Newer Therapies in the Management of Osteoporosis

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Introduction

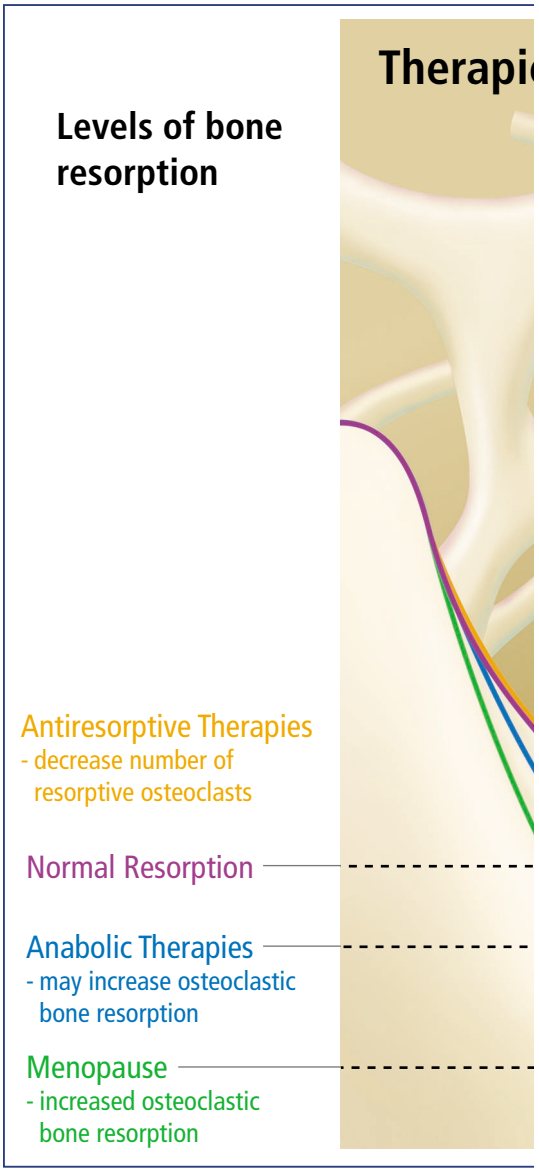
Osteoporosis is a disease characterized by low bone mass and bone strength, resulting in an increase in bone fragility and susceptibility to fractures.[1] It is asymptomatic prior to fractures, which most commonly occur in the vertebral body, hip and forearm.

Dual energy x-ray absorptiometry is the technology used to measure bone mineral density at the sites of interest. This technology has revolutionized our approach to this disease. In 1994, the World Health Organization (WHO) published diagnostic guidelines for osteoporosis, which are based on an individual's bone mineral density (BMD) according to a T-score.[2] The T-score is defined as the number of standard deviations (SD) above or below the mean BMD at peak bone mass at age 30 years. A T-score of -2.5 or lower defines osteoporosis. At risk individuals can now be diagnosed early, thereby allowing the use of highly effective interventional strategies which prevent further bone loss and potentially debilitating fractures. Unfortunately, currently once significant bone mass has been lost, there are no commercially available therapies that are proven to increase bone density. This will likely change in the next few years.

Current Therapies

Increased osteoclastic bone resorption is the major defect in the pathophysiology of osteoporosis. The normal bone-remodeling unit, composed of osteoclastic bone resorption coupled to osteoblastic bone formation, is disrupted (Figure 1). In addition, the number and activation of osteoclasts are increased and bone formation is relatively decreased. This results in bone loss. Current therapies in the prevention and treatment of osteoporosis are designed to decrease bone resorption. These therapies, known as antiresorptives (Figure 1), include estrogen,[3,4] bisphosphonates such as alendronate[5-8] and risedronate,[9-11] raloxifene[12,13] and calcitonin.[14] All have been shown to stabilize bone density but do not cause substantial increases in bone mass. They act to inhibit the action and decrease the number of resorptive osteoclasts, thus preventing further bone loss. The small increases in bone mineral density reported with these drugs are likely due to persistent osteoblastic bone formation in areas previously resorbed, rather than to a true effect on increasing new bone formation. All antiresorptive agents have been shown to decrease vertebral fractures.[3,6,9,10,13,14] However, the most serious fractures involve the hip, and contribute substantially to morbidity, mortality and health care costs.[15] Only the bisphosphonates, alendronate and risedronate, have been shown to significantly reduce the risk of developing hip fractures.[7,11]

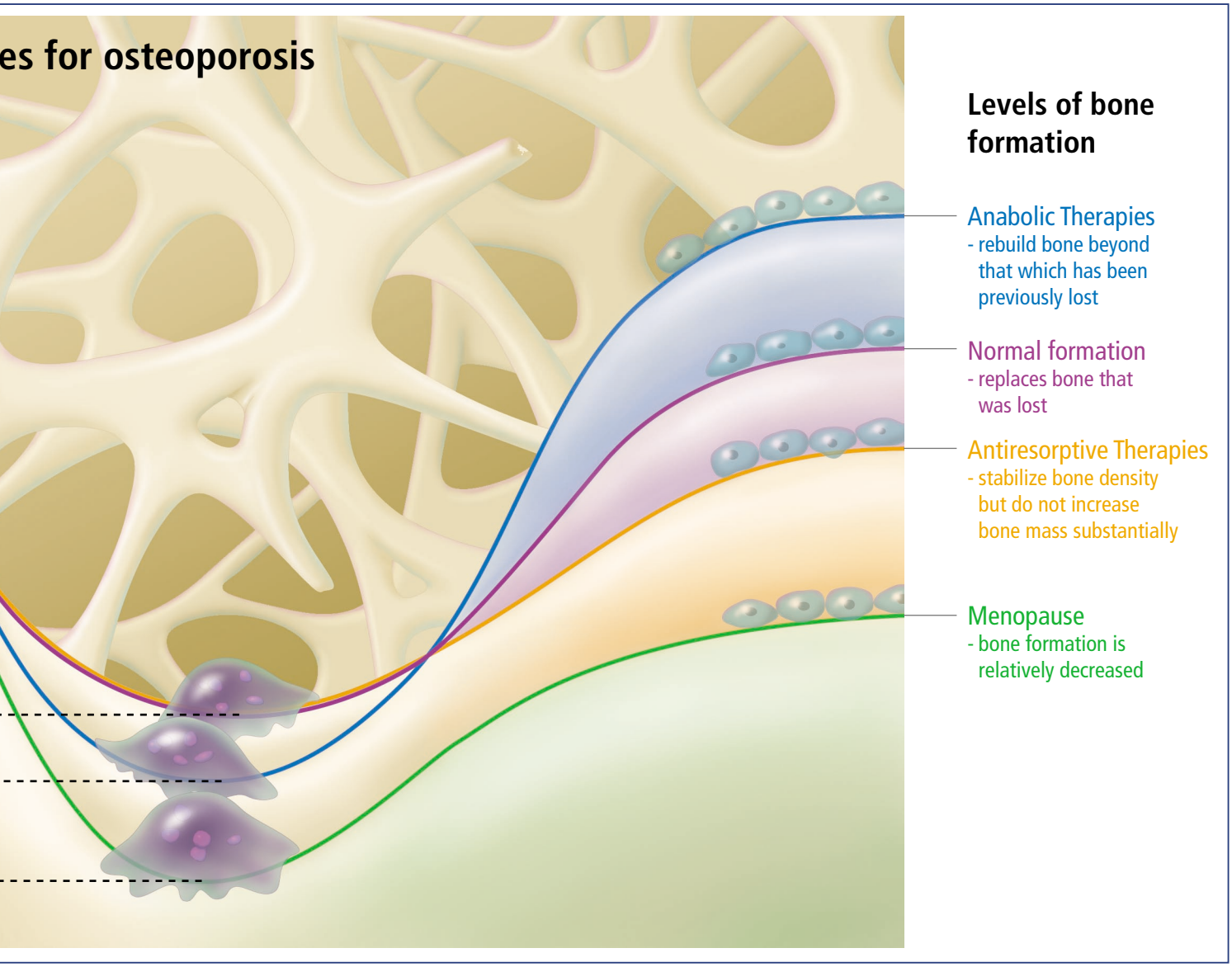
While all of these current antiresorptive therapies are ideal in preventing bone loss, they are not able to significantly stimulate bone formation. In contrast, an anabolic agent that can stimulate bone formation, in excess of 10% per year, should be able to restore trabecular bone microarchitecture, increase bone strength and rebuild bone beyond that which has been previously lost (Figure 1). Such an approach would be ideal for patients with advanced disease. There have been two recent encouraging reports[16,17] of use of an anabolic agent that have sparked the interest of investigators. As the findings are reviewed, it is important to recall past studies investigating sodium fluoride's anabolic effect on bone. Sodium fluoride produced dramatic linear increases in spinal bone mineral density, as much as 30% in some studies. Unfortunately, other studies indicated that, in some patients, treatment with fluoride decreased bone mineral density in cortical sites.[18-19] Increased hip fractures resulted over time. It is necessary, therefore, for studies of anabolic therapies to demonstrate a significant reduction in hip fractures before they become accepted therapies in the treatment of osteoporosis.



Anabolic Therapies

Mundy *et al.* recently reported on the anabolic effects of statins, drugs that are on the market to lower cholesterol and reduce the risk of heart attack. The statins were shown to cause a substantial increase in bone formation in rodents[16] by enhancing the expression of the gene bone morphogenetic protein-2 (BMP-2), which is an autocrine-paracrine factor for osteoblast differentiation.[20] Most of the statins tested increased bone formation. The most potent of the newer statins, both as inhibitors of HMG-CoA reductase and as stimulators of bone formation, are atorvastatin and cerivastatin (the latter is no longer marketed). These compounds are several orders of magnitude more potent in their effects on bone than are mevastatin, lovastatin, simvastatin or fluvastatin. The only statin that did not demonstrate an effect was pravastatin, a synthetic compound which does not exist in the pro-drug (closed ring or lactone) form. Pravastatin is less lipophilic than the other statins, and this property may be responsible for its lack of efficacy on bone cells.

The presumed mechanism by which the statins improve bone mineralization in the animal model is by inhibiting the enzyme, HMG- CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. Whether the statins will have similar effects on human bone is not known. Since this exciting report, there have been many subsequent reports on the effect of statins in humans. The results conflict and many remain in abstract form. There are currently five[21-25] studies in full publication that have measured the association between statin use and fracture risk. Four are observational[21-23,25] and one reanalyzed data from a randomized trial performed to evaluate cardiovascular end points.[24] A statistically significant inverse association with hip fracture risk was reported in three studies,[21-23] supporting an anabolic effect of statins. The remaining two studies did not demonstrate a reduction in the risk of fracture.[24,25] Pravastatin was used in one of these studies, which is the only statin that did not increase bone formation in rats.[24] Prospective studies will be needed to



confirm the anabolic effects of statins on bone and fracture risk reduction.

Recently, Neer *et al.*[17] published a convincing study demonstrating a substantial increase in BMD after 20 months of daily administration of parathyroid hormone (1-34). This study randomized 1637 postmenopausal women with prior vertebral fractures to receive 20 or 40 ug of parathyroid hormone or placebo as a daily subcutaneous injection. BMD increased from baseline by nine and 13% in the lumbar spine and three and six percent in the femoral neck in the 20 and 40 mg group, respectively. In the placebo group, the lumbar spine BMD increased by 1.1% but the femoral neck BMD decreased by 0.7%. The risks of developing vertebral and nonvertebral fractures were also decreased in the parathyroid hormone treated women compared to those receiving placebo. The ability of parathyroid hormone to stimulate bone formation by 13% in less than two years is a phenomenal increase, especially compared to the maximum increase in BMD of 5–7% after three years of the conventional antiresorptive therapies.

The effects of parathyroid hormone on the skeleton, calcium metabolism and bone diseases have been known since the early 1900s.[26,27] If given continuously, intact parathyroid hormone results in a persistent elevation of serum parathyroid hormone concentrations. This leads to an increase in osteoclastic bone resorption over bone formation. The net result is bone loss. When given intermittently to humans as daily injections, parathyroid hormone also increased osteoclastic bone resorption but bone formation is increased to a greater extent. The net result is bone formation.[28,29] This mode of delivery increases osteoblast number and bone formation[30] and is speculated to decrease apoptosis of the osteoblasts and stimulate differentiation of bone lining cells and preosteoblasts to form mature osteoblasts.

The first clinical trial using parathyroid hormone was performed in the 1980s, 14 years after synthetic human parathyroid hormone became available. Parathyroid hormone (1-34) comprises the first 34 amino acids of intact parathyroid hormone (1-84). The region 1-34 is responsible for the anabolic effect of parathyroid hormone. Since 1980, there have been three randomized clinical trails using parathyroid hormone (1-34) in combination with either HRT[31,32] or calcitonin[33] in postmenopausal women with osteoporosis, one using parathyroid hormone in glucocorticoid-induced osteoporosis in postmenopausal women[34] and one using parathyroid hormone in men with idiopathic osteoporosis.[35] The study by Neer *et al.* is the first large-scale study to use parathyroid hormone alone compared to placebo. Side effects are similar in all studies and include hypercalcemia, nausea, headache, leg cramps and irritation at the site of injection. However, the study was terminated early by its sponsor because of the finding of osteosarcoma in rat studies. All of the studies investigating PTH (1-34) reported significant increases in lumbar spine BMD without adverse effects on cortical bone. The study by Neer *et al.* confirmed the antifracture efficacy of vertebral fractures originally documented by Lindsay *et al.* in 1997.[3] The effect of parathyroid hormone on hip fracture reduction remains to be determined.

Conclusion

The long awaited age of anabolic therapies to increase bone formation is rapidly approaching. However, as with all newly developed therapies, we should maintain a healthy skepticism until the ultimate endpoint is proven. Hip fractures which contribute substantially to morbidity, mortality and health care cost must be reduced. ◆

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Antiplatelet Therapy Everyone?

In 1994, the Antithrombotic Trialists Collaboration published its first collaborative overview of randomized trials of antiplatelet therapy, demonstrating the efficacy of aspirin in the secondary prevention of myocardial infarction and stroke. Since that time, further trials have been conducted in patients having coronary artery procedures and in patients with acute stroke, stable angina, atrial fibrillation, peripheral arterial disease and diabetes mellitus. As a result, the group has recently conducted a meta-analysis of antiplatelet therapy among patients at high risk of occlusive vascular events, extending the direct evidence of benefit from antiplatelet therapy to a much wider range of patients.

The Collaborative studied randomized trials, available before 1997, in which antiplatelet regimens were compared to control, or to another antiplatelet regimen, in high-risk patients. They reviewed 287 studies involving 135,000 patients in comparisons of antiplatelet therapy versus control, and 77,000 in comparisons of different antiplatelet regimens. The main outcome measure was 'serious vascular event,' which included non-fatal myocardial infarction (MI), non-fatal stroke or vascular death.

In acute stroke patients, evidence showed that patients should start antiplatelet therapy as soon as possible after acute ischemic stroke, preferably after confirmation by computed tomography, and be continued long-term.

The best aspirin dosage? Based on this analysis, high doses of 500–1500 mg / aspirin daily are no more effective than the less gastrotoxic medium (160–325 mg / day) or low doses (75–150 mg / day). The evidence supports daily doses of aspirin in the range of 75–150 mg for the long-term prevention of serious vascular events, in high-risk patients. A loading dose of 150-300 mg can be provided if an immediate antithrombotic effect is required.

What about other antiplatelet drugs? For patients undergoing percutaneous coronary interventions, adding a short intravenous infusion of glycoprotein IIb / IIIa antagonist reduces the risk of early arterial or stent thrombosis, a benefit that may be maintained for at least six months. The addition of dipyridamole to aspirin has not been clearly shown to produce additional reductions in serious vascular events, but may further reduce the risk for stroke. Studies are ongoing.

Clopidogrel and ticlopidine act by blocking ADP activation of platelets and may be complementary to aspirin in their antiplatelet effects. Promising results have been found in a large trial assessing the effects of adding clopidogrel to aspirin for patients with unstable angina, and a study of acute MI patients is ongoing. For patients who have a definite contraindication to aspirin therapy, clopidogrel might be an appropriate alternative.

Among individuals at high risk of occlusive vascular disease, the proportional risk reductions with antiplatelet therapy are roughly similar in most categories of patients, although smaller in acute stroke. Unless some definite contraindications exist, antiplatelet therapy should be considered routinely for all patients whose medical history implies a significant risk of occlusive vascular disease, and should be continued for as long as the risk remains high. ◆

Source

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ; 2002:71-86.