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Mini-Review Article

Hylonome

Determinants of skeletal fragility and bone quality

C.H. Turner

Biomechanics and Biomaterials Research Center, Indiana University, Indianapolis, IN, USA

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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 like 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, like 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, also is used to assess mechanical integrity of bones, but is not a direct measure of fragility.) 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. Osteomalacia results in weak, ductile bones. Like osteopetrosis, osteomalacia 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. From a biomechanical standpoint, an ideal drug to cure bone fragility would improve strength and decrease brittleness.

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, 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

Corresponding author: Charles H. Turner, Ph.D., Director of Orthpaedic Research, Orthopaedic Surgery, Indiana University School of Medicine, 541 Clinical Drive, Room 600, Indianapolis, IN, 46202, USA
E-mail: turnerch@iupui.edu

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to maintain tissue integrity by selectively removing damaged bone and replacing it with new bone. 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, 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 much differently than bisphosphonates. PTH-(1-34) 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, i.e., small increases in porosity can decrease bone strength substantially. High dose (5 mg/kg) PTH-(1-34) increased cortical porosity by over 12% in monkeys. 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. 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. These results suggest that improvements in bone mass resulting from PTH-(1-34) therapy outweigh any negative effects on bone tissue quality.

Reference

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