# Skeletal fragility definition

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**Summary**

**Strategies to reduce fracture risk must be based on the understanding of the mechanisms that underline the increased incidence of fractures with age and with bone diseases that reduce bone stock. There is evidence that in addition to bone minerals density, other factors influence bone strength. This study reviews the biomechanical aspects of age-related fractures, including the interacting roles of traumatic loading and bone strength, and the factors that determine the resistances of bones to fracture. Although low bone mineral density (BMD) is among the strongest risk factors for fracture, a number of clinical studies have demonstrated the limitations of bone mineral density measurements in assessing fracture risk and monitoring the response to therapy. These observations have brought renewed attention to the broader array of factors that influence skeletal fragility, including bone size, shape, micro-architecture and bone quality. Bone fragility can be defined by biomechanical parameters, including ultimate force, ultimate displacement and energy absorption. Many osteoporosis treatments build bone mass but also change tissue quality. Antiresorptive therapies, such as bisphosphonates, substantially reduce bone turnover, impairing microdamage repair and causing increased bone mineralization, which can increase the brittleness of bone. Anabolic therapies, such as teriparatide, increase bone turnover and porosity, which offset some of the positive effects on bone strength. Osteoporosis therapies may also affect bone architecture by causing the redistribution of bone structure. Restructuring of bone during treatment may change bone fragility, even in the absence of drug effects on BMD.**

*KEY WORDS: bone; osteoporosis fracture.*

## Bone Mineral Density and Skeletal Fragility

Although low Bone Mineral Density (BMD) is among the strongest risk factors for fracture, many clinical studies (1-4) have demonstrated the limitations of bone mineral density measurements in assessing fracture risk and monitoring the response to therapy. These observations have brought attention to the broader array of other factors that may influence skeletal fragility, including bone size, shape, and microarchitecture. The foregoing has led to attempts at understanding the concept of bone quality. It is difficult to define and includes ideas such as toughness, strength, resistance to failure, load-bearing and capacity. Emerging definitions include a number of factors in a single common notion that includes bone intrinsic material properties, bone geometry, bone microdamage, as well as bone mass. The function of bone remodeling in skeletal homeostasis is to remove damaged bone tissue and replace it with healthy intact bone distributed appropriate to the loads placed on it. Any remodeling in excess of that required for these purposes can only weaken the skeleton. Thus, we have come to realize that suppression of remodeling by agents such as antiresorptive or estrogen-like drugs are effective and safe because they reduce excessive remodeling to levels approximating optimal remodeling rates needed for repair bone tissue.

Osteoporosis is defined as *"a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture"*. This definition underscores the role of bone strength and implies that understanding bone strength is the key to understanding fracture risk. Whereas low BMD is among the strongest risk factors for fracture, it was demonstrated the limitations of BMD measurements in assessing fracture risk and monitoring the response to therapy (5,6). These observation have brought renewed attention to the broader array of factors that influence bone strength and fracture risk. From a mechanical perspective, fractures represent a structural failure of the bone whereby the forces applied to the bone exceed its load-bearing capacity. The forces applied to the bone will depend on the specific activity and will vary with the rate and direction of the applied loads. The ability of a bone to resist fracture depends on the amount of bone, the spatial distribution of the bone mass, and the intrinsic properties of the materials that form the bone. Bone strength reflects the integration of two main features: bone density and bone quality.

Bone density is expressed as grams of mineral per area or volume, and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover and mineralization.

Osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made. The mechanism whereby excessive remodeling results in a fragile skeleton has not been completely worked out but we may hypothesize several mechanisms. First, remodeling always weakens the skeleton, at least transiently. However, when appropriate to the repair of microdamage, the transient weakness caused by a remodeling site is compensated by the improvement in strength from the removal and replacement of damaged bone tissue. However, remodeling in excess of that need for maintenance and repair can only contribute weakness to the skeleton. Excess remodeling causes loss of trabecular connectivity and loss of trabecular elements. Further, remodeling sites themselves, Howship's lacunae, weaken trabeculae under load. Finally, the excessive remodeling results in many areas of under-mineralized bone matrix. These areas will not bear load because their stress is shielded by those areas of the skeleton that are stiffer because their os-

teoid is better mineralized. Thus, there are several mechanisms whereby excessive remodeling weakens the skeleton.
Osteoporosis drugs generally fall into two broad categories: bone resorption inhibitors and stimulators of bone formation. Each of these strategies has produced treatments that reduce fracture risk substantially. However, these drugs are not completely free of potentially negative effects on bone tissue. Tissue fragility can be characterized by measurements of intrinsic biomechanical properties; some drugs may affect bone tissue properties. Strong inhibitors of bone resorption, like bisphosphonates, can reduce bone turnover by 80-90%, causing a gain in bone mineral density. Due to reduced turnover, the mean tissue age of the bone is increased with bisphosphonate treatment as is bone mineralization. Increased mineralization affects a number of biomechanical properties of bone: stiffness is increased, while ultimate displacement is decreased. Consequently, increasing mineralization improves the structural rigidity of bone while at the same time making the tissue more brittle. Work to failure tends to decrease as bone becomes more highly mineralized, suggesting that hypermineralized bone is more fragile. Another potential side effect of bisphosphonates is impairment of microdamage repair. Bone remodeling helps to maintain tissue integrity by selectively removing damaged bone and replacing it with new bone. This repair mechanism is blunted by bisphosphonates. At present, there is no evidence that microdamage accumulation occurs during treatment with clinical doses of bisphosphonates. Teriparatide affects bone tissue much differently than bisphosphonates. Teriparatide increases bone turnover substantially, effectively reducing mean tissue age, thus decreasing tissue mineralization, and increasing cortical bone porosity. Lowering mineralization weakens bone tissue and increasing porosity further weakens bone. Increases in porosity cause disproportionate decreases in bone strength, small increases in porosity can decrease bone strength substantially. However, most of this increase in porosity occurred at the endocortical surface of bone. This surface carries the smallest mechanical stress when subjected to bending. Porosity on the periosteal surface, where mechanical stress is highest, was increased only slightly.

## Bone Resistance

As a long bone grows, the mass of bone inside the periosteal envelope is fashioned into a cortex with a thickness determined by the growth of the endocortical surface relative to the periosteal surface. The accrual of mass happens in proportion to the enlarging whole bone, so the volumetric BMD is constant or increases slightly during growth and is no different in either sex. Loss of bone mineral occurs out of proportion to the loss of bone mass because the high remodelling rate results in a fall in bone mineral content of the existing bone tissue; old bone that has undergone more complete secondary mineralization is removed and replaced by younger bone that has undergone primary, but less complete secondary, mineralization. The bone densitometer measures bone mineral mass and cannot distinguish whether the fall in density is due to proportionate loss of bone mass with its mineral, due to degenerative balance, or whether it is the result of higher remodelling replacing more mineralized old bone with less mineralized young bone. The biomechanical importance of the different mineral content is uncertain, but bone that is too highly mineralized could become more brittle, and bone that is incompletely mineralized could lose its stiffness. As endosteal bone loss proceeds as a person ages, periosteal apposition takes place, increasing the cross sectional area of bone and resulting in the dispersion of the load on a larger area, reducing the load/unit area on the bone. Furthermore, periosteal apposition reduces the net loss of bone from the whole bone. Consequently, the fall in volumetric BMD of the whole bone is less than would have occurred had there been no periosteal apposition. Cortical bone loss is less in men than in women because periosteal bone formation is greater, not because endosteal resorption is greater in women than men. On the contrary, the absolute amount of bone lost from the endosteal surface is greater in men than in women because they have a larger skeleton. Thus, bone loss reflects the net result of all the periosteal bone formed during ageing minus all the bone irreversibly removed from the endosteal surface, which is itself a function of the size of the negative bone balance in each basic multicellular unit and the number of units (7-9).
Findings of studies in twins and family members have established that differences in traits such as bone size, shape, and BMD between individuals of the same age are largely attributable to differences in their genes, not differences in environmental exposures. Progress in the study of the genetics of bone fragility is slow because the phenotype is poorly defined; fractures are too rare to allow detection of an association with genes that regulate a structural determinant of bone strength. BMD, the two dimensional estimate of mineral mass, is too ambiguous a phenotype to allow detection of the cell-specific and surface-specific genetic determinants of the above complex traits (10).

## Basis of Bone Fragility

More women sustain fractures than men because they start with a smaller skeleton at peak and trabecular bone loss proceeds by more architectural disruption; women have a skeleton that adapts less well to aging by periosteal apposition, periosteal bone formation increases the cross sectional area of the bone less, so that the load per unit area on the bone decreases and bone loss is offset less in women. Consequently, a higher proportion of elderly women than elderly men have bone size and volumetric BMD reduced to below a critical level at which the loads on the bone are near to, or greater than, the bone's structural ability to tolerate them (11,12). The structural differences responsible for higher fracture rates in women than in men could be used as a model to explain the structural basis of differences in fracture rates within a sex. The reduced vertebral size in women and men with spinal fractures, compared with age-matched and sex-matched controls, is growth related and could be partly the result of reduced age-related periosteal apposition. The reduced volumetric BMD in women and men relative to controls is probably the result of attainment of a lower peak cortical thickness, and fewer and thinner trabeculae. Bone loss during ageing and after the menopause in women, or hypogonadism in men, reduces the already reduced peak volumetric BMD, and produces architectural damage that predisposes to vertebral fracture with minimum trauma. Women and men with normal or larger peak bone size might have a skeleton that better tolerates bone loss until old age, when continued cortical bone loss thins the cortex and increases intracortical porosity, further reducing bone strength at a time when increased prevalence of muscle weakness, reduced coordination, and propensity to fall predisposes to hip fractures. Whether women and men who sustain fractures have excessive or more rapid bone loss than the rest of the population is not clear (13,14). The notion of excess bone loss needs evidence of greater net resorption in individuals with than without fractures. This idea requires evidence of a more negative bone balance in the basic multicellular units of patients, due to a greater volume of bone resorbed in each unit, a lower volume of bone formed in each unit, or both. Alternatively, if basic multicellular unit imbalance is negative, but no more negative in patients than in controls, greater bone loss requires evidence of a higher remodelling rate in patients with fractures than in controls. Histomorphometric and biochemical evidence for higher resorption in the basic multicellular unit, lower bone formation in the unit, or higher remodelling rate in fracture cases than in controls is conflicting (15,16). Although a higher group mean for indices of resorption, or a lower group mean for indices of bone formation, is reported in people with frac-

tures, the range of the data is more impressive than the difference in the means, suggesting reduced volumetric BMD in patients is likely to have a heterogenous cause.

## Conclusions

While we have advanced our thinking regarding skeletal fragility by understanding that the measurements of bone density explain less than half of the determination of risk of fracture we must devise measures that take into account defective bone quality. The problem of measuring bone quality has become even more important given that we desperately need clinical surrogates of fracture in order to test and develop new drugs that reduce the risk of fracture in patients with osteoporosis. Bone quality can be understood as an umbrella term that describes the set of characteristics that influence bone strength and explains the interrelationships of these characteristics. Bone strength depends on the structural and material properties of bone, both of which are influenced by the rate of bone turnover. Not all determinants of bone strength are well represented by a BMD measurement. Greater understanding of the concept of bone quality will ultimately help improve the assessment of fracture risk and monitoring of patients receiving treatment for osteoporosis. Bone is a composite material, and the integrity of each component contributes to bone strength. From the size of bones to the levels of collagen molecules and mineral crystals, any modification of these determinants influences bone strength (17,18). The ability of bone to resist failure depends on the ability of its material and structural properties to absorb energy imposed during loading and to release it when unloaded. The relative contribution of each determinant in the occurrence of fractures remains unknown, but the study of disease provides avenues to identify and explore the pathogenesis of these defects. The level of the bone remodelling influences tissue mineral density and collagen cross-linking, producing structural abnormalities such as stress risers, whereas an imbalance in the volume of bone resorbed and formed compromises the structure of bone.
A better knowledge of the relative importance of the different determinants of the bone "quality" in the determination of skeletal strength and fragility will improve the understanding of the pathogenesis of bone fragility in metabolic bone diseases.

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