

Nutritional modulators of bone remodeling during aging¹⁻³

Gregory R Mundy

ABSTRACT

Bone mass declines progressively with age in both men and women from the age of ≈ 30 y. Increased longevity will inevitably be associated with an increase in the incidence of osteoporosis, its associated complications, and incurred health care costs. Current pharmacologic approaches focus on inhibiting bone resorption in those with osteoporosis but do little to improve bone mass. Increased understanding of the cellular events responsible for normal bone formation has led to multiple pathways that can be targeted to positively influence bone mass. Bone morphogenetic proteins (BMPs) have been shown to stimulate bone formation, and the *BMP2* gene was recently linked to osteoporosis. BMP-2 therefore represents one potential molecular target to identify new agents to simulate bone formation. Research is accumulating on the positive effects of dietary sources that stimulate the *BMP2* promoter and their effects on bone formation. Flavonoids and statins occur naturally in food products and have been shown to promote bone formation. It may be possible to influence peak bone mass by dietary means and to decrease the risk of osteoporosis in later life. To ease the future burden of osteoporosis, focusing on prevention will be key, and this could include dietary interventions to stimulate bone formation. *Am J Clin Nutr* 2006;83(suppl):427S–30S.

KEY WORDS Osteoporosis, flavonoid, statin, lovastatin, bone mass, osteoclast, osteoblast, osteoblast proliferation, osteoblast differentiation, resorption inhibitor, red yeast rice, bone morphogenetic protein, BMP, bone remodeling, myeloma, nutritional supplements, dietary supplements

INTRODUCTION

Under current conditions, as more persons in the population live to 100 y of age, the projected increase in longevity will inevitably be accompanied by an increase in the prevalence of osteoporosis and its associated complications. Osteoporosis is responsible for >1.5 million fractures in the United States each year, and it is estimated that those fractures cost upwards of \$17.9 billion annually (1).

For the elderly person in otherwise good health, osteoporosis can be devastating, leading to fractures from minor trauma. A pelvis fractured while getting out of bed, a fractured humerus sustained in brushing against a door, and the more typical compression fractures of the spine and fractures of the hip frequently lead to the need for institutional care and are associated with increased morbidity and mortality. Almost one-quarter of patients aged >50 y die within 1 y of hip fracture (2).

Bone mass declines progressively with advancing age, regardless of sex, although bone loss is greater in women than in men

and is accelerated in the 5–7 y after menopause (3, 4). The rate of bone resorption due to increased osteoclast activity exceeds the rate at which osteoblasts are capable of forming new bone (5), which results in the depletion of calcium, collagen, and protein from bone; increased porosity; and an accompanying increased risk of fracture.

Current pharmacologic approaches to osteoporosis are directed at those who already have the disease or are destined to develop the disease, which is often too little and too late for the aged person with severe osteoporosis accompanied by hip and vertebral fractures. The ideal therapy for osteoporosis needs to be oral, to be safe, to restore bone loss, to inhibit bone resorption, to have desirable pharmacokinetics, and to be effective for disease prevention as well as for treatment.

CURRENT THERAPY

Although most fractures occur in older women, the evidence suggests that, with current therapies, the fracture rate can be reduced by $\approx 50\%$ (6). For the elderly person, however, 1 major fracture per year rather than 2 is not an ideal achievement.

The mainstays of current pharmaceutical therapy are bone resorption inhibitors (bisphosphonates, selective estrogen receptor modulators, and calcitonin), which are useful during the peak years of bone loss in women (ie, in peri- and postmenopausal women) (7). Hormone replacement therapy offers effective antiresorptive protection against osteoporosis (1), but its risk-benefit profile, especially for cardiovascular disease, discourages widespread use (8, 9). Although the antiresorptives slow bone loss, they cause or allow little improvement in bone mass. Bone formation stimulators, such as anabolic agents and parathyroid hormone, are also needed before osteoporosis onset.

There is less activity than might be (**Figure 1**) expected in the area of new drug development for osteoporosis, perhaps because of the cost of bringing new drugs to market in this field for an elderly population. The numbers of patients required to complete phase III studies are prohibitive, and the many hundreds of millions of dollars in “to-market” costs discourage corporate investment in new drug development for osteoporosis. This is compounded by the intolerance of regulatory agencies for new drugs

¹ From the University of Texas Health Science Center at San Antonio, Texas.

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³ Reprints not available. Address correspondence to GR Mundy, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229-3900. E-mail: mundy@uthscsa.edu.

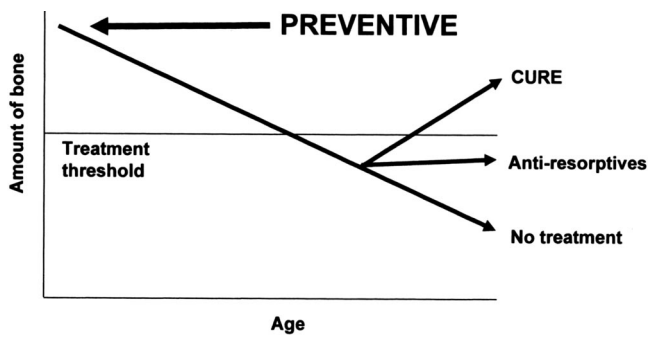


FIGURE 1. Therapeutic approaches to osteoporosis, whereby bone mass generally falls below a threshold before treatment is applied. Curing osteoporosis would ultimately require restoration of bone mass, but most therapies do not stimulate rates of bone formation above the threshold. Optimizing bone mass through prevention will be key to lessening the effects of bone loss with aging.

without a pristine safety profile, because they will be targeted to a chronic disease in a fragile population.

If existing pharmacologic options are not adequate or justifiable as prevention and are too late once the disease is established, what can or should be done? Certainly, we must consider more approaches to primary prevention and the optimization of bone mass in the population. Optimizing bone mass will not make osteoporosis disappear, but it may lessen its impact, and this is especially important if we are going to live well for longer. Primary prevention will be key, with the goal of finding agents in addition to calcium and vitamin D that can optimize peak bone mass, thereby maximizing the buffer available before bone demineralization compromises structural integrity; that can slow the natural rate of bone demineralization, so that existing structural integrity is conserved as much as possible; and that can minimize those factors responsible for accelerated demineralization (eg, smoking, lack of load-bearing activity, and poor diet).

Research done over the past 10 y to identify available pharmaceuticals that could be used prophylactically and therapeutically to optimize bone mass and stimulate new bone formation has coincidentally discovered several dietary supplements that may also be effective. It may be possible to influence peak bone mass and skeletal integrity by dietary means, and evidence exists that soy protein extracts and constituents can influence bone mass (2, 10). Furthermore, we now understand some of the physiologic mechanisms by which these supplements exert this influence.

BONE REMODELING

An understanding of the cellular events responsible for normal bone formation is critical to identifying the properties required for any agent that influences bone mass by stimulating or accelerating new bone formation. The cellular events of focus are osteoblast differentiation, the production of a collagenous bone matrix, and ultimately the mineralization of that bone matrix. The growth factors that control this process are divided into 2 families. The first comprises the growth factors responsible for the initial stages of bone formation, including transforming growth factor β , insulin-like growth factor I, fibroblast growth factor, and the platelet-derived growth factors (PDGFs) (11). These cause osteoclast apoptosis, as well as osteoblast chemotaxis and proliferation. They attract osteoblasts to sites of bone resorption

where they carry out normal bone formation. The second family of growth factors, the bone morphogenetic proteins (BMPs), is unique: these are the growth factors involved in the process of osteoblast differentiation that drive the process of bone formation and mineralization.

BONE MORPHOGENETIC PROTEINS

Since the late 1980s, BMPs have been known to stimulate new bone formation. BMPs represent molecular targets used to identify and develop new agents to simulate the bone-forming process (12, 13). Much is understood about the signal transduction pathway for the BMPs. BMP-2 stimulates the differentiation of mesenchymal cells into osteoblasts and chondrocytes. BMP-2 binds to its receptor, a Ser/Thr kinase, which phosphorylates and activates the intracellular signaling molecules Smad 1 and Smad 5. This in turn leads to the expression of the transcription factor Cbfa1 (Runx2), which results in the expression of several proteins critical for bone formation (14).

Another important pathway in osteoblast differentiation is the Wnt/LRP5 pathway. Several studies found that persons with a naturally occurring mutation in the *LRP5* gene had very thick bones and did not suffer from fractures (15, 16). Osteoporosis occurs in transgenic mice that lack the *Lrp5* gene (17) and in patients with a dysfunctional LRP5 receptor (18). DKK1, a natural inhibitor of the Wnt/LRP5 pathway, is overexpressed in the plasma cells in multiple myeloma, contributing to the characteristic punched out lesions in bone typically seen in this disease (19). This finding has important implications for the treatment of myeloma and its associated bone disease, raising the possibility that a single treatment may affect both neoplastic cells and host cells to decrease tumor burden and repair the associated osteolysis. Mice lacking the gene coding for sFRP1, another antagonist for Wnt, exhibit higher trabecular bone mineral density (BMD), volume, and mineral apposition rates than in normal mice (20).

This Wnt/LRP5 pathway is also linked to the BMP pathway by a cascade of anabolic transcriptional events. The signal starts at the Hedgehog signaling pathway, moving through the BMPs and Wnt/LRP5, and ultimately leads to expression of the critical genes involved in osteoblast differentiation. This pathway provides multiple potential molecular targets that may be manipulated in the process of bone formation. The focus on BMPs is based on an idea that stimulation of this process will in turn lead to the downstream events involved in osteoblast differentiation and produce beneficial effects on bone mass. The goal is to find pharmaceutical or dietary agents to stimulate BMP-2 expression, osteoblast differentiation, and bone formation.

BMP-2 and osteoporosis: a link

In addition to the characterization of the *BMP2* gene promoter and signal transduction pathways, *BMP2* was recently linked to osteoporosis. Linkage analysis in extended osteoporosis families in Iceland found 3 variants in the *BMP2* gene: a missense polymorphism and 2 anonymous single-nucleotide polymorphism haplotypes associated with osteoporosis (21). The association was seen with many definitions of an osteoporotic phenotype, including osteoporotic fractures and low BMD, both before and after menopause. The authors concluded that a region on the short

arm of chromosome 20, where the *BMP2* gene is located, contains a gene or genes that appear to present a major risk factor for osteoporosis and osteoporotic fractures. The evidence further supports the view that *BMP2* is one of the major genes involved in osteoporosis and bone metabolism.

Dietary sources of BMP-2 stimulants: flavonoids and statins

Statins, drugs widely used for lowering serum cholesterol, have been found to enhance new bone formation (22–24) and reduce risk of fractures (25, 26). Postmenopausal women were studied to determine the relation between statin use and BMD (27). Statin use was associated with a significantly higher score at the hip than in nonusers and a trend toward higher scores at the lumbar spine. The results of 18 observational studies of the use of oral statins are equivocal, some showing useful effect and others showing no effect of chronic doses on bone. A meta-analysis (4 prospective studies, 8 observational studies, and 2 clinical trials; sample sizes varied depending on analyses) reported that when all of the published studies are subjected to this type of analysis, it can be concluded that statin use (for lowering serum lipids) is associated with increases in BMD and reduced fracture risk at the hip and vertebrae (25). The clinical benefits are, however, not large and may be obscured in part by widespread use of compounds less active in bone (namely, pravastatin).

Data are also accumulating on the positive effects of flavonoids on BMD and bone formation (2, 28, 29). Flavonoids are a class of phytoestrogens, plant-derived chemicals, that when absorbed via the gut mimic the actions of estrogen (2) and that have been found to increase *BMP2* gene transcription (30). Flavonoids are often used as food supplements, and many of these compounds show biological activity.

Ipriflavone, a commercially available synthetic flavonoid, inhibits osteoclast differentiation and bone resorption in vitro (31, 32) but also stimulates human osteoblast differentiation (33). In vivo, ipriflavone increases bone mass in immobilized rats and also the biomechanical properties of rat bone (34, 35). It also prevents bone loss in ovariectomized rats and in postmenopausal women (36, 37).

Genistein has been shown to prevent bone resorption by promoting bone formation. In a US community-based cohort study of women aged 42–52 y, the Study of Women's Health Across the Nation, dietary intake of genistein correlated with BMD in Japanese women living in the United States (10). This study found that premenopausal, but not perimenopausal, Japanese women whose genistein intakes were greater (ie, those in the highest tertile) had higher spine and femoral neck BMD than did women in the lowest tertile. Another study showed that genistein reduced both trabecular and compact bone loss after ovariectomy in rats and that this protective effect differed from that of estrogen because it depended on stimulation of bone formation rather than on suppression of bone resorption (38). Genistein triggers transcriptional activation of the murine *Bmp2* gene with estrogen receptor alpha ($ER\alpha$), but not $ER\beta$ (30). To varying degrees then, certain flavonoids can exert biological effects on bone turnover in vitro and in vivo.

Red yeast rice (*Monascus purpureus* Went), a herbal product widely used in China, was also found to have a powerful effect on the *BMP2* promoter and on osteoblast differentiation in bone formation assays (39). Commonly used as an ingredient in Chinese cuisine or as a nutraceutical, red yeast rice is an excellent

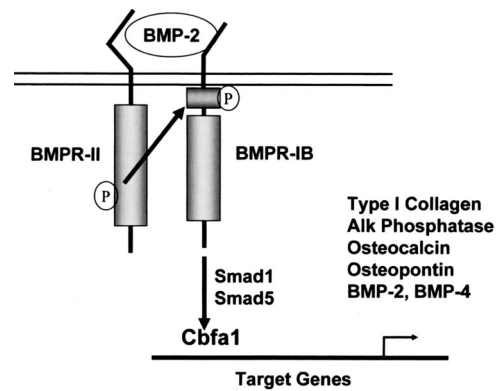



FIGURE 2. The signal transduction pathway for bone morphogenetic protein 2 (BMP-2). BMP-2 binds to its receptor (BMPR), which phosphorylates and activates the intracellular signaling molecules Smad 1 and Smad 5. This in turn leads to the expression of the transcription factor Cbfa1 (Runx2), which results in the expression of several proteins critical for bone formation. Alk, alkaline.

source of monocolins (statins), flavonoids, and phytonutrients (40). Red yeast rice is best known for its lipid-lowering effect (41), which is assumed to be associated with its statin content; its effect on osteoblast differentiation may be linked to and dependent on high (Figure 2) concentrations of both statins and flavonoids.

CONCLUSION

The increase in the population's longevity will inevitably be associated with future increases in the prevalence of osteoporosis. The primary pharmacologic focus on inhibiting bone resorption in those with osteoporosis will do little to improve bone mass. Research done over the past 10 y has uncovered several dietary components that may optimize bone mass and stimulate new bone formation. As we now better understand some of the physiologic mechanisms by which these components exert this influence, we are in a position to target various stages in the process of bone formation that can positively influence bone mass. Bone morphogenetic proteins are one such target that can be used to identify new agents to simulate bone formation. If laboratory results can be confirmed in clinical studies, it is very possible that by manipulating the diet, we will have another component of preventative therapy to optimize bone mass and prevent or mitigate the ravages of osteoporosis.

Timing of intervention will be important where the maximum benefit may be in prevention rather than therapy of osteoporosis. We need to think about primary prevention and find pharmaceutical or dietary agents to stimulate bone formation and optimize bone mass in the population. Although optimizing bone mass will not make osteoporosis disappear, it may lessen the damage. Decreasing morbidity and mortality surrounding osteoporosis is especially important if we want to live longer in a healthy manner. To ease the future burden of osteoporosis, focusing on prevention will be the key, and this should include dietary interventions to stimulate bone formation. 

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