

## *Review Article*

# **Biomechanics of Bone: Determinants of Skeletal Fragility and Bone Quality**

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**Abstract.** 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). Bone fragility is influenced by bone size, shape, architecture and tissue 'quality'. 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 parathyroid hormone (PTH-(1–84)) or teriparatide (PTH-(1–34)), 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 bone mineral density (BMD). This effect may explain why some drugs can affect fracture incidence disproportionately to changes in BMD. For instance, in a recent clinical trial, PTH-(1–34) therapy caused a dose-related increase in spinal BMD without any dose-dependent effect on the observed decrease in spinal fracture incidence. This apparent disassociation between spinal BMD and bone fragility is probably due to effects of PTH-(1–34) on bone architecture within vertebral bodies. While it has been shown that BMD is highly heritable, bone mineral distribution and architecture are also under strong genetic influence. Recent findings suggest that different genes regulate trabecular and cortical structures within lumbar vertebrae, producing a

wide range of bone architectural designs. These findings suggest that there is no single optimal bone architecture; instead many different architectural solutions produce adequate bone strength.

**Keywords:** Bone density; Fracture; Osteoporosis

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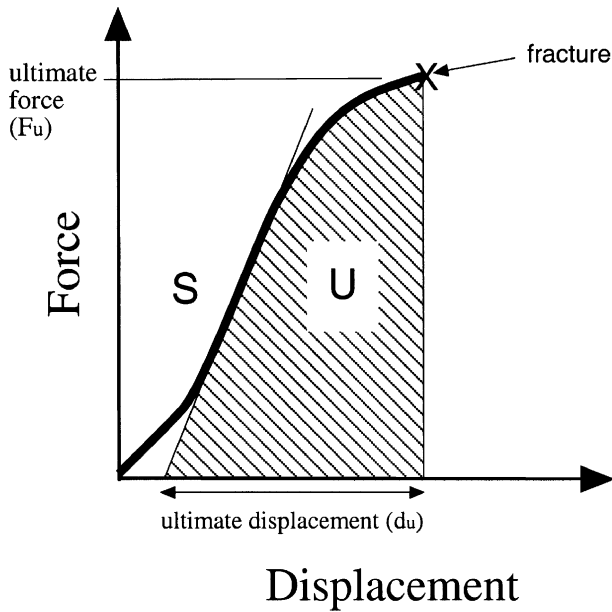
## **Introduction**

Bone fragility can be defined broadly as the susceptibility to fracture. However, bones fracture for different reasons, so there are several different biomechanical definitions of bone fragility. One function of bones is to carry loads. Fractures occur when loads exceed the bone strength, so weakened bones should be considered fragile. For example, osteoporotic vertebral bodies might fracture during normal daily activities such as opening a window or rising from a chair. These non-traumatic or fragility fractures result from substantially weakened bone. On the other hand, hip fractures result mainly from trauma associated with falls or impact. During a traumatic loading, such as a fall to the ground, fracture will occur if the energy from the fall exceeds the mechanical energy that the bone can absorb. Consequently, with trauma even strong bones should be considered fragile if they are unable to absorb energy due to excessive brittleness. This may sound like a contradictory statement – how can strong bones be fragile? – but from a biomechanical perspective, fragility is not defined only by bone strength.

The biomechanical definition of bone fragility includes at least three components: strength, brittleness and work to failure. (A fourth biomechanical measure, stiffness, is also used to assess mechanical integrity of

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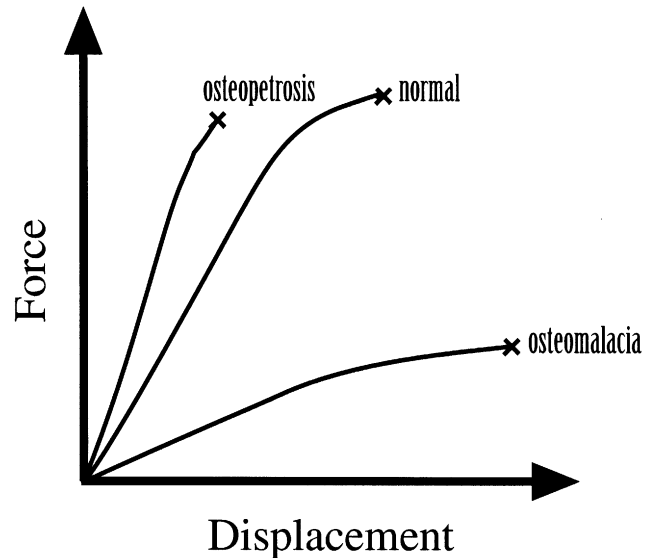


**Fig. 1.** A force–displacement curve resulting from a biomechanical test of a bone specimen. The height of the curve (ultimate force) represents strength, the area under the curve is the work to failure ( $U$ ), the maximum slope of the curve is the stiffness ( $S$ ) and the width of the curve is the ultimate displacement (reciprocal of brittleness).

bones, but is not a direct measure of fragility.) These parameters can be derived from a biomechanical test in which a bone specimen is loaded until it breaks. What results is a force–displacement curve (Fig. 1). Bone strength (ultimate force) is defined as the height of the curve, and work to failure is the area under the curve. Brittleness can be estimated from the reciprocal of the width of the curve (ultimate displacement).

Skeletal diseases can cause fragile bones by affecting bone structure in different ways. For instance, osteopetrosis and osteomalacia both cause increased risk of fracture. However, these diseases result in grossly different bone biomechanical characteristics. Osteopetrosis causes stiff, brittle bones. Osteopetrotic bones absorb very little energy before breaking (reduced work to failure) and are therefore more susceptible to fracture resulting from trauma (Fig. 2). Osteomalacia results in weak, ductile bones. Like osteopetrosis, osteomalacia often reduces work to failure. However, osteomalacic bones can deform considerably before the fracture. Due to their weakness the bones often bend under load and deform, which can result in the bowed long bones seen in rickets patients. No such bowing is possible in osteopetrotic bones; instead fracture occurs after very little deformation.

How can bone fragility be reduced? There are at least three ways to make the skeleton stronger. First, increase bone mass – larger bones can carry more load. Second, distribute bone mass effectively, i.e., put bone tissue where the mechanical demands are greatest. Third, improve the material properties of bone tissue such that the bone is stronger at a tissue level. Structural changes to the bone, such as adding or redistributing mass, affect



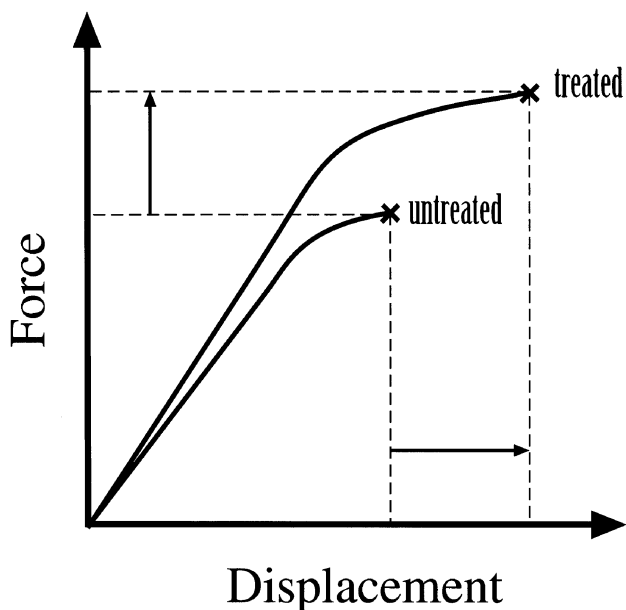
**Fig. 2.** Force–displacement curves for normal healthy bone, osteopetrotic bone, or osteomalacic bone. Osteopetrosis reduces the displacement before failure and thus increases brittleness. Osteomalacia decreases brittleness but greatly reduces the force at failure and thus weakens bone.

its biomechanical properties at an organ level. These whole bone properties are called extrinsic biomechanical properties [1]. Bone tissue properties are called intrinsic biomechanical properties (Table 1). These include ultimate stress and strain, Young's modulus and modulus of toughness. Specialized techniques such as nanoindentation and acoustic microscopy allow the measurement and high-resolution mapping of intrinsic Young's modulus of bone samples [2]. Other intrinsic tissue properties (besides Young's modulus) are difficult to measure directly and are usually inferred from whole bone biomechanical tests [1]. An effective treatment for bone fragility should improve the extrinsic biomechanical properties of bone but at the same time not substantially impair the intrinsic properties.

From a biomechanical standpoint, an ideal drug to cure bone fragility would improve strength and decrease brittleness (Fig. 3). It is rare for a treatment to achieve this combination of effects. One example is teriparatide

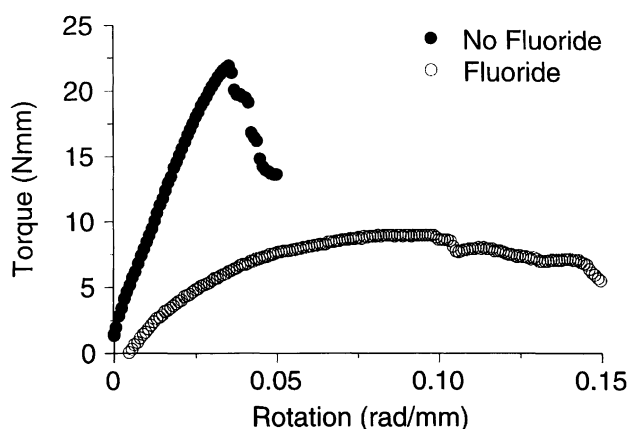
**Table 1.** Biomechanical measurements that characterize bone fragility

Measurement	Units	Description
Ultimate force ( $F_u$ )	N	Extrinsic – strength
Ultimate stress ( $\sigma_u$ )	N/mm <sup>2</sup> or MPa	Intrinsic – strength
Ultimate displacement ( $\delta_u$ )	mm	Extrinsic – reciprocal of brittleness
Ultimate strain ( $\epsilon_u$ )	no units	Intrinsic – reciprocal of brittleness
Stiffness ( $S$ )	N/mm	Extrinsic
Young's modulus ( $E$ )	N/mm <sup>2</sup> or MPa	Intrinsic – stiffness
Work to failure ( $U$ )	N-mm or mJ	Extrinsic – energy absorbed
Modulus of toughness ( $u$ )	N/mm <sup>2</sup> or MJ/m <sup>3</sup>	Intrinsic – energy absorbed



**Fig. 3.** An ideal treatment for bone fragility would increase bone strength (force at failure) while also decreasing brittleness (by increasing displacement at failure).

(PTH-(1–34)) treatment in rats. Rats treated with 40  $\mu\text{g}/\text{kg}$  PTH-(1–34) for 6 months showed a 167% increase in ultimate stress of the lumbar vertebrae combined with a 73% increase in ultimate strain (reciprocal of brittleness). The combination of these two effects caused a 356% increase in vertebral toughness [3]. However, the effectiveness of PTH-(1–34) treatment in rats may not be matched in clinical use because PTH-(1–34) stimulates intracortical remodeling and increases cortical porosity in bones of primates and humans (discussed below). For many drugs used to reduce bone fragility, improved bone



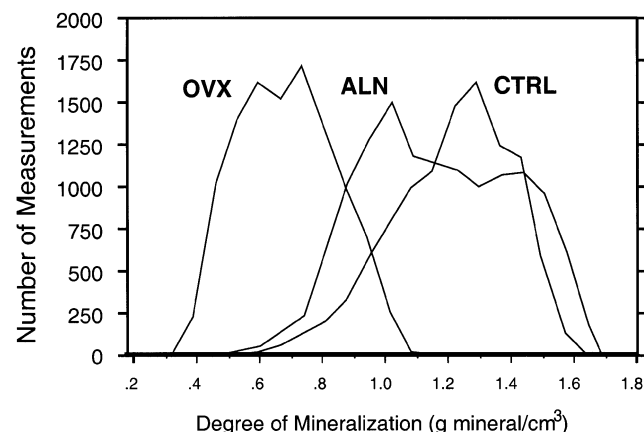
**Fig. 4.** Soaking mouse bones in fluoride solution reduced torsional strength (torque) by 62%. The ductility of the bone (rotation to failure) was substantially increased. The biomechanical characteristics of a fluoride-treated bone are similar to those of an osteomalacic bone (Fig. 2). However, the fluoride-treated bones were not calcium deficient, suggesting that fluoride decreased strength through a different mechanism from osteomalacia. (Reprinted from Silva and Ulrich [7], used with permission.)

mass and structure are combined with negative effects on intrinsic biomechanical properties. A good example is fluoride treatment. While fluoride can improve bone mass [4,5], fluoride incorporation into bone mineral reduces intrinsic biomechanical properties [6]. Simply soaking bone samples in fluoride solution can reduce bone strength by as much as 62% [7] (Fig. 4).

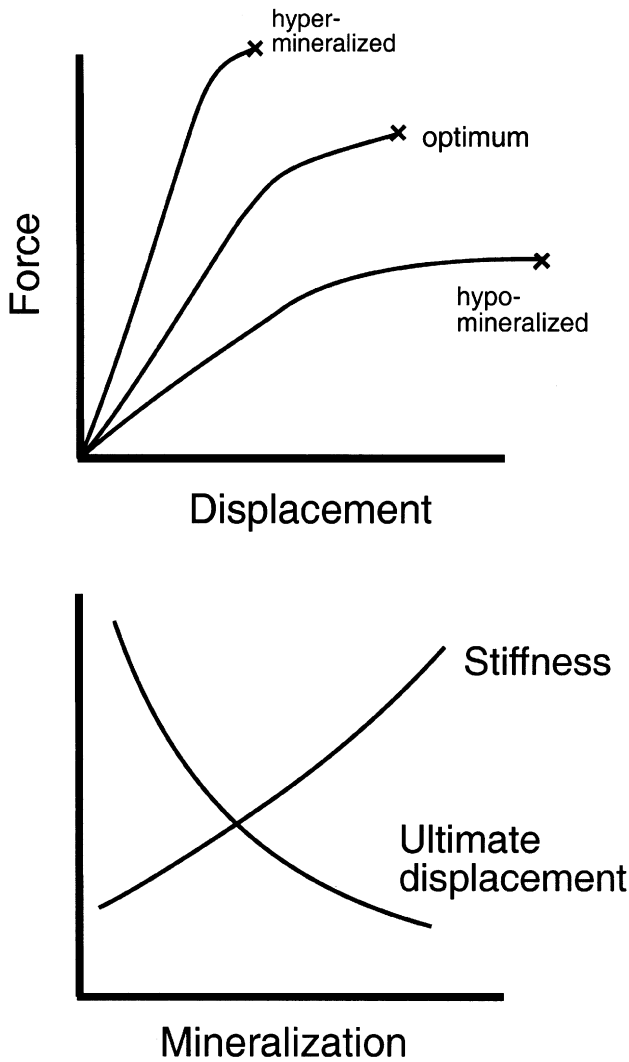
### Effects of Osteoporosis Treatments on Bone Quality

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, often termed bone quality, can be characterized by measurements of intrinsic biomechanical properties. As discussed above, fluoride is one example of a drug that compromises bone quality. Other drugs also may affect bone tissue properties. We will focus this discussion on bisphosphonates and PTH-(1–34).

Strong inhibitors of bone resorption, such as bisphosphonates, can reduce bone turnover by 80–90% [8], 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 [9] (Fig. 5). Increased mineralization affects a number of biomechanical properties of bone: stiffness is increased, while ultimate displacement is decreased [10,11]. Consequently, increasing mineralization improves the structural rigidity of bone while at the same time making the tissue more brittle [11]. Properly mineralized bone has the best combination of stiffness and brittleness, while poorly mineralized bone tends to be very weak, and hypermineralized bone is brittle (Fig. 6). Work to failure tends to decrease as bone becomes more highly



**Fig. 5.** Treatment with bisphosphonate (ALN) for 2 years increased bone mineralization in baboons, compared with ovariectomized controls (OVX). However, bone mineralization during bisphosphonate treatment did not surpass control levels (CTRL). (From Meunier and Boivin [8], used with permission.)



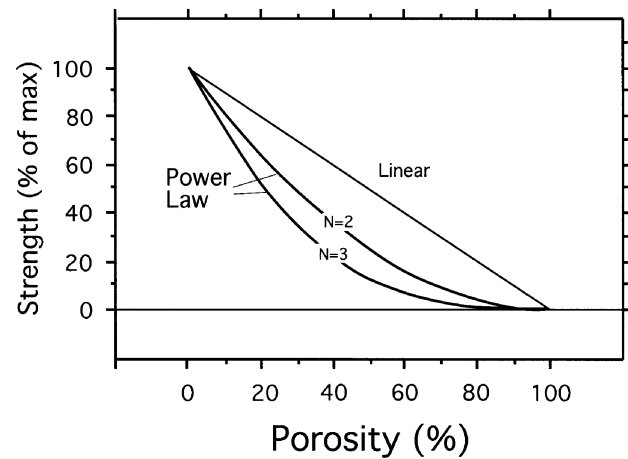
**Fig. 6.** Stiffness of bone increases with increasing mineralization, but bone tissue also becomes more brittle (decreased ultimate displacement). Increased brittleness reduces work to failure as bone becomes more highly mineralized.

mineralized [11], suggesting that hypermineralized bone is more fragile.

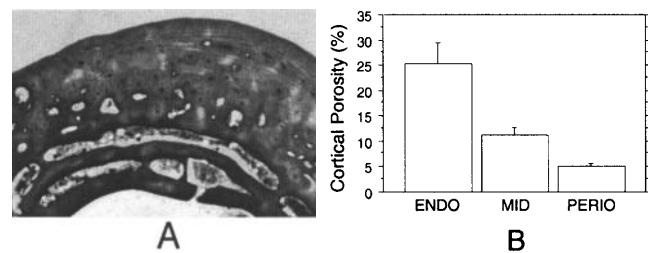
The study by Meunier and Boivin [9] clearly showed a shift towards higher mineralization in bone tissue after bisphosphonate treatment, yet there is presently no evidence to suggest that this shift in mineralization is severe enough to be considered hypermineralization. Therefore, it is unclear whether bisphosphonate treatment might increase mineralization sufficiently to impair bone quality. 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 [12]. This repair mechanism is blunted by bisphosphonates. The number of microcracks within the ribs of dogs increased dramatically during bisphosphonate treatment and, with very high doses, treatment can result in decreased tissue toughness [13], suggesting

an increase in bone fragility. At present, there is no evidence that microdamage accumulation occurs during treatment with clinical doses of bisphosphonates.

PTH-(1-34) affects bone tissue very differently from bisphosphonates. PTH-(1-34) increases bone turnover substantially [14,15], effectively reducing mean tissue age, thus decreasing tissue mineralization, and increasing cortical bone porosity. As shown in Fig. 6, lowering mineralization weakens bone tissue and increasing porosity further weakens bone. Increases in porosity cause disproportionate decreases in bone strength, i.e., small increases in porosity can decrease bone strength substantially (Fig. 7). High-dose (5 µg/kg) PTH-(1-34) increased cortical porosity by over 12% in monkeys [14]. However, most of this increase in porosity occurred at the endocortical surface of bone (Fig. 8). This surface carries the smallest mechanical stress when subjected to bending. Porosity on the periosteal surface, where



**Fig. 7.** For ceramic materials and bone, the relationship between strength and porosity generally fits a power law:  $Strength = k(1-P)^N$ , where  $P$  is porosity and  $k$  is a constant. It was initially reported [16] that bone strength was best fit to porosity with a power ( $N$ ) of 2 and the Young's modulus of bone was best predicted by  $N=3$ . Subsequently it was shown that bone strength and Young's modulus are linearly proportional [17] and thus should follow the same power law relationship with porosity. Hence the power ( $N$ ) that best fits the strength-porosity relationship for bone tissue probably falls between 2 and 3. The power law relationship dictates that small changes in porosity can cause large decreases in bone strength.

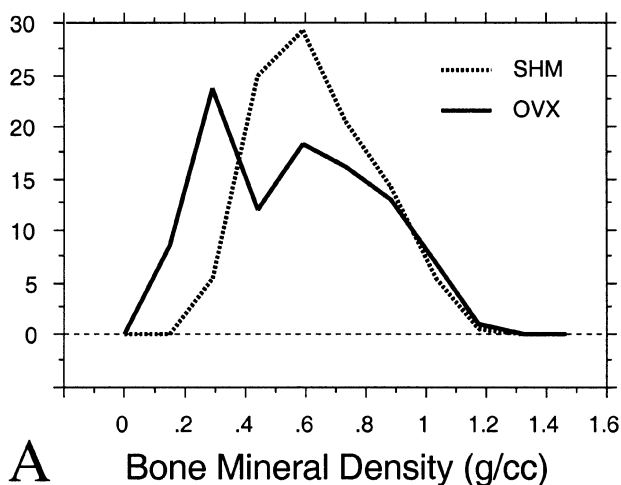


**Fig. 8.** **A** Photomicrograph of the cortex from a monkey humerus after 18 months of treatment with 5 µg/kg of PTH-(1-34). **B** Distribution of the porosity of the monkey humerus across the cortex from the endocortical region (ENDO) to the middle region (MID) to the periosteal region (PERIO).

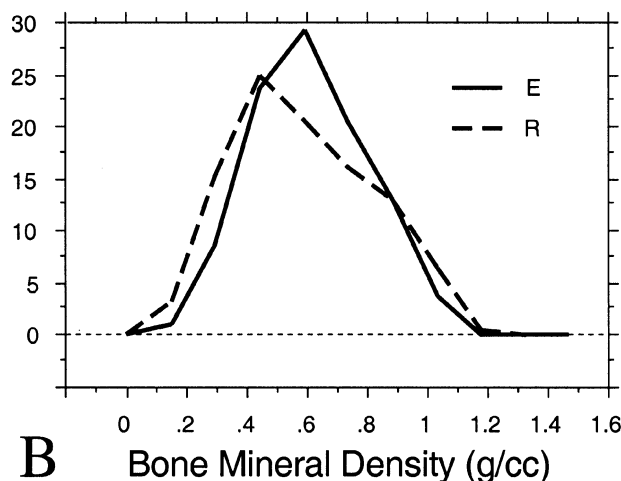
mechanical stress is highest, was increased only slightly. As a result of this favorable distribution of porosity after PTH-(1-34) treatment, and the fact that PTH-(1-34) increased cortical thickness, the whole bone bending strength of the humerus was not significantly reduced after 18 months of PTH-(1-34) therapy [14]. These results suggest that improvements in bone mass resulting from PTH-(1-34) therapy outweigh any negative effects on bone tissue quality.

### Effects of Drugs on Bone Architecture

Drug therapies for osteoporosis not only affect bone mass but also reorganize bone architecture. The effect on bone architecture varies depending on the mode of action of the drug. Redistribution of bone mineral can be



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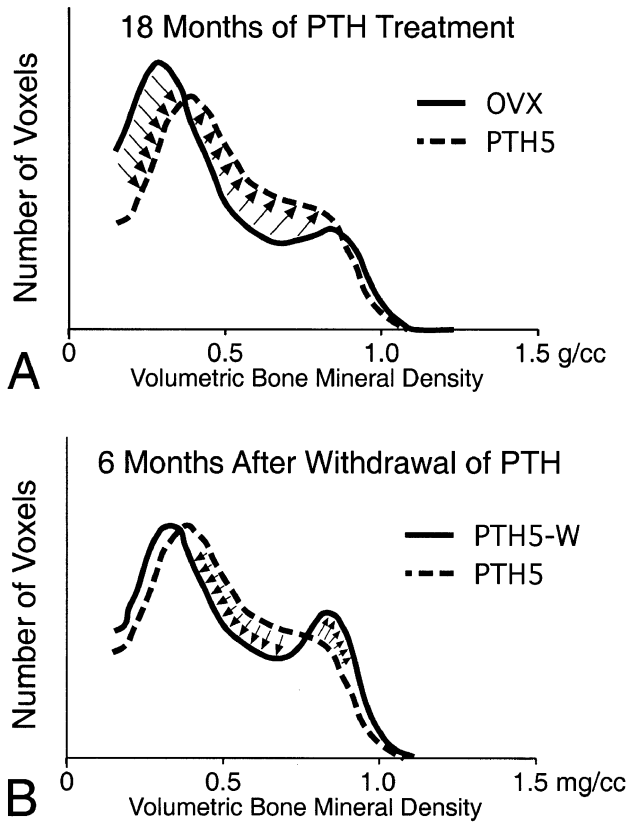
B

**Fig. 9.** Bone mineral density histograms for lumbar vertebra (L6) from rats 10 months after ovariectomy (OVX; SHM, sham-operated controls) (A), or treatment with raloxifene (R) or estradiol (E) (B). Volumetric BMD was measured using peripheral quantitative computed tomography (pQCT). The y-axis is the percentage of voxels with a given vBMD value. (Data taken from the study of Sato et al. [18].)

measured using high-resolution computed tomography. The distribution of bone mineral within a bone structure, e.g., a vertebral body, can be represented by a histogram showing the number of voxels (volume) containing a certain volumetric BMD (vBMD). This histogram changes shape after drug therapy is initiated, illustrating the redistribution of bone mineral from cortical to trabecular compartments, or vice versa. For instance, analysis of vertebral peripheral quantitative computed tomography (pQCT) data taken from rats 10 months after ovariectomy shows a shift in vBMD (Fig. 9A). The volume with the highest vBMD mostly remains the same, while the volume with medium vBMD is reduced and the volume with lower vBMD increases. This study included drug intervention with estradiol and raloxifene. Of these drug therapies, estradiol treatment caused the vBMD histogram to remain similar to sham-operated controls, while raloxifene partially retained the control-type vBMD histogram (Fig. 9B). Biomechanical measurements largely mirrored the vBMD histograms: Vertebral strengths resulting from raloxifene and estradiol treatments were similar to one another and not different from sham controls [18]. It is possible that changes in bone architecture, even in the absence of a change in average BMD, might change biomechanical properties.

The restructuring of bone architecture by redistribution of mineral has been thoroughly studied in the lumbar vertebrae of monkeys treated with PTH-(1-34) [19]. PTH-(1-34) treatment causes a substantial increase in the volume of mid-vBMD bone combined with a decrease in volume of low-vBMD bone (Fig. 10A). There is a slight decrease in volume of bone with the highest vBMD, due presumably to increased cortical porosity. The overall result is a decrease in the lowest and highest density bone volume and a substantial increase in bone volume at mid-vBMD levels. Interestingly, the trend does not simply reverse once PTH-(1-34) is withdrawn. Instead, withdrawal causes a disproportionate increase in the highest vBMD bone volume, so the vBMD histogram after PTH-(1-34) treatment and withdrawal has a much different shape from prior to PTH-(1-34) treatment (Fig. 10B). Clinical studies demonstrate that areal BMD at the hip continues to increase after PTH-(1-34) withdrawal [20]. This continued improvement in BMD is probably due to filling in of the cortical porosity and some secondary mineralization of newly formed bone matrix, i.e., an increase in the volume of high-BMD bone.

Bone mineral redistribution resulting from PTH-(1-34) treatment could cause a partial disassociation between the BMD measured using dual-energy X-ray absorptiometry (DXA) and bone fragility, providing a plausible explanation why there was no difference in vertebral fracture prevention between two doses of PTH-(1-34) in a recent clinical trial [21], even though the higher dose produced a more favorable increase in spinal BMD. The clinical findings could reflect a tradeoff between increased porosity and trabecular hypertrophy; the negative biomechanical effects of porosity are more prominent at the higher PTH-(1-34) dose, thus partially



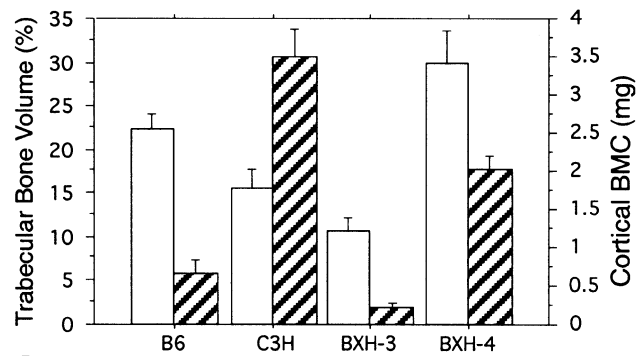
**Fig. 10.** **A** Effects of 18 months of PTH-(1-34) treatment on the distribution of vBMD within the lumbar vertebra (L5) of adult monkeys. **B** Effects of 12 months of PTH-(1-34) treatment followed by 6 months of withdrawal on the distribution of vBMD. OVX indicates ovariectomized control; PTH5 indicates 18 months treatment with 5 µg/kg of PTH-(1-34) per day; PTH5-W indicates 12 months treatment with 5 µg/kg of PTH-(1-34) followed by 6 months withdrawal. (Adapted from [19].)

reducing the fracture efficacy in relation to BMD. With the higher dose of PTH-(1-34), the observed change in spinal BMD was larger than the corresponding fracture prevention, so the fracture efficacy was overestimated by BMD measurements. With bisphosphonate therapy, BMD changes substantially underestimated the anti-fracture efficacy. Cummings et al. [22] observed that the anti-fracture effects of alendronate were substantially greater than predicted by models of fracture risk based upon areal BMD measurements, particularly in the first year of therapy. These clinical observations are consistent with the biomechanical mechanism of bisphosphonate therapy. Bisphosphonates decrease cortical porosity and resorption spaces on trabecular surfaces, and thereby should increase bone strength even with small changes in BMD (remember bone strength increases disproportionately to decreased porosity: see Fig. 7). Conversely, PTH-(1-34) increases cortical porosity and this effect must be overcome by increasing cortical thickness or with a large increase in trabecular bone density. Hence, it is reasonable to expect that PTH-(1-34) would need to provide a larger increase in BMD

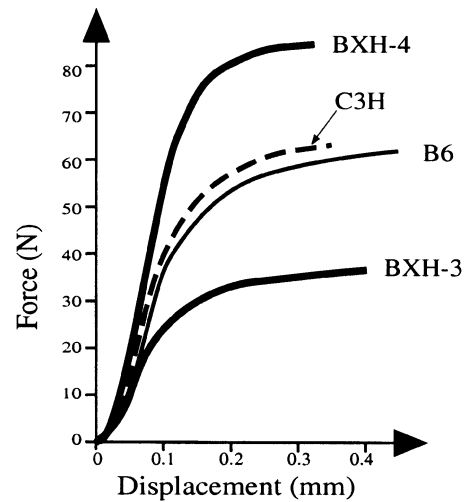
to achieve the same anti-fracture effects as bisphosphonates in the early stages of therapy.

### Genetic Influences on Bone Architecture

Studies in twins suggest that about 70% of the variability in peak BMD is genetically based [23-25]. Genetics also influence the structure and architecture of bone. The C3H/HeJ (C3H) strain of mice has much greater vertebral BMD compared with the C57BL/6J (B6) strain [26]. However, the vertebral architectures in these mice are quite different: C3H has a greater proportion of BMD in the vertebral cortex than in the trabecular regions, while B6 has less cortical bone mineral and more trabecular bone (Fig. 11A). Even with



**A**



**B**

**Fig. 11 A,B.** Genetic influences on vertebral fragility in mice. **A** Trabecular bone volume (*open bars*) and cortical bone mineral content (BMC, *striped bars*) vary considerably among inbred mouse strains. **B** Force-displacement curves for the L5 vertebrae from inbred strains of mice. B6 had good trabecular bone volume and modest cortical BMC, while C3H had high cortical BMC combined with a deficiency in trabecular structure. These two strains had similar biomechanical properties. These structural traits were distributed differently in BXH strains. (Each BXH strain has 50% B6 and 50% C3H alleles.) BXH-3 had poor cortical bone mass and trabecular volume, while BXH-4 had the best trabecular bone volume. BXH-4 had the least fragile vertebrae and BXH-3 vertebrae were the most fragile [27].

these large differences in the distribution of BMD within the vertebral bodies, the biomechanical properties of B6 and C3H vertebra are similar (Fig. 11B).

The genetic regulation of vertebral architecture was illuminated by observations of BXH recombinant inbred strains of mice. Each of the BXH RI strains contains a unique combination of genetic alleles from the B6 and C3H strains, so the allelic effects on vertebral fragility and architecture could be observed. Of the 12 BXH mouse strains, BXH-3 and BXH-4 had the greatest range in vertebral fragility [27]. BXH-3 mice have low cortical BMC and low trabecular volume, while the BXH-4 strain has a moderate cortical BMC level, but much higher trabecular bone volume. When comparisons were done among B6, C3H and BXH strains, BXH-3 had fragile vertebrae and the BXH-4 vertebrae were the strongest (Fig. 11B). These findings suggest that different genes regulate trabecular and cortical structures within lumbar vertebrae contributing to variation in vertebral architecture and strength, thus opening the possibility for a wide range of bone architectural designs that result in sufficient bone strength. Consequently drug therapies should not be discounted if they do not restore ideal bone architecture, because 'ideal' bone architecture may be highly variable among individuals. Instead the bone architecture after treatment should merely be biomechanically sufficient.

## Conclusions

Bone fragility can be reduced by increasing bone mass, improving tissue properties, or by reorganizing bone architecture. Drug therapies for osteoporosis typically improve bone mass, but also may affect bone quality (tissue fragility) and architecture. Depending on the type of therapy, treatment dose and duration, improvements in bone mass may be offset by detrimental effects on bone quality or architecture. Bone mineral density and architecture are under strong genetic control, hence bone fragility is probably influenced by several genes providing large variation in 'normal' bone architecture.

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