[68] Evidence is accumulating to support the view that antiresorptive agents preserve architecture. Results of 2 clinical trials demonstrated that administration of alendronate to postmenopausal women can significantly decrease the development of cortical porosity and increase the degree and uniformity of bone matrix mineralization.[69,70] Similarly, assessment of iliac crest bone biopsies from patients before and after administration of risedronate indicated that rise-

dronate can prevent deterioration of trabecular microarchitecture in early postmenopausal women[71] and in women with osteoporosis.[72]

Crystal Size. There are no clinical studies that have evaluated the effects of bisphosphonate therapy on bone crystal size, and studies using dogs have indicated that 1 year of treatment with either alendronate or risedronate has no effect on crystal size.[73]

Collagen. At present, there is no information about the impact of antiresorptive agents on collagen. Results from a study by Paschalis et al demonstrated that estrogen therapy may have an effect on the mineral crystallinity and collagen cross-link ratio properties of bone tissues.[74]

IMPLICATIONS FOR CLINICAL PRACTICE

The effects of therapies for osteoporosis on BMD are not necessarily predictive of their effects on fracture risk for patients. Decreased fracture risk in those receiving antiresorptive therapy may occur without a measurable effect of treatment on BMD. At present the "gold standard" for assessing the benefits of antiresorptive therapy should be the ability of treatment to decrease fracture risk rather than any surrogate marker or combination of markers.

To date, alendronate, risedronate, and estrogen are the only antiresorptive agents proven to reduce nonvertebral (including hip) fractures as well as vertebral fractures **(Table 1)**.[59,75-80] Bisphosphonates are generally well tolerated, although they have the potential for gastrointestinal complications.[81] In alendronate postmarketing surveillance, the following GI adverse reactions were reported: esophagitis, esophageal erosion/ulcer, rare esophageal stricture or perforation, and oropharyngeal ulceration.[82,83] This potential, however, appears low. In reported cases, it was found that many patients were not following proper dosing instructions, which underscores the importance of advising patients to review package inserts carefully.[84]

In rare circumstances, osteonecrosis of the jaw has been reported in patients using bisphosphonates. However, in over 90% of the reported cases, the patients who had developed it had cancer and were receiving repeated, large doses of the agents intravenously.[85] Furthermore, many of these patients were also receiving chemotherapy and corticosteroids, agents that are known to interfere with healing. Although the risk appears to be rare, patients who may require oral surgery or extensive dental procedures may want to stop taking a bisphosphonate prior to the procedure and not restart it until healing has occurred. The recommended dosage for treatment of osteoporosis with oral alendronate is 70 mg once a week or 10 mg daily.[84] The recommended dosing for oral risedronate is 35 mg once a week or 5 mg/day.[86]

TABLE 1

Effects of Therapy on Hip and Other Nonvertebral Fractures[59,75-80]

	Significant Reduction in Fracture Risk	
Agent	**Nonvertebral Fractures**	**Hip Fractures**
Calcitonin	–	–
Raloxifene	–	–
Ibandronate	–	–
Alendronate	✔	✔
Risedronate	✔	✔

While the Women's Health Initiative trials showed significant reduction in the risk of hip fractures with hormonal therapy ($P<.05$),[87] estrogen is no longer recommended for treatment of osteoporosis because it was associated with increased risk of ischemic events in older patients and invasive breast cancer.[81] Estrogen is approved for the prevention of osteoporosis in postmenopausal women and is available in numerous formulations. As is the case for any therapy, potential risks must always be considered in relation to potential benefits.

Research is on-going to determine if the use of combination therapy, such as bisphosphonates and parathyroid hormone, will yield additional benefit in bone remodeling. The results to date are conflicting.[88]

CONCLUSIONS

Bone fragility can be defined by biomechanical parameters, including ultimate force (a measure of strength), ultimate displacement (reciprocal of brittleness), and work to failure (energy absorption). These properties of bone are influenced by a number of variables, including bone size, shape, architecture, and turnover. Although measurements of BMD should be used as part of an assessment of bone fragility, they are not sufficient on their own for determining fracture risk or for evaluating the effects of therapy on the multiple parameters that comprise that quality.

Antiresorptive therapies, such as bisphosphonate treatments, have multiple beneficial effects on bone that act together to decrease the risk of fractures. These agents reduce bone turnover and increase mineralization, preserve microarchitecture, and may decrease bone fragility, even in the absence of marked effects on BMD. This may explain why therapies for osteoporosis can affect fracture incidence disproportionately to changes in BMD and why reductions in fracture risk for patients receiving antiresorptive therapy occur prior to significant increases in BMD. All of this evidence supports the view that at present, the "gold standard" for assessing the benefits of antiresorptive therapy should be the ability of treatment to decrease fracture risk, rather than any surrogate marker or combination of markers.

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DETERMINANTS OF BONE STRENGTH AND IMPACT OF ANTIRESORPTIVE THERAPY

Continuing Education Credit Information and Posttest Assessment

Determinants of Bone Strength and Impact of Antiresorptive Therapy is a self-study newsletter designed for clinicians who manage/treat patients at risk for osteoporosis. Continuing medical education (CME) credit will be awarded to physicians who successfully complete this activity. Participation should take approximately 1.5 hours.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the ACCME through the joint sponsorship of the University of Cincinnati College of Medicine and IMED Communications. The University of Cincinnati College of Medicine is accredited by ACCME to sponsor continuing medical education for physicians.

Physicians

The University of Cincinnati College of Medicine designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurse Practitioners

This program has been approved for 1.5 contact hours of continuing education by the American Academy of Nurse Practitioners. Program ID: 0606216.

Physician Assistants

This program has been reviewed and is approved for a maximum of 1.5 hours of AAPA Category 1 (Preapproved) CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of June 30, 2006. Participants may submit the posttest at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

To complete this activity and receive credit, the participant should:

- Read the learning objectives
- Read and review the newsletter
- Complete the posttest and evaluation form and mail it to:
  The University of Cincinnati
  Office of CME, PO Box 670567
  Cincinnati, OH 45267-0567

  Or fax to: 513-558-1708

  Or submit via the Web at: http://webcentral.uc.edu/cme/

Participants must receive a score of 70% or better to receive credit. Be sure to submit the posttest and evaluation form on or before June 30, 2007. After that date the activity will no longer be designated for credit.

Certificates will be mailed within 4 to 6 weeks. It is recommended that participants keep a copy of their completed materials until they received their certificate.

Posttest Assessment (Please record your answers in the space provided)

1. Which of the following are important components of bone strength?
   a. Ability to resist deformation
   b. Ability to absorb energy
   c. Accommodation of repetitive loading
   d. All of the above
2. Greater bone strength in older than in younger children and in young men than in young women is primarily the result of which of the following?
   a. Higher trabecular connectivity
   b. Higher BMD
   c. Lower porosity
   d. Larger bone size
3. Which of the following is a reason more rapid remodeling may lead to reduced mineralization of bone?
   a. Reduced collagen deposition
   b. Decreased time for completion of mineralization in each remodeling cycle
   c. Requirement for larger crystal size
   d. Decreased mobilization of calcium from the extracellular fluid
4. Which of the following contribute(s) to the microarchitecture of bone and thus bone strength?
   a. Trabecular orientation
   b. Trabecular thickness and spacing
   c. Extent of trabecular interconnection
   d. All of the above
5. A 10% loss in bone mass attributable solely to a reduction in the number of trabeculae has been predicted to result in a __% decline in bone strength.
   a. 15 b. 30 c. 45 d. 63
6. Bones with a preponderance of larger crystals may have reduced resistance to load.
   a. True b. False
7. A 50-year-old white woman has a __% risk of osteoporotic hip fracture in her remaining lifetime.
   a. 4 b. 8 c. 16 d. 32
8. Which of the following results supports the view that BMD should not be used alone for prediction of fracture risk?
   a. BMD is difficult to determine in clinical practice
   b. BMD measurements have poor reproducibility
   c. BMD is substantially inferior to ultrasound for prediction of fractures
   d. Fractures are common in individuals with BMD above the "osteoporosis" range
9. Which of the following biomarkers is an index of bone formation?
   a. Bone-specific alkaline phosphatase
   b. Deoxypyridinolines
   c. N-terminal telopeptide cross-linked collagen type I
   d. C-terminal telopeptide cross-linked collagen type I
10. Antiresorptive therapy may improve bone strength by which of the following mechanisms?
    a. Increasing bone turnover
    b. Decreasing trabecular density
    c. Reducing the number of resorption sites
    d. Decreasing collagen cross-links

Posttest Answers **Expiration Date: June 30, 2007**

1.____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____

Program Evaluation

Please circle the letter that best reflects your opinion of the statements below, using the following scale:

a. Strongly disagree b. Disagree c. Agree d. Strongly agree e. Does not apply

1. The program objectives were fully met.	a	b	c	d	e
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.	a	b	c	d	e
3. The educational activity has enhanced my professional effectiveness and improved my ability to:					
a. Treat/manage patients	a	b	c	d	e
b. Communicate with patients	a	b	c	d	e
c. Manage my medical practice	a	b	c	d	e
4. The information presented was without promotional or commercial bias.	a	b	c	d	e
5. The program level was appropriate.	a	b	c	d	e
6. I intend to change my clinical practice as a result of the information presented in this CME program.	a	b	c	d	e

Please explain: _____

_____

_____

7. Suggestions regarding this material, or recommendations for future presentations:

_____

_____

_____

Registration Form

Name (please print) _____

Degree _____ Specialty _____

Address _____

City _____ State _____ ZIP_____

E-mail _____

Phone _____ Fax _____

I verify that I have completed this CME activity (signature)

_____

Actual time spent on the activity (up to 1.5 hours) _____

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IMPORTANT CME MATERIALS ENCLOSED

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Additional CME Opportunities are available at the website of
The Office on Women's Health of the US Department of Health and Human Services at:
http://www.womenshealth.gov/HealthPro/eduandasso/contedu.cfm