Antiresorptive Therapies for Osteoporosis

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KEYWORDS

• Antiresorptives • Bisphosphonates • Osteoporosis • Fracture • Osteonecrosis

KEY POINTS

- Antiresorptive agents are the most commonly used medications in osteoporosis.
- The end result of antiresorptive agent use is a net decrease of bone turnover and an increase in bone mineralization.
- Bone turnover consists of a stepwise process of resorption and formation of bone. When the balance favors resorption, a net loss in bone strength and quality is seen.
- Although rare, one of the main concerns when treating patients with bisphosphonates and monoclonal antibodies against receptor activator of nuclear factor-κB ligand is osteonecrosis of the jaw.

Bones have a versatile nature, being stiff enough to resist deformation, and flexible enough to absorb energy by deforming. Made up of type I collagen and calcium hydroxyapatite crystals, they achieve these characteristics by being 60% mineralized.[1] Depending on their structure and composition, bones are able to lengthen, shorten, and widen to allow for loading and movement. Long bones serve as levers, whereas the vertebral bodies retain a spring action. They adapt through modeling and remodeling, undergoing reconstruction by the bone multicellular unit. This unit is made up of osteoclasts and osteoblasts that work in symphony to resorb and replace bone that has sustained an insult. These cells move in waves over microcracks and surrounding matrix, breaking down damaged areas and depositing new lamellar bone in its place (**Fig. 1**). In this process, osteoclasts are always followed by osteoblasts. It is through this mechanism that the peak strength of a bone is achieved during the formative years, and then maintained in adulthood. At any time, there will be bone that was resorbed but not yet replaced, and this is known as the remodeling space. Depending on what stage in life one is in, the balance of formation and resorption will vary. During growth, the balance is positive with bone formation in the forefront, whereas during aging the balance tips negatively when the remodeling rate increases (**Fig. 2**).[2]

Osteoporosis is a disorder of compromised bone strength resulting in an increased risk of fracture. It is estimated that 55% of people over 50 years old have osteoporosis. In the United States, this comes out to about 10 million people with osteoporosis and 34 million with osteopenia.[3] In 2002, it is estimated that osteoporosis cost the economy 18 billion with hospital and nursing home admissions. This is not surprising; 1 in 5 fracture patients ends up in nursing homes.[4] Putting osteoporosis into perspective, women over 50 years of age have a lifetime risk of osteoporosis of 50% versus a 12% risk of developing breast cancer, and men over 50 years of age have a 20% lifetime risk of osteoporosis versus a 17% risk of prostate cancer.[5] Some risk factors for developing osteoporosis include low bone mineral density (BMD), age greater than 50 years, hormone

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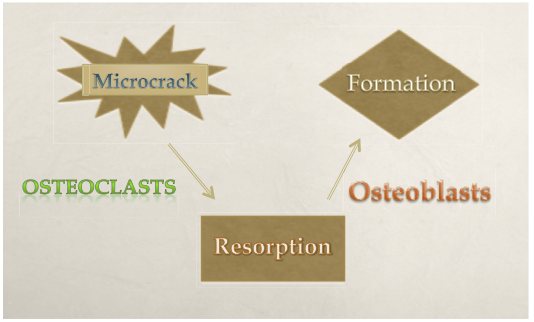

Fig. 1. Bone remodeling.

deficiency, smoking, certain medications such as corticosteroids or chemotherapy, and excessive alcohol use. It is a huge public health problem, especially because 80% of high-risk patients with 1 osteoporotic fracture are neither identified nor treated.[2] As mentioned, there exists a negative balance in bone resorption and formation, with resulting bone loss beginning around ages 18 to 30. Antiresorptive medications used for treatment of osteoporosis reduce the rate of remodeling and therefore promote completion of bone formation in remodeling sites present before commencement of treatment.

Antiresorptive medications and anabolic agents comprise the 2 main treatment options for osteoporosis. There are currently 5 classes of antiresorptive agents approved for use: bisphosphonates, monoclonal antibodies against receptor activator of nuclear factor-κB ligand (RANKL), selective estrogen receptor modulators (SERMs), estrogens, and calcitonin (**Table 1**).[6] There is abundant evidence demonstrating the efficacy of antiresorptives in preventing fractures, especially in postmenopausal women. We currently have only 1 anabolic therapeutic agent, teriparatide, which is usually reserved for patients with severe osteoporosis or

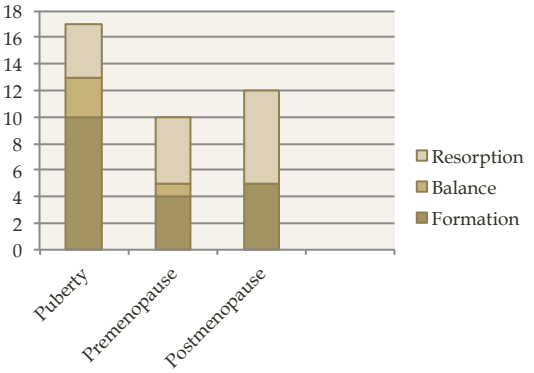

Fig. 2. Balance of bone formation and resorption.

Table 1
Antiresorptives & fracture efficacy

Drugs	Vertebral	Nonvertebral	Hip
Alendronate	X	X	X
Ibandronate	X	None	None
Risedronate	X	X	X
Zoledronic Acid	X	X	X
Denosumab	X	X	X
SERMs*	X	None	None
Estrogen	X	X	X
Calcitonin	X	None	None

* Selective estrogen receptor modulators.

at a high risk of fracture. For the purposes of this article, we focus on the antiresorptive medications.

Bisphosphonates are the most widely used class of osteoporosis treatments. The compounds are synthetic analogs of inorganic pyrophosphate, where the central oxygen is replaced by a carbon atom. The differences between molecules are owing to variable side chains off the central molecule. Adding a hydroxyl group to the central carbon enhances the affinity to calcium crystals. The addition of a nitrogen atom to the other side chain attached to the central carbon has significant impact on decreasing bone resorption. The first molecule, etidronate, was initially designed to soften toward order for industrial purposes. The first biological use of etidronate began in the 1960s as a treatment of decreasing unwanted calcium deposition is soft tissues, namely, heterotopic ossification.[7] Further research suggested that this drug would also impair osteoclast mediated bone resorption. The initial theory was that this was owing to stabilization of hydroxyapatite crystals. Further investigation showed that this was a direct effect on osteoclast function. Initial compounds, which did not have a nitrogen atom attached to the central carbon, seemed to be nonspecific inhibitors at the adenosine triphosphate function and caused cell apoptosis. Compounds that contained a nitrogen atom as part of the central side were eventually found to have a very specific effect of inhibition of farnesyl pyrophosphate synthase, an enzyme related to the hydroxymethylglutaryl–mevalonic cholesterol synthesis pathway. Inhibition of this enzyme seems to affect prenylation, or binding to fat chains, of small intracellular regulatory proteins, which decreases function of the osteoclasts. There is a very good correlation between the potency of the aminobisphosphonates in vitro on inhibition of this enzyme and the antiresorptive efficacy of the compounds.