

# Bone fragility: current reviews and clinical features

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## Summary

Bone strength is determined by a number of important factors, including bone mass and bone shape. A reduction in bone strength is clearly related to fracture. Bone fragility results from a reduction in bone mass and density. If there is a reduction in the connectivity of bone and impact from a mechanical load occurs, bone will fracture. Rather than considering bone fragility as being the result of a reduced amount of bone, we recognize that bone fragility is the result of changes in the material and structural properties of bone. A better understanding of the contribution of each component of the material composition and structure, and how these interact to maintain whole bone strength is obtained by the study of metabolic bone diseases. Disorders of collagen, of mineral content composition and distribution, disorders of remodeling and other diseases produce abnormalities in the material composition and structure that lead to bone fragility.

**KEY WORDS:** bone, fragility, fracture.

## Introduction

Bone must be able to resist deformation so that loading is possible. If bone is not sufficiently stiff for the loads imposed on it, it will deform beyond its peak strain and crack. Bone must also be flexible, able to deform to allow energy absorption during impact loading. If bone is not sufficiently flexible the energy imposed on it will be released in the only way possible by cracking because it cannot deform "enough" to absorb it when loaded. Bone must also be light to allow movement. These seemingly contradictory properties, stiffness yet flexibility, and lightness yet strength, are determined by bone's material composition and how this material is fashioned into a three-dimensional structure with geometric properties that confer structural strength. A change in the material or structural components of

bone or the inability of bone modelling and remodelling to adapt these material and structural properties to the prevailing loads produce bone fragility.

## The anisotropy of bone: collagen and mineral components

Bone is a specialized connective tissue composed of an organic matrix of type I collagen. It is specialized in that it is mineralized with an inorganic phase comprising calcium hydroxyapatite-like crystals. The organic matrix provides flexibility, whereas increasing amounts of mineral confer increasing degrees of material stiffness (1). In bone tissue, collagen fibrils are stiffened by integration of the mineral phase. Collagen molecules are staggered within the fibers to provide spaces for nucleation of the calcium apatite crystals. The presence of the organic phase increases bone strength. The orientation of collagen fibers is important in determining the mechanical properties. Furthermore, the orientation of collagen fibers is related to the direction of load. The strength of bone is higher in the direction of physiological loading that corresponds to the orientation of osteons in the cortical bone (2) (Figs. 1a,b).

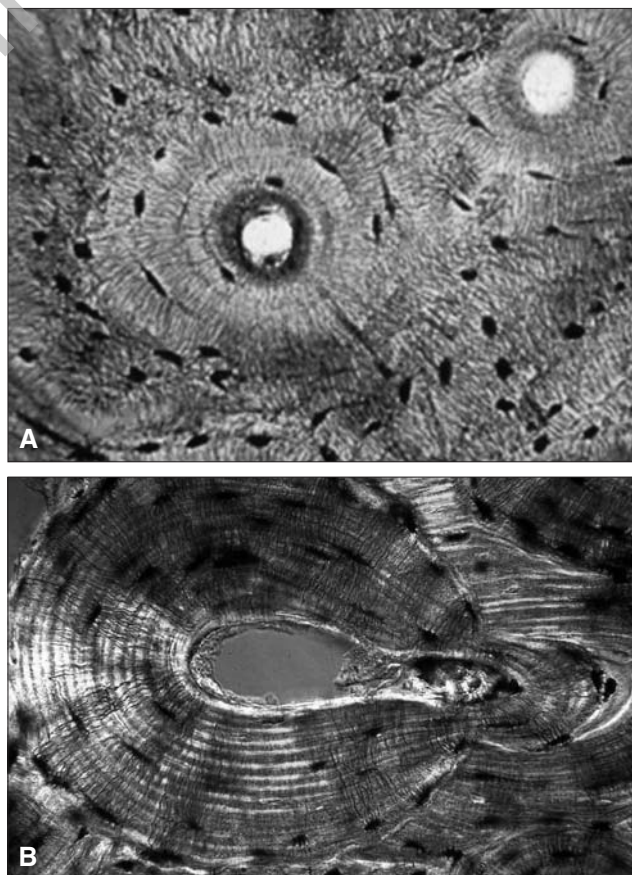


Figure 1 - Traditional (a) and polarized light microscopy (b) shows the orientation of osteons in the cortical bone.

### The structural design of bone

The structural design of the skeleton is achieved using minimal mass by taking advantage of the strength of bone achieved through its geometric properties. Long bones are levers needed for loading and movement rigidity is favored over flexibility. Fashioning the long bone with a medullary cavity achieves strength yet lightness. By shifting the cortical shell outward using a marrow cavity, the expanded marrow space effectively creates a void space and achieves lightness, whereas the further displacement of the cortical shell from the neutral axis increases bending strength. Minimizing the need for material to build wider bones is achieved by having wider bones with a narrower cortex so that a given cross-section of bone has a constant bone area. Long bones grow in length by endochondral apposition and in width by deposition of bone on its outer or periosteal surface. Resorptive excavation of a marrow cavity shifts the thickening cortex away from the neutral axis, thereby increasing resistance to bending. The conical metaphyses are fashioned by periosteal bone resorption and formation, whereas endochondral bone formation forms the trabecular network. External and internal contours differ at each point along and around the shaft, reflecting local modelling and remodelling in response to regional loading needs. The expanded marrow space achieves lightness in trabecular regions such as the vertebral body, and the material used is fashioned like a porous sponge to function more like a spring than lever. Interconnecting trabecular plates achieve lightness and favor structural flexibility over stiffness. These structures can absorb more energy than long bones by deforming before cracking, but they sacrifice the ability to tolerate large loads.

Males and females generally have similar vertebral trabecular volumetric density and similar vertebral heights; the larger vertebral cross-sectional area in males contributes to sex differences in bone strength. The number, thickness, spacing, distribution, and connectivity of trabeculae reflect the trabecular network and determine bone strength. For the same deficit in trabecular density, loss of connectivity has more deleterious effects on strength than thinned but well-connected fractures have four times as many unconnected trabeculae as women without fracture, despite a similar bone mineral density (BMD) (3).

### Bone modelling and remodelling

The cellular activities of bone modelling and remodelling determine the material composition and structure of bone. Bone modelling refers to the deposition of new bone without prior bone resorption. Bone remodelling is characterized by the appearance of focally and temporally distinct regions of resorption followed by bone formation that constitutes the basic multicellular units (BMUs). The purpose of bone modelling and remodel-

ling during growth is to build peak bone strength. After the completion of growth, bone modelling continues in adulthood modestly to increase bone size further, whereas bone remodelling maintains bone strength by removal of microdamage.

The bone remodelling is initiated on a bone surface usually covered by a very thin layer of unmineralized matrix and lining cells. These cells may respond to stimuli (hormones, cytokines) that initiate the remodelling. After the resorption phase, osteoblasts secrete the bone matrix, which refills the resorption lacunae. Under normal conditions, the remodelling process of resorption followed by formation is closely coupled in BMU and results in no change of bone mass when the amounts of resorbed and newly formed bone are similar. The coupling between resorption and formation is controlled by several factors that are poorly defined. The absence of coupling formation occurring without prior resorption, is observed only under pathological conditions such as bone metastasis. The frequency of initiation of a new remodelling sequence characterized the bone turnover. Abnormalities in the rate and balance of bone remodelling play a pivotal role in the pathogenesis of bone loss and structural decay. A high remodelling rate contributes to bone fragility by reducing the time available for secondary mineralization; bone is removed and replaced with new, less densely mineralized bone, which reduces its material stiffness. High bone remodelling itself also alters collagen composition by impairing isomerization, maturation, and cross linking. The high remodelling rate produces stress concentrators excavated regions of bone that concentrate stress predisposing to microdamage.

In presence of a negative BMU balance produced by an increase in the volume of bone resorbed, a decrease in the volume of bone formed or both, each remodelling event during the high remodelling rate after menopause, and in disease states, accelerates bone loss and structural decay producing trabecular thinning, tunnelling in the trabeculae, cortical thinning, and porosity (4). The resorptive phase of the remodelling cycle is responsible for the removal of microdamages, whereas the formation phase replaces bone and restores its material composition and structure.

### Causes of bone fragility

There are many causes that may be related to bone fragility as reported in Table I.

- Primarily due to abnormal collagen

#### A. Osteogenesis imperfecta (OI)

OI is an inherited disorder characterized by increased bone fragility with recurrent fractures that leads to skeletal deformities in severe cases. The phenotypic expression is heteroge-

Table I

Pathologies	Abnormal collagen	Increased bone turnover	Mineralization defect
Osteogenesis imperfecta	Yes No in adults	Yes in youngs	No
Paget's disease	Yes	Yes	No
Osteomalacia	No	No	Yes
Postmenopausal osteoporosis	No	Yes	No
Hyperparathyroidism	No	Yes	No
Hypogonadism in man	No	No	No
Corticosteroid-induced osteoporosis	No	No	No

neous with the most severe forms being fatal in the perinatal period to mild forms diagnosed only in adulthood. OI is characterized by a low bone mass, a reduced trabecular thickness and number and a decreased bone formation at the cellular level. The bone turnover is increased in children but decreased in adults (5). Animal studies and studies in human subjects suggest that skeletal fragility in OI is due to the defect in collagen synthesis, whereas the abnormalities in bone turnover and mineral are inconsistent.

#### B. Paget's disease of bone

Paget's disease of bone is a localized disease characterized by increased bone remodelling, bone hypertrophy, and abnormal bone structure. The illness occurs in 2-3% of individuals over age 60. The consequences are pain, bone deformities, fractures of long bones or vertebrae, secondary osteoarthritis from deformity of bone near joints, and neurological complications. Paget's disease may affect only one bone or may involve several bones. Bone fragility in Paget's disease probably results from the accelerated bone turnover and the consequent disorganization of the matrix. Fragility occurs despite an increase in bone density/size at most skeletal sites. In affected bone, resorption is dramatically increased with abnormal osteoclasts containing numerous nuclei. Bone formation is also increased with numerous osteoblasts actively synthesizing bone matrix, which is rapidly mineralized (6). The accelerated bone turnover leads to the formation of abnormal woven bone with an irregular arrangement of collagen fibers that are not deposited in a lamellar fashion. The excessive bone formation results in the bone hypertrophy and osteosclerosis with thick and numerous trabeculae. The woven bone is not specific for Paget's disease but reflects an extremely high rate of bone turnover. The alteration of the bone texture due to abnormal turnover is likely to impair bone strength.

- Primarily due to abnormal mineral density

#### Primary mineralization defect: osteomalacia

Osteomalacia is characterized by a defect of mineralization due to calcium and phosphate deficiencies that mainly result from a poor gut absorption due to vitamin D deficiency. Most common is vitamin D deficiency due to lack of sunlight exposure or intestinal malabsorption, but disorders of the vitamin D metabolism contribute (defect of hydroxylation, increased renal excretion, and increased catabolism by anticonvulsants). Osteomalacia may be drug-induced (fluoride or etidronate) or the result of aluminum exposure in parenteral nutrition or hemodialysis. Clinical features are pain, fissures, and fractures, which may occur after minimal trauma (7). The

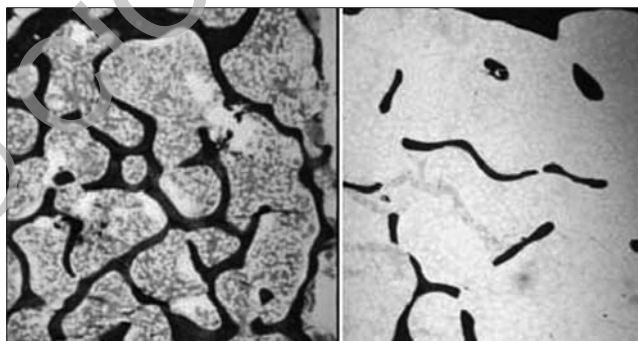


Figure 2 - On the left is normal bone and on the right bone from a patient with osteoporosis.

consequence of vitamin D deficiency is a fall of blood calcium concentration that induces a secondary hyperparathyroidism. The effect of hypocalcemia is a defect of bone mineralization, and the effect of secondary hyperparathyroidism is an increase in bone turnover. In contrast, in phosphate deficiency, parathyroid level and vitamin D status are normal, and the consequence of hypophosphatemia is osteomalacia. The reduced mechanical properties of osteomalacic bone results from the delayed primary mineralization, which is the cause of the small amount of mineralized tissue. Bone tissue is characterized by an accumulation of osteoid and a decrease in mineralization rate with a prolongation of the mineralization lag time the delay between the deposition of the matrix and the onset of the mineralization. In hypophosphatemic osteomalacia, bone tissue mass may be increased but the mineralized bone volume is decreased.

- Primarily due to abnormal remodeling rate and balance (turnover)

#### A. High bone turnover with negative BMU balance

A balance between the volumes of bone resorbed and formed in each BMU maintains bone mass. When the volume of bone resorbed increases and/or the volume of bone deposited in each BMU decreases, a negative BMU balance results producing bone loss and structural decay. Bone loss and structural decay are amplified when remodelling rate increases. A negative BMU balance is found in postmenopausal, corticosteroid-induced osteoporosis and in some endocrine diseases (Fig. 2).

1. *Postmenopausal osteoporosis.* Osteoporosis is defined by a BMD lower than 2.5 SD from the young adult mean. This decreased BMD variably reflects the contributions of growth and age-related deficits in bone size, tissue mass, and the degree of mineralization of the bone. Fragility fractures occur in up to 50% of postmenopausal women, but half of the fractures occur in persons without osteoporosis, confirming that bone density is not the only determinant of bone strength in postmenopausal osteoporosis. Bone fragility in postmenopausal osteoporosis is the result of a decrease in bone mass and architectural decay in cortical and trabecular bone (8) (Fig. 3).

There is an increase in bone remodelling and, within each remodelling unit, a reduced bone formation and increased bone resorption. Abnormalities in the material properties of bone (collagen and mineral) may contribute, but their relative contribution to skeletal fragility in postmenopausal osteoporosis is unclear. Increased bone remodelling after menopause in women, hypogonadism in some men, and secondary hyperparathyroidism in both sexes accelerates bone loss because

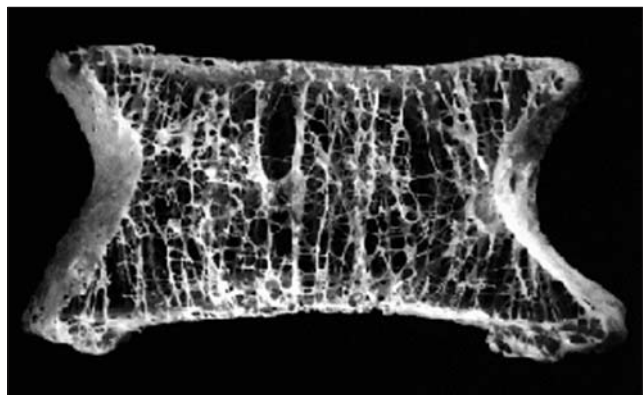


Figure 3 - Macroscopic feature of osteoporotic vertebra with collapse and trabecular thinning.



each BMU has a negative bone balance due to an imbalance in the volumes of bone resorbed and formed and a decrease in the duration of bone formation by the osteoblasts.

**2. Hyperparathyroidism.** Primary hyperparathyroidism is common and usually asymptomatic. The skeletal manifestations are variable and include bone pain and fractures at several sites including vertebral, distal radius, and pelvis. Osteopenia at various degrees may be observed and localized on the cortical bone, trabecular bone, or both. The major consequence of primary hyperparathyroidism is an increase in the rate of bone remodelling. Increased bone resorption is shown by the extended resorption surfaces and increased osteoclast number. The augmentation of formation associates an increase in the osteoid surfaces, osteoblast number, and mineral apposition rate, which is the rate of the primary mineralization. Despite this accelerated bone remodelling, cancellous bone volume is maintained with a thinning of trabeculae but a preservation of connectivity (9). In contrast to postmenopausal osteoporosis, the coupling between resorption and formation remains balanced in primary hyperparathyroidism with an augmentation of the osteoblastic activity and lifespan or a decreased erosion depth that results in a normal or increased balance at the BMU level. In contrast, cortices are thinner and more porous (10). Long bones are affected by increases in inner and, to a greater extent, in outer diameters resulting from the stimulation of the subperiosteal apposition and endocortical resorption. The reduction in bone density, which may explain the increased fracture risk at cortical sites, may be partly counteracted by the increase in the cross-sectional bone area. Thus, bone strength in hyperparathyroidism is a function of many variables, such as bone density, bone size, and microarchitecture.

#### B. Other abnormalities of bone turnover with negative BMU balance

**1. Osteoporosis in men.** Fragility fractures occur in men. The incidence of fractures is higher in men than women from adolescence through middle life as a result of more severe trauma, but bone fragility may also contribute to the fracture risk. After 50 yr, the incidence of fractures increases with aging in men. The age-adjusted incidence of both hip and vertebral fractures in men is about half of that in women. In addition, several other factors may contribute, including nutritional deficiencies, inactivity, hypogonadism, or alcoholism. Men with vertebral or hip fractures have reduced bone size. As in women, osteoporosis in men is characterized by decreased bone mass with a similar magnitude associated with a reduced cortical thickness and an increased porosity. Modifications of bone microarchitecture have been reported in osteoporotic men with vertebral fracture independently of BMD when compared with osteoporotic men without fracture. The bone microarchitecture is characterized by a lower trabeculae number and an increased trabecular separation. In contrast, in another study performed in younger men, no significant difference in trabecular architecture was observed between men with crush fractures and controls, except for a trend in decreasing number of free-ends. The reduced bone size may be due to reduced periosteal apposition during growth, aging, or both (11). Bone loss results mainly from a decreased bone formation. In addition, increased bone resorption contributes.

**2. Corticosteroid-induced osteoporosis.** Bone loss and fracture risk are related to the dose and duration of glucocorticoid exposure. Bone loss is rapid during the first 12 months, with a significant decrease of lumbar spine BMD since the third month of treatment, observed even with a low dose (10 mg/d) of prednisone. The fracture risk increases rapidly: the vertebral frac-

ture incidence has been reported to be 2-fold higher in a large cohort of corticosteroid-treated patients compared with controls but decreases after cessation of therapy. Fracture risk is greater at predominantly trabecular sites such as the vertebrae and ribs, and the risk of hip fracture is also doubled in glucocorticoid-treated patients (12). However, the prevalence of fractures in corticosteroid-induced osteoporosis is higher than expected from the decreased BMD, suggesting that the low bone strength induced by glucocorticoid may be partly independent of the changes of BMD. Glucocorticoids induce apoptosis of osteocytes in animals as in humans. The mechanism by which osteocytes contribute to bone strength is still unknown, but osteocytes have been hypothesized to play a major role in the targeted remodelling, acting as mechanosensor and transducer in bone, and to be involved in the detection and repair of microcracks. The loss of viable osteocytes disturbs the osteocyte-canalicular network resulting in a failure to detect microcracks and consequently to induce their repair. In patients with hip fracture, the number of viable osteocytes is decreased by 25%, and no fracture callus is observed when the osteocyte viability is low. The main effect of glucocorticoids on bone is a dramatic inhibition of the osteoblastic activity that results in a decreased wall width of trabecular packets and consequently a thinning of trabeculae. An increased bone resorption has also been reported (13).

#### Conclusions

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. 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. Bone fragility in OI results from abnormal quantity and quality of collagen synthesis, which disturb the mineral crystal size. Modifications of the mineral phase as in osteomalacia decrease bone strength. 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" (intrinsic properties of bone matrix, bone architecture, and turnover) 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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