J Musculoskel Neuron Interact 2004; 4(4):402-403

Perspective Article

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# A cure for osteoporosis?

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**Keywords**: Bone Mass, Bone Quality, Teriparatide, Bisphosphonates

It seems reasonable that a cure for osteoporosis should accomplish two things. First, fracture risk should be reduced so that it is equivalent to that of a young, healthy adult and second the treatment should have a sustained effect so the patient is not required to take daily medication for the rest of his or her life.

Fracture incidence increases exponentially with age and can be over 20-fold greater in an elderly population compared to a young healthy population. To normalize a 20-fold increase in fracture rate, a treatment should reduce fractures by 95%. Hip fracture risk increases almost 10-fold in people with hip BMD that is osteoporotic (over 2.5 s.d. below normal). To "cure" a person with osteoporotic BMD, fracture risk must be reduced by 90%. Aging also increases fracture risk independent of BMD and fracture risk is increased further in a person who has had a previous osteoporotic fracture. Current anti-resorptive treatments reduce fracture risk by about 50% and PTH reduces fracture risk by 65%, compared to "placebo" (this usually means calcium and vitamin D supplements). If these therapies were combined, the best we should expect is an 83% reduction in fractures provided that the effects of the therapies are independent and additive. This is encouraging, assuming that the maximum effect can be achieved.

Efforts to find a cure for osteoporosis will be hampered by many effects of aging that worsen fracture risk. These include 1) changes in intervertebral disc structure, 2) irreversible changes in bone architecture, 3) a higher frequency of falling, and 4) diminished bone quality. To reduce risk and achieve a cure one must overcome all of these problems, so a curative treatment may be required to build bone mass in elderly people to beyond what it is in young healthy adults.

Intervertebral discs harden and calcify with age. This changes stress transfer between the vertebral bodies. Biomechanical studies have shown that damaged disks result in more stress and microdamage in the adjacent bone. In addition, the center region of a vertebral body loses more bone than the periphery sometimes resulting in a void in the center. Current anabolic treatments cannot build bone where there is no scaffold, so bone will be formed most around the periphery thus creating a stronger bone but with inefficient architecture. To overcome the problems of bad spine biomechanics and poor architecture, vertebral bodies of elderly people will most likely need to be augmented beyond those of young healthy adults.

Elderly people fall more, which increases the risk of a fracture, particularly at the hip. Hip protectors can reduce hip fracture risk by over 90%. This intervention is far more effective than the drug treatments but patient compliance is poor and the protectors only guard against hip fractures. With regard to the hip, bone loss is not uniform but occurs more rapidly at the inferior aspect of the femoral neck, which worsens the resistance to hip fracture.

Bone quality is greatly affected by bone turnover. Bisphosphonates may reduce turnover too much, resulting in microdamage accumulation. However, weaker anti-resorptives like raloxifene and estrogen have little effect on microdamage. PTH greatly increases turnover resulting in bone porosity. A more effective therapy should cause only moderate reductions in turnover while also stimulating bone formation. This might be achieved with a combination of drugs or with an entirely new approach.

In conclusion, a cure for osteoporosis should probably reduce fracture risk by >90%. To do this, one must overcome the challenges of age-related changes in spine biomechanics, increased numbers of falls, and poor bone architecture. In addition, we should make every effort to identify a treatment regimen that creates a permanent reduction in fracture risk after the treatment is discontinued. It is probably inappropriate to declare that a treatment is a cure unless it results in permanent improvements in bone structure after discontinuation. To this end there

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*Accepted 4 August 2004*

are several fundamental questions that should be answered.

Our current view of bone biology presumes that bone gained after anabolic treatment will be lost after the treatment is discontinued. Experimental evidence tends to support this view. It is important for us to understand why bone is removed after discontinuation of anabolic treatment. Is this a homeostatic function of bone biology that works through a mechanism like the "mechanostat"? If so, there is little hope that the effects of treatment will be maintained after discontinuation because the mechanostat will always adjust the bone structure back to where it was before treatment. On the other hand, the change in bone biology after treatment discontinuation might be a transient reaction to a biological perturbation. If the latter view is correct, it is possible to maintain treatment effects by minimizing the transient biological reaction. This might be done with a short anti-resorptive regimen or by "weaning" the patient off the anabolic treatment.