Low Bone Mass May Not Be the Only Cause of Skeletal Fragility in Osteoporosis (42919)

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The Paradigm

Postmenopausal osteoporosis has emerged as one of the most important health problems of our time (1). It occurs among the middle-aged and elderly and is manifest as fractures of all parts of the skeleton, particularly the spine, hip, and wrist. Clinicians and investigators have attributed the excessive skeletal fragility in postmenopausal osteoporosis largely to reduced bone mass. (Implicitly, this means bone loss since these patients do not begin fracturing until middle age or late in life.) Certainly, it is reasonable and logical to assume that the mechanical strength of a structural material such as the skeleton would depend on the mass of that material present. And there is a considerable body of empiric data which supports this conclusion (2–4).

Accordingly, research in this area has been focused on an array of phenomena related to achieving and maintaining bone mass such as the nature of change in bone mass with age, the mechanism of bone loss with estrogen deprivation, the effect of immobilization, the action of various growth stimulators in the bone microenvironment, the mechanism of coupling of resorption and formation, the effect of exercise and physical activity on bone mass, and others. It is clear that excess skeletal fragility has been viewed as tantamount to insufficient bone mass. Almost all of the attempts at prevention and treatment of postmenopausal osteoporosis have been directed at achieving greater peak skeletal mass, preventing skeletal loss, and stimulating the production of new bone tissue.

Measurements of Bone Mass

Since the early 1970s accurate and precise measurements of bone mass have been available (5–7). The technology has developed to include measurements of the extremities, the spine, the entire skeleton, or just about any region of interest. The QCT measurement of the spine has been a particularly important advance because it can give true bone density measurements.

Early on, investigators began to notice that there was considerable overlap between the bone mass measured in normals and in patients using any of these techniques (8). Many have thought this is due to the fact that any cross-sectional survey of normals (who are not fracturing) would contain members who are actually fracture patients who have not yet fallen or suffered other sufficient trauma to result in a "clinical" fracture. Thus, they are about to be patients some time in the future and if we could only identify them, they would fall in the group with low bone mass.

However, this view has become a bit tenuous for several reasons. For one thing, the overlap has been too great. Clinicians have observed many subjects with bone mass measurements well above average who fracture with apparently slight trauma, while, on the other hand, they have also observed many subjects with very low bone mass who have survived rather severe trauma without fracture. Frost (personal communication) has pointed out that the bone mass present in the usual osteoporotic patient should be sufficient for structural support given the material properties of bone tissue and the stress of mechanical support.

These facts have led a number of investigators to search for factors other than low bone mass to explain the presence of abnormal susceptibility to fracture among the elderly. This communication summarizes one area of this search, namely, the area of bone histomorphometry, and the analysis is limited to trabecular bone although changes in microstructure may also affect the mechanical strength of cortical bone as well. Of course, this will not exhaust the number of other possible explanations for the overlap in bone mass between patients with osteoporosis and matched normals.

Microarchitecture and Mechanical Strength

Trabecular bone such as found in the bodies of the vertebrae or the ilium is made up of a complex structure of curved plates and bars (19). This arrangement permits maximum strength per unit of tissue because of the extensive connectivity between the trabecular elements. It can be thought of as a system where the vertical compressive forces fall on bars that are connected with one another by a series of plates which inhibit buckling. The bars then can sustain considerable compressive force without failing.

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Parfitt et al. (9) first pointed out that one of the age-related changes that accompanied bone loss was a loss of trabecular elements. In transiliac biopsies from normal subjects, they found that trabecular bone volume decreased with age but this loss of bone was not due to global thinning of trabeculae. Instead, there was loss of trabeculae with increase in the space between them and reduction in their number. They pointed out that this change in microstructure would be expected to reduce the mechanical strength of the trabecular skeleton out of proportion to the loss of tissue. Others have made similar observations (10–12) and have also reported that patients with osteoporosis characterized by vertebral fractures exhibit findings similar to the age-related ones, only worse. In sections from transilial biopsies from normals and osteoporosis patients examined in the author's laboratory, perforations of trabecular plates surrounded by osteoclasts have been seen in serial sections. This suggests that a resorption cavity has perforated a plate and resorption continues around its edges.

One implication from this is that osteoclast function is at fault for the bone loss by erosion of excessively deep cavities such that trabecular plates are perforated. This may even be an event predictable by the chances that resorption cavities appear simultaneously on opposite surfaces of a plate, with perforation occurring when they meet.

However, the most important implication of this is that the mechanical strength of the skeleton could be reduced out of proportion to the amount of bone lost. The trabecular bars have lost some of their connections to one another, and thus have become more susceptible to buckling and collapse when subjected to the compressive force of weight bearing.

Relevance to the Spine

These findings in the ilium needed to be corroborated in the vertebral body, because unlike the vertebrae, the ilium does not support a major portion of the compressive forces applied to the skeleton. This was done by Mosekilde (13) who examined vertical cylinders taken from the centrum of L3 in "normals" (autopsies) who ranged in age from 15 to 87 years. He found a significant age-related decrease in the mean horizontal trabecular thickness, whereas the mean thickness of the vertical trabeculae was unchanged with age. Furthermore, he found a significant increase in the average distance between both the horizontal and vertical trabeculae with age. This work confirmed that the architectural changes reported in transilial biopsy specimens are present in the vertebral body as well.

The foregoing discussion has provided a mechanism to explain skeletal fragility out of proportion to the amount of bone lost. One could speculate that some of the overlap between bone mass in controls and patients who are fracturing could be due to preservation of trabecular connectivity in some who have "low" bone mass but are not fracturing.

Bone "Quality"

The classical teaching has been that osteoporosis is characterized by reduced quantity of bone tissue, but the remaining bone is normal. Indeed, the static histology of trabecular or cortical bone in patients with osteoporosis looks entirely normal though reduced in amount. However, two abnormalities have been described as features of aging and osteoporosis that could affect the quality of the bone as a structural material independently of reduced bone mass even though the microscopic appearance is normal. One was described by Frost (14) characterized by prolonged remodeling periods, and the other first by Courpron *et al.* (15) and subsequently by others (16) characterized by reduced wall thickness of completed osteons coupled with maintenance of trabecular thickness. The mechanism for reduction of mechanical strength in both cases is reduced efficiency in the repair of microdamage.

"Off-Time." Small structural defects appear and accumulate in bone as they do in any structural material when it is subjected to repeated submaximal strain. These defects would result in mechanical failure (fracture) unless there was a mechanism for self-repair. The remodeling system constitutes the repair mechanism for eliminating microdamage in bone tissue (14).

This system appears to lose efficiency with age and in osteoporosis. Frost (14) first noted that bone biopsies from patients with osteoporosis demonstrated an excess of remodeling sites that were abnormal because of the absence of tetracycline labeling. This had to mean that bone formation paused during the formation cycle, but subsequently resumed. Resumption had to occur because there was no excess accumulation of forming sites, i.e., the fraction of surface occupied by forming sites was not increased. Because of this "Off-time," the period of bone formation at the remodeling site was prolonged to extreme lengths, in some cases more than 1 year. Bone turnover in these patients was markedly slowed. He postulated that this could result in inefficient repair of microdamage, allowing it to accumulate to a greater degree than normal. This in turn could lead to excessive fragility, out of proportion to the degree of bone loss.

This hypothesis for skeletal fragility needs more support from empiric data. The presence of Off-time has been seen by several investigators (17, 18) and few doubt its presence. However, to prove that this compromises skeletal strength requires more experimentation which with present methods is difficult.

Unremodeled Bone Tissue. The mean wall thickness measurement is the average distance between the resting trabecular surface and the cement line. When coupled with the appositional rate, it has been used

mostly to estimate the length of time required to complete formation at the remodeling site. However, it has also been used to evaluate efficiency of bone remodeling when coupled with measurements of trabecular thickness. Courpron *et al.* (15) first demonstrated that one of the age-related changes in bone histology in normals (autopsy subjects) is reduction in mean wall thickness while trabecular thickness remains unchanged. More recently, this has been demonstrated in biopsies from normal living volunteers (12) and in patients with osteoporosis (16). In patients, the reduction in mean wall thickness is more pronounced than in the age-matched normals.

The combination of reduced mean wall thickness and normal trabecular thickness means that the unremodeled central part of the trabeculum constitutes a greater fraction of the bone tissue. This greater accumulation of unremodeled bone would also lead to a greater accumulation of unrepaired microdamage and reduced mechanical strength. Again, the comparison between living normals and patients with osteoporosis in the author's laboratory (16) has shown that patients have an exaggeration of this increase in the fraction of the unremodeled bone in the central parts of the trabeculae.

Summary

Skeletal fragility in postmenopausal osteoporosis is not due solely to reduction in bone mass. This fact explains some of the overlap in bone mineral measurements observed between patients who are fracturing and age- and sex-matched normals who are not. Changes in skeletal architecture and bone remodeling occur with age which can account for some of the fragility. These changes are exaggerated in patients with postmenopausal osteoporosis who are suffering spine fractures.

Three abnormalities have been described by histomorphometric methods which can account for skeletal fragility out of proportion to the degree of bone loss. They are: (i) loss of trabecular connectivity such that vertical weight-bearing bars lose their cross-attachments with each other, thus becoming susceptible to buckling; (ii) inefficient and prolonged microdamage repair due to periods of pause in the formation phase of remodeling; and (iii) accumulation of unrepaired microdamage in unremodeled bone tissue in the central part of trabeculae due to reduced osteon wall thickness coupled with maintenance of trabecular thickness. Recognition of these abnormalities should broaden our approach to the study of skeletal fragility in the syndrome of postmenopausal osteoporosis.

These concepts borrow from the ideas of several investigators: Frost, Heaney, Parfitt, Kimmel, and others. The author acknowledges their seminal contributions with considerable gratitude.

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