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## Review

# A review of anabolic therapies for osteoporosis

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### Abstract

Osteoporosis results from a loss of bone mass and bone structure such that the bone becomes weak and fractures with very little trauma. Until recently, the approved osteoporosis therapies prevented more bone loss by altering osteoclast activity and lifespan. Recently, attention has turned away from osteoclast inhibition to agents that can stimulate the osteoblast to form new bone, or anabolic agents. This article reviews both approved and experimental anabolic agents that improve bone mass by improving osteoblast activity, or increasing osteoblast number. The use of the anabolic agents to improve bone mass and strength followed by agents that prevent the new bone mass from being lost may offer the ability to cure osteoporosis and reduce bone fracture healing time.

**Keywords:** anabolic; bone morphogenic protein-2 (BMP-2); bone morphogenic protein-7 (BMP-7); parathyroid hormone rhPTH (1-34); parathyroid hormone hPTH (1-84)

### Introduction

Osteoporosis is a disease causing skeletal fragility due to low bone mass or architectural changes in bone structure, and results in fractures from low impact. It is also a disease that increases with the age of the patient. Throughout adult life, the skeleton turns over or remodels to remove old bone tissue and lays down new bone tissue. Bone remodeling is a tightly coupled process in which an area of the bone undergoes osteoclastic bone resorption and then the location of the bone resorption is filled in by osteoblasts. This bone remodeling cycle is synchronized, with resorption and formation being equal, until metabolic or lifestyle changes occur that unbalance the system [1]. Events such as the menopause, taking glucocorticoids, or aging are examples of situations in which bone resorption is greater than bone formation, with a resulting loss of bone mass and structure. In adults, most bone diseases are in bone remodeling, while in children many bone diseases result from remodeling defects [1].

Over the past 10 years, many patients with osteoporosis have been treated with antiresorptive agents (estrogens, bisphosphonates, calcitonin) that reduce osteoclast bone resorption. These agents prevent bone from being broken down, allow remodeling spaces to fill in, and improve bone strength and reduce fracture risk. These agents introduced both the prevention of and treatment of osteoporosis [2-4].

Today, another type of bone-active agents is available in the United States, recombinant human parathyroid hormone (rhPTH) (1-34), which can increase bone mass and strength, and treatment with these bone agents is referred to as 'anabolic therapy'. These anabolic bone-active agents primarily work by stimulating new bone formation on quiescent bone surface that is not simultaneously undergoing remodeling. In addition, these agents increase bone mass to a greater degree than just filling in the bone remodeling space. These new agents have the potential to restore bone

bFGF = basic FGF; BMD = bone mineral density; BMP = bone morphogenic protein; eNOS = endothelial nitric oxide synthase; FGF = fibroblast growth factor; GH = growth hormone; HRT = hormone replacement therapy; IGF = insulin-like growth factor; IL-6 = interleukin-6; OP-1 = osteogenic protein 1; PTH = parathyroid hormone; rhBMP = recombinant human BMP; rhPTH = recombinant human PTH; TGF = transforming growth factor; VEGF = vascular endothelial growth factor.

mass, bringing it back toward normal, and may reduce the risk of osteoporotic fracture more than the currently available antiresorptive agents.

This article provides an overview of a number of anabolic therapies, including parathyroid hormone (PTH), growth hormone (GH), insulin-like growth factor (IGF) 1, strontium, fluoride, bone morphogenetic protein (BMP)-2, BMP-7 (also called osteogenic protein-1 [OP-1]), basic fibroblast growth factors (bFGFs) and vascular endothelial growth factor (VEGF), as examples of approved anabolic therapies and those currently under development. Since a number of excellent reviews on anabolic agents have been published in the past few years, we refer the reader to additional reviews on some of these anabolic agents [5,6].

## Parathyroid hormone

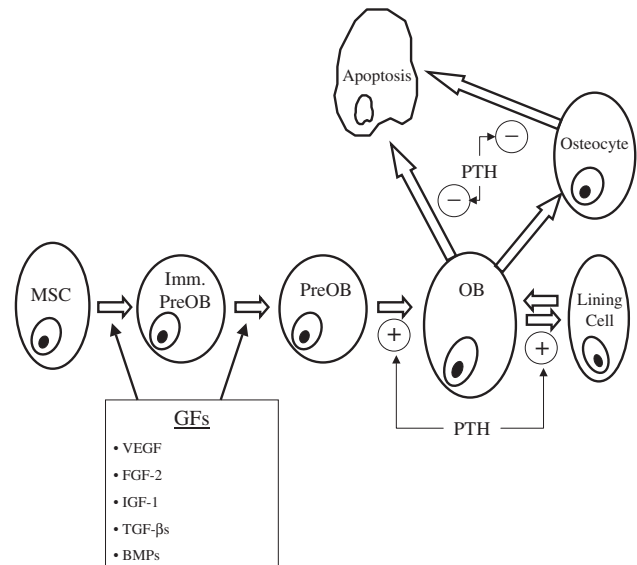
### Proposed mechanisms of action

Hyperparathyroidism is associated with a continuously high serum level of PTH, and bone loss occurs over time [7,8]. However, when PTH is administered by a daily subcutaneous injection, an increase in bone mass occurs in both animals and humans [9–12]. In humans, the anabolic effect of PTH is most pronounced in the trabecular bone. However, histomorphometric studies of iliac crest biopsies from clinical studies of PTH find both thickened trabeculae and increased cortical cross-sectional diameter and increased trabecular number and connections [12]. This could result from PTH stimulating bone-forming cells on the trabecular surface. In addition, by increasing the production of FGF and IGF-1 in the localized bone environment, osteoprogenitor cells adjacent to the endocortical bone surface are stimulated to differentiate into osteoblasts and form osteoid, new bone spicules, and connections [13,14]. Interestingly, PTH injections also stimulate the osteoclast-stimulating cytokines (receptor activator of nuclear factor  $\kappa$ B ligand [RANKL] and IL-6), thus increasing bone resorption simultaneously with the bone-formation actions [15–20]. However, both animal and clinical studies show that PTH exerts major action on bone formation on the trabecular bone surface, followed by some periosteal and endocortical bone surfaces. The bone resorption appears to be localized haversian remodeling within the cortical bone wall [5,12,21] (Fig. 1).

### PTH treatment for postmenopausal osteoporosis

Recombinant human PTH (1-34) has now been approved in the United States as monotherapy for the treatment of postmenopausal women with osteoporosis and men with low bone density and osteoporosis. Neer and colleagues performed a large placebo-controlled trial using daily rhPTH (1-34) of 20 or 40  $\mu$ g, or placebo, for a median follow-up of 21 months [11]. With both rhPTH (1-34) doses, lumbar spine bone mineral density (BMD) increased by 9 to 13%, femoral neck BMD increased by up to 3%, and radial BMD decreased by 2 to 4% [11].

**Figure 1**



Cell differentiation from mesenchymal stem cells (MSCs) to osteoblasts and osteocytes. Parathyroid hormone (PTH) promotes osteoblast proliferation via several mechanisms. PTH stimulates preosteoblasts (PreOBs) and osteoblasts to make growth factors (GFs), which promote proliferation of MSCs to PreOBs. PTH stimulates the conversion of bone-lining cells to osteoblasts, and it prevents osteoblast and osteocyte apoptosis. BMP, bone morphogenetic protein; FGF, fibroblast growth factor; IGF-1, insulin-like growth factor 1; TGF- $\beta$ , transforming growth factor  $\beta$ ; VEGF, vascular endothelial growth factor. Adapted from Whitfield [13].

However, compared with placebo-treated subjects, the risk of new vertebral fractures was reduced in both groups given rhPTH (1-34) by about 65% and the risk of nonvertebral fractures was reduced by about 35%. Interestingly, patients treated with rhPTH (1-34) had less back pain and less height loss than placebo-treated patients. Adverse side effects including headache, nausea, and hypercalcemia were reported in 3% of subjects in the 20- $\mu$ g group and 11% in the 40- $\mu$ g group [5,11]. The daily dose of rhPTH (1-34) approved by the US Food and Drug Administration is 20  $\mu$ g a day by subcutaneous injection for up to 24 months [5,11,13].

### PTH treatment in men with osteoporosis

Two randomized, placebo-controlled studies with PTH were done in men with osteoporosis. Kurland and colleagues randomized men to either PTH (1-34) or placebo for 18 months. Lumbar spine BMD increased by 14% and femoral neck BMD increased by about 3% with PTH in comparison with the placebo-treated group [12,22]. The investigators also performed iliac crest biopsies on eight subjects before and after PTH treatment and performed standard two-dimensional histomorphometry and microcomputed tomography for a three-dimensional assessment. The three-dimensional assessment of trabec-

ular bone showed an increase in trabecular bone volume and trabecular connections [12]. The histomorphometric assessment showed bone formation on both the periosteal and endocortical surface, with a suggestion of less erosion surface. The investigators suggested that PTH might be improving bone mass and bone strength by producing a positive bone balance during remodeling [5,12,22].

Orwoll and colleagues performed a large randomized, placebo-controlled trial of PTH in 437 men with osteoporosis (either idiopathic or hypogonadal) [23]. The men were randomized to placebo or 20 or 40 µg of daily subcutaneous injections of rhPTH (1-34) for an average duration of 11 months. The BMD of the lumbar spine increased in the treatment groups by 6 to 9% and the femoral neck BMD by 1.5 to 3%, and the radial BMD decreased by <1%. Study subjects followed up for 18 months after discontinuation of PTH had a nearly 50% reduction in the risk of vertebral fracture [23].

#### **PTH in combination with other antiresorptive agents**

Previously, there was a concern that PTH treatment would increase the trabecular bone mass at the expense of cortical bone. To protect the skeleton from enlarged remodeling space created by PTH treatment as well as to attempt to obtain further gain in bone density and prevent any decline, a number of investigators evaluated the use of PTH in the presence of antiresorptive agents that would prevent cortical bone remodeling and bone loss. Initial combination studies were performed with hormone replacement therapy (HRT), since bisphosphonates were not yet available. Current combination studies are evaluating bisphosphonate treatment together with or after PTH therapy [5].

Lindsay and colleagues performed the initial randomized, controlled trial of estrogen with PTH (1-34) in postmenopausal women with osteoporosis for 3 years [24]. PTH treatment resulted in BMD increases in the lumbar spine of nearly 13% and in the total hip of about 4%. The incident vertebral fracture risk was also reduced in the PTH-treated group [5].

Roe and Arnaud and colleagues performed an randomized, controlled trial of PTH (1-34) at 40 µg per day with HRT in postmenopausal women for 2 years [25]. After 2 years, the BMD of the lumbar spine as measured by dual-energy x-ray absorptiometry increased by nearly 30% and that of the femoral neck increased by about 8%, in comparison with estrogen alone. Quantitative-computed-tomography measurements of the lumbar spine for trabecular bone volume increased by nearly 80% in the PTH-treated group compared with the placebo group [25] and three-dimensional quantitative computed tomography of the hip showed significant increases in cortical bone

thickness directed centrally on the endocortical surface of the femoral neck [26]. However, since the newly formed bone on the endocortical surface was less mineralized than the cortical bone in the hip, the real changes in hip cortical bone were not well reflected by BMD, because it is a ratio of bone mineral content to bone area.

Recently, Rittmaster and colleagues conducted a randomized, controlled trial with PTH (1-84) treatment for 1 year, followed by alendronate (10 mg/day) for 1 to 2 years [27]. After the 2-year treatment period, the group given a high dose of PTH had about a 14% increase in lumbar spine BMD; however, the placebo group that was treated with alendronate for the second part of the study had a gain of about 6%. It appears that PTH treatment followed by a bisphosphonate was additive in this study. One explanation for the additional gains in bone mass after PTH therapy is that PTH increased bone mass but also opened up remodeling space, especially in the cortical bone compartment. Alendronate treatment allowed remodeling space opened up by PTH to fill in, thereby allowing a substantial increase in bone mass. Whether this type of sequential therapy of an anabolic agent followed by an antiresorptive agent will reduce the risk of fracture is not known. However, additional studies should now be performed to assess whether fracture risk is reduced with this type of sequential therapy [28–30].

Since PTH has been approved for the treatment of osteoporosis, a number of questions have arisen. At present, we do not know if the combination of PTH plus a bisphosphonate will be additive or synergistic to the anabolic bone response [28–30]. Also, we are not sure if patients who have been treated for several years (>3) with a bisphosphonate such as alendronate will have a good anabolic response to PTH. Small pilot studies suggest that patients who are treated for 3 years with a bisphosphonate, alendronate, and are then treated with PTH have a delayed response in biochemical markers of bone turnover and increases in bone mass over the first year compared with patients treated with raloxifene for 3 years prior to PTH [31]. Additional research is needed to determine when best to prescribe PTH in patients chronically treated with a bisphosphonate. At this time, there is no contraindication to treating patients with PTH that have been treated with a bisphosphonate; however, we have no data to support the use of the PTH with a bisphosphonate.

The approval of rhPTH (1-34) was a dramatic step forward in the treatment of osteoporosis. However, a number of other PTH fragments are now being studied. Some are at the preclinical stage and some have gone on to clinical evaluation. Examples are listed but are not limited to PTH (1-84), PTHrP, PTH (1-31), PTH (2-34), PTH (8-84), and PTH (1-28), PTH (13-34), PTH (3-34) [13]. Interesting results were reported from a small placebo-controlled

clinical trial of women with osteoporosis who were treated for 3 months with PTHrP [32]. The study subjects had a 4.7% increase in lumbar spine mass in the PTHrP group, associated with an increase of 60% above the baseline level in the serum osteocalcin, a measurement of bone formation. However, during this 3-month study, the bone resorption markers serum N-telopeptide (NTX) crosslinks and urine deoxypyridinoline (DPD) crosslinks did not change from the baseline levels in the PTHrP or the placebo group [32]. These results suggest that PTHrP, unlike PTH (1-34), may be a more effective uncoupler of bone turnover, as PTHrP did not increase bone resorption at 3 months while all clinical studies of PTH (1-34) and PTH (1-84) show bone resorption markedly increased by 3 months. Additional, large and longer-term studies are needed to determine the durability of this finding [32].

### Growth hormone and insulin-like growth factor 1

GH is critical for the development and maintenance of bone mass [33]. It exerts its bone effects via IGF-1. GH secretion decreases with aging, and therefore so does that of IGF-1. GH deficiency is associated with an increased incidence of fracture in adults [34,35,5]. Studies have suggested that recombinant human GH may improve muscle and bone mass in men over 60 years of age [36], and recombinant human GH has been shown to improve muscle and bone mass in patients with GH deficiency, and has been approved by the Food and Drug Administration for this use.

Mechanisms for the role of IGF-1 in bone metabolism have yet to be clearly defined [37]. In the process of bone remodeling, once bone resorption occurs, growth factors, e.g. IGFs and transforming growth factors (TGFs), are released from bone matrix and promote the recruitment of osteoblasts and osteoclasts to the bone surface. Mice, which lack the IGF-1 gene, have relatively low cortical bone density. IGFs are present in the skeleton, as well as circulation. Type I IGF receptors are present on both osteoblasts and osteoclasts. Most skeletal IGF-1 is derived from local osteoblasts and plays a role in cell differentiation in the osteoblast lineage. Hormones known to exert effects on bone turnover in part regulate IGF-1 expression. Specifically, PTH and estradiol have been shown to enhance IGF-1 transcription in rats [5,37].

There has been concern about the safety of therapeutic GH/IGF-1, because of epidemiologic studies suggesting an association of normal to high serum IGF-1 levels with breast, prostate, and colon cancer [38–40]. Also, use of GH may result (theoretically) in direct metabolic side effects such as diabetes mellitus.

However, GH has been used in osteoporosis studies. Recently, Landin-Wilhelmsen and colleagues performed a

randomized, placebo-controlled trial of postmenopausal women with osteoporosis [41]. The use of subcutaneous recombinant human GH for 18 months in combination with HRT, followed by HRT alone for 30 additional months, resulted in a 14% increase in lumbar spine bone mineral content at the 4-year follow-up versus HRT and placebo. Interestingly, not only did the group given HRT + GH experience an increase in the bone mineral content of the spine and hip within the group and relative to the HRT-only group, but also the lumbar spine and femoral neck bone area was increased from baseline to year 4 in the group given HRT + GH [41]. Therefore, these results demonstrate that GH with HRT was more effective than HRT alone at increasing both bone mineral content and bone size. However, additional studies will need to be performed to determine if the risk of fracture is reduced by GH therapy and if GH has a reasonable safety profile, given that the action of GH on bone is through IGF-1. Finally, the risk of cancer in this group of patients is unknown.

### Strontium

Strontium is chemically similar to calcium and has been shown to play both an anabolic and an antiresorptive role in bone metabolism, in both preclinical and clinical studies [5]. Recent clinical studies, reviewed below, have demonstrated a therapeutic role for strontium ranelate in postmenopausal osteoporosis.

The anabolic and antiresorptive properties of strontium on bone have been demonstrated *in vitro*. Strontium increases the synthesis of collagen and other proteins in osteoblasts and has been shown to increase replication of osteoblast progenitor cells [5,42]. It has been shown to directly induce inhibition of osteoclast bone resorption in rat osteoclast assays incubated with bone slices and to inhibit osteoclast differentiation in a chicken bone marrow culture. In preclinical rat studies, Marie and colleagues reported that treating ovariectomized osteopenic rats with a strontium salt for 60 days improved the bone mineral content and increased the trabecular bone volume to the levels found in sham-treated rats [43].

A large, randomized, double-blind, placebo-controlled trial (PREVOS) was performed to determine if strontium can prevent bone loss due to estrogen deficiency [44]. Strontium treatment (1 g/day) for 2 years in early postmenopausal women gave significant improvements in bone mineral density compared with the placebo, in the lumbar spine (by about 2.4%), femoral neck (3.3%), and total hip (4.1%) ( $P < 0.001$ ). More recently, in a phase III study, the SOTI trial [45], 1649 postmenopausal women with osteoporosis were randomized to treatment with strontium (2 g/day) or placebo. Strontium ranelate reduced the risk of new vertebral fracture over 3 years by 41% compared with placebo ( $P < 0.001$ ). Another phase III study, TROPOS (treatment of peripheral osteoporosis)

was performed using strontium [46]. This study was a randomized, double-blind, placebo-controlled trial with 5091 postmenopausal women, to determine the efficacy of oral strontium ranelate at preventing new nonvertebral fractures and on femoral neck BMD. The treatment group showed a significant increase of femoral neck BMD, by 6.5% of baseline values, and a 33% decreased risk of new nonvertebral fractures ( $P < 0.001$ ). Both studies demonstrated an uncoupling of bone turnover, as the bone formation marker serum alkaline phosphatase increased with strontium treatment and the bone resorption marker serum C-terminal telopeptide of collagen I decreased. This uncoupling of bone turnover, with formation increasing and resorption decreasing, may lend support to the anabolic and antiresorptive properties of strontium on bone. While the adverse event profile was favorable for strontium in both large randomized studies, both additional safety and a better understanding of the bone actions of strontium ranelate are still required.

### Statins

One of the most interesting findings in the bone field recently is the observation that lipophilic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), specifically lovastatin, atorvastatin, cerivastatin, pitavastatin, and simvastatin, may alter bone metabolism [13]. Recent attention has focused on the role of statins, widely prescribed for treatment of cardiovascular disease, as agents capable of promoting bone growth. Possible mechanisms of statins in bone formation involve stimulation of BMP-2 and endothelial nitric oxide synthase (eNOS) [13,47–50]. Statins have been shown to stimulate BMP-2 synthesis in cultured animal and human bone cells. eNOS is found sequestered in invaginations of the osteoblast membrane. Knockout mice lacking the eNOS gene demonstrate reduced bone formation. Statins have been shown to increase the expression and activity of the eNOS gene and to inhibit eNOS-induced osteogenesis in the mouse calvaria system. In studies with human osteoblasts, however, eNOS inhibition did not prevent the action of statins on bone formation [48,49,13].

Preclinical animal studies found statins decreased glucocorticoid-induced bone loss in rabbits and increased bone formation in mouse calvariae [47,51]. In both preclinical rat studies and a small clinical study measuring serum markers of bone remodeling in 14 postmenopausal women using statins, a relative decrease was found in markers of bone resorption, but there was no change in markers of bone formation [13,52].

The clinical studies evaluating statins and bone effects have been from observational cohorts of women taking statins or from data obtained from randomized, controlled clinical trials with information on statin use and fracture endpoints. A meta-analysis of these data report a statisti-

cally significant 57% reduction (CI 0.25–0.75) in the risk of hip fractures and nonspine fractures 0.69 (CI 0.55–0.88) [53]. However, the effects of statins on bone was also evaluated in two large randomized, placebo-controlled studies in which reduction of cholesterol and cardiovascular endpoints were the primary outcomes [54,55]. In both of these randomized controlled studies, statins did not reduce the risk of fracture. Also, in another large clinical study, the Women's Health Initiative Study, women who used statins did not have a significant decrease in fractures after 3 years [56]. While individuals entering a statin trial for cardiovascular disease or the Women's Health Initiative may not have osteoporosis or risk factors for osteoporosis, it does bring into question whether statins have a bone effect that we can measure clinically. Therefore, until a study of statins is performed that evaluates the effects on fracture reduction in patients with osteoporosis, definite recommendations of statin for bone health cannot be made.

### Growth factors and bone morphogenetic proteins

Cytokines expressed during bone formation either from fractures or from other anabolic hormones (PTH, GH) are potential therapeutic agents for stimulating bone growth and bone repair. These include, but are not limited to, IGF-1, TGF- $\beta$ s, fibroblast growth factors (FGFs), VEGF, and BMPs [5,13].

#### Transforming growth factor $\beta$

Osteoblasts and adipocytes are derived from bone marrow mesenchymal stromal cells. TGF- $\beta$  is the most abundant bone growth factor [57]. It is stored in bone matrix and released during bone resorption. TGF- $\beta$  plays a role in proliferation, differentiation, and cytokine expression of bone. It has been shown to increase bone matrix formation in rats and in cultured human bone marrow fibroblasts. Its administration in *in vitro* experiments resulted in increased cell growth and increased matrix proteoglycan secretion and collagen synthesis. It also reduced adipogenesis (which is increased in osteoporosis). Additionally, TGF- $\beta$  was shown to increase VEGF expression by osteoblasts in fetal rat calvarial cells [58].

#### Fibroblast growth factor

FGFs have been shown to act as mitogens on fibroblasts, osteoblasts, and chondrocytes, cells involved in bone growth and fracture healing. In cultured human bone marrow fibroblasts, administration of bFGF yielded an increase in fibroblast colony and size. bFGF administered to growing rats resulted in an increase of the numbers of osteoblast precursor cells, followed by an increase of osteoblasts, and ultimately an increase in endosteal and endochondral bone formation [59]. Pun and colleagues [60] and Lane and Wronski [14,61,62] have demonstrated increased cortical bone mass and trabecular bone

spicule formation within tibial diaphysis and metaphysis of ovariectomized osteopenic rats treated with bFGF. Interestingly, bFGF and PTH, when given to osteoporotic ovariectomized rats for 6 weeks, resulted in similar increases in trabecular bone volume; however, bFGF increased the number of trabeculae and the connectivity whereas the major effect of PTH is on trabecular thickness [62].

#### **Vascular endothelial growth factor**

VEGF is a growth factor that is known to induce neovascularization and is expressed by osteoblasts. It has been shown to promote osteoblast differentiation and migration, as well as to be essential in bone healing [63]. In addition, the bone-forming actions of PTH may result from production of VEGF that increases both differentiation of mesenchymal cells to osteoblasts and endothelial cells. Street and colleagues have demonstrated that inhibiting VEGF function in mice with femoral fractures decreased bone formation and callus mineralization. In mouse femur and rabbit radii fracture models, local application of slow-release VEGF improved callus calcification and volume [63].

#### **Bone morphogenetic protein-2**

Recombinant human bone morphogenetic protein (rhBMP)-2 plays an important role in bone formation and has been shown to enhance fracture healing. It has been shown to induce mesenchymal differentiation into osteoblasts by promoting recruitment of osteoprogenitor cells. BMP-2 has also been shown to stimulate transcription of the *cbfa1* gene, which is essential for osteoblast differentiation [64–66]. In fracture healing, there is increased BMP receptor expression in osteogenic cells near the fracture, in fibroblast-like spindle cells, and in fibroblasts involved in endochondral ossification [67]. Welch and colleagues showed that rhBMP-2 enhanced tibial fracture healing in goats [68]. Subsequently, Bouxsein and colleagues, in a placebo-controlled study, showed improved ulnar 'osteotomy' healing in mature rabbits that were treated with an absorbable collagen sponge containing rhBMP applied to the osteotomy site [69]. In their study, osteotomy healing time was reduced by 33%, the area of mineralized callus was 20–60% greater as measured by quantitative computed tomography scanning, and histologically the callus appeared more symmetric in the rhBMP-2 treatment group [69]. More recently, Govender and colleagues performed a prospective, randomized, controlled study with 450 patients in 11 countries who had sustained open tibial fractures [70]. They compared outcomes in three groups. The control group received standard-of-care therapy, that is, fracture fixation with intramedullary nailing. The two study groups received standard-of-care therapy and intraoperative placement of an absorbable collagen sponge containing rhBMP-2 at 6 or 12 mg. The treatment group given the higher dose had a 44% reduced risk of requiring a secondary intervention due to delayed union versus the con-

trols [70]. BMP-2 has now been approved by the Food and Drug Administration for human fractures (press release, 21 November 2002, Wyeth Pharmaceuticals Inc., Madison, NJ, USA). Recently, BMP-2, when placed in a sponge in an implant cage device (InFUSE bone graft, Wyeth Pharmaceuticals Inc.), reduced the time to lumbar interbody fusion in humans [71]. BMP-2 had also been approved for lumbar interbody spinal fusion with the InFUSE bone graft device in the United States [72].

#### **Bone morphogenetic protein-7**

Like BMP-2, BMP-7 (OP-1) induces ectopic bone formation *in vivo*, and in preclinical and clinical fracture models it promoted bone repair [73–78]. In clinical trials, OP-1, delivered with a type-1 collagen carrier, promoted bridging of a critical defect in the fibula of patients that underwent tibial osteotomy [75]. In addition, OP-1 was found to be equivalent to the gold-standard, autogenous bone graft in a clinical study of patients with nonunions [76]. Based on the result of these clinical trials, OP-1 was granted a humanitarian device exemption for the treatment of established nonunions (press release, 17 October 2002, Stryker Inc., Kalamazoo, MI, USA).

Interestingly, the promotion of bone-healing benefits by both BMP-2 and OP-1 is believed to be due to their ability to stimulate the proliferation and differentiation of mesenchymal and osteoprogenitor cells, and both are angiogenic. The angiogenic effect of OP-1 may be direct and with BMP-2 it may be through VEGF.

#### **Fluoride**

Fluoride has been used for years as an anabolic agent for osteoporosis treatment. It does stimulate the osteoblasts to lay down osteoid and bone mass increases. However, fluoride itself is incorporated into the bone-mineralized matrix, and because fluoroapatite is not as strong as hydroxyapatite, the resulting bone is therefore not as strong as normally mineralized bone [13]. Clinical trials from the early 1990s [79,80] using high-dose fluoride (75 mg twice a day) to treat postmenopausal osteoporosis showed dramatic improvements in lumbar spine BMD in fluoride-treated subjects compared with the placebo group [79]. However, there was no improvement in the incidence of fractures of the lumbar spine and there was an increase in peripheral skeletal fractures with fluoride treatment compared with the control group. In these trials, adverse gastrointestinal effects were common [79]. In a review of the initial studies, investigators believed the subjects may have given too high a dose of fluoride, which weakened the bone matrix. Therefore, additional clinical trials were done using a lower-dose, slow-release formulation (NaF slow release, 25 mg twice a day) and was found to have a better side-effect profile and to give a significant reduction in the risk of lumbar spine fracture in comparison with the placebo group after about 3 years [81]. In

addition, a few studies done with fluoride and a bisphosphonate, etidronate, resulted in a synergistic improvement in BMD in men with osteoporosis [82]. These trials were small, however, and the potential therapeutic role of fluoride in the treatment of osteoporosis has yet to be determined. The challenge relating to the use of fluoride as a bone-building agent is to determine a dose that is safe and builds strong bone. It is possible that a low dose of fluoride with a bisphosphonate may be a viable therapy. Since the cost of fluoride is low, from a public health prospective, and the medication has a good safety profile, additional studies to determine fracture reduction should be pursued.

## Conclusion

A renewed excitement for anabolic therapies for the treatment of osteoporosis and bone fractures has recently occurred with the approval of rhPTH (1-34), BMP-2, and BMP-7. The use of anabolic therapies has shown increased bone mass, a reduced risk of fracture in individuals with osteoporosis, and increased speed of healing of bone fractures and fusions. However, after demonstrating that anabolic agents are effective, we now need to turn our attention to determining how best to use these powerful growth factors and hormones. The potential for short courses of anabolic therapies followed by maintenance therapy with antiresorptive agents may make it possible for patients with osteoporosis to increase their bone mass and maintain bone strength so that their risk of fracture is reduced. Bone growth factors may provide the opportunity to restore lost bone trabecular structure, followed by a therapy such as PTH that can thicken and further strengthen the bone matrix. The challenge now is to find the most efficacious treatment regimens of anabolic agents to prescribe to patients with osteoporosis.

## Competing interests

None declared.

## References

- Lee CA, Einhorn TA: **Introduction to normal bone physiology and pathophysiology.** In *Osteoporosis*. 2nd edition. Edited by Marcus R, Feldman D, Kelsey J. San Francisco, CA: Academic Press; 2001:3-19.
- Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE: **Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures.** *Lancet* 1996, **348**:1535-1541.
- Chesnut CH 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, Kiel D, LeBoff M, Maricic M, Miller P, Moniz C, Peacock M, Richardson P, Watts N, Baylink D: **A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures.** *Am J Med* 2000, **109**:267-276.
- Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR: **Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial.** *JAMA* 1999, **282**:637-645.
- Rubin MR, Bilizekin JP: **New anabolic therapies for osteoporosis.** *Curr Opin Rheumatol* 2002, **14**:433-440.
- Crandall C: **Parathyroid hormone for treatment of osteoporosis.** *Arch Intern Med* 2002, **162**:2297-2309.
- Albright F, Aub JC, Bauer W: **Hyperparathyroidism: a common and polymorphic condition illustrated by seventeen proven cases from one clinic.** *JAMA* 1934, **102**:1276-1287.
- Albright F, Reifenstein EC: *The Parathyroid Glands and Metabolic Bone Disease.* Baltimore: Williams & Wilkins; 1948.
- Hock JM, Gera I, Fonseca J, Raisz LG: **Human parathyroid hormone (1-34) increases bone mass in ovariectomized and orchidectomized rats.** *Endocrinology* 1988, **122**:2899-2904.
- Lane NE, Thompson JM, Strewler G, Kinney JH: **Intermittent treatment with human parathyroid hormone (hPTH 1-34) increased trabecular bone mass but not connectivity in osteopenic rats.** *J Bone Miner Res* 1996, **10**:1470-1477.
- Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsmann AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH: **Effect of parathyroid hormone (-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.** *N Engl J Med* 2001, **344**:1434-1441.
- Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetic K, Muller R, Bilezikian J, Lindsay R: **Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study.** *J Bone Miner Res* 2001, **16**:1846-1853.
- Whitfield JF: **How to grow bone to treat osteoporosis and mend fractures.** *Curr Rheumatol Rep* 2003, **5**:45-56.
- Lane NE, Yao W, Kinney JH, Modin G, Baloosh M, Wronski TJ: **Both hPTH (1-34) increase trabecular bone mass in osteopenic rats however they have different effects on trabecular bone structure.** *J Bone Min Res* 2003, in press.
- Lane N, Yao W, Arnaud C: **Association of serum RANKL and OPG levels with other biochemical markers of bone turnover in glucocorticoid-induced osteoporosis patients treated with hPTH (1-34) [abstract].** *J Bone Miner Res* 2002, **Suppl 1**:F366.
- Lane NE, Yao W, Arnaud CD: **Changes in serum RANKL, OPG and IL-6 during hPTH (1-34) administration in patients with glucocorticoid induced osteoporosis.** *J Bone Miner Res* 2003, **Suppl 1**: in press.
- Mitnick MA, Grey A, Masiukiewicz U, Bartkiewicz M, Rios-Velez L, Friedman S, Xu L, Horowitz MC, Insogna K: **Parathyroid hormone induces hepatic production of bioactive IL-6 and its soluble receptor.** *Am J Physiol Endocrinol Metab* 2001, **280**:E405-E412.
- Greenfield EM, Horowitz Lavish SA: **Stimulation of parathyroid hormone of interleukin-6 and leukemia inhibitory factor expression in osteoblasts is an immediate-early gene response induced by cAMP signal transduction.** *J Biol Chem* 1996, **271**:10984-10989.
- Fu Q, Jilka RL, Manolagas SC, O'Brien CA: **Parathyroid hormone stimulates receptor activator of NFkB ligand and inhibits osteoprotegerin expression via protein kinase A activation of cAMP-response element binding protein.** *J Biol Chem* 2002, **277**:48868-48875.
- Lee S-K, Lorenzo JA: **Parathyroid hormone stimulates TRANCE and inhibits osteoprotegerin messenger ribonucleic acid expression with osteoclast-like cell formation.** *Endocrinology* 1999, **140**:3552-3561.
- Burr DB, Hirano T, Turner CH, Hotchkiss C, Brommage R, Hock JM: **Intermittently administered human parathyroid hormone (1-34) treatment increases intracortical bone turnover and porosity without reducing bone strength in the humerus of ovariectomized cynomolgus monkeys.** *J Bone Miner Res* 2001, **16**:157-165.
- Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP: **Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers.** *J Clin Endocrinol Metab* 2000, **85**:3069-3076.
- Orwoll ES, Scheele WH, Paul S, Adams S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA: **The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis.** *J Bone Miner Res* 2003, **18**:9-17.
- Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, Dempster D, Cosman F: **Randomized controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with**



- osteoporosis. *Lancet* 1997, **350**:550-555.
25. Roe E, Sanchez S, del puerto G, et al.: **Parathyroid hormone 1-34 (hPTH 1-34) and estrogen produce dramatic bone density increases in postmenopausal osteoporosis-results from a placebo-controlled randomized trial [abstract].** *J Bone Miner Res*, 1999, **Suppl 1**:S137.
  26. Cann C, Roe EB, Sanchez SD, et al.: **PTH effect in the femur: envelope-specific responses by 3DQCT in postmenopausal women [abstract].** *J Bone Miner Res* 1999, **Suppl 1**:S137.
  27. Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kendler DL, Rosen CJ: **Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate.** *J Clin Endocrinol Metab* 2000, **85**:2129-2134.
  28. Black DM, Rosen C, Greenspan S, Ensrud K, Bilezikian J, McGowan J: **PTH and bisphosphonates in the treatment of osteoporosis: design of the PTH and alendronate (PATH) trial [abstract].** In *ASBMR 23rd annual meeting*, 2001:5287.
  29. Finkelstein JS, Hayes A, Rao A, Neer RM: **Effects of parathyroid hormone, alendronate or both on bone mineral density in osteoporotic men [abstract].** *J Bone Miner Res* 2002, **Suppl 1**:1007.
  30. Neer R, Hayes A, Rao A, Finkelstein J: **Effects of parathyroid hormone, alendronate, or both on bone density in osteoporotic postmenopausal women [abstract].** *J Bone Miner Res* 2002, **Suppl 1**:1039.
  31. Ettinger B, San Martin JA, Crans G, Pavo I: **Early response of bone turnover markers and bone mineral density to teriparatide (rhPTH 1-34) in postmenopausal women previously treated with an anti-resorptive agent [abstract].** *J Bone Miner Res* 2002, **Suppl 1**:1136.
  32. Horwitz M, Stewart A, Greenspan SL: **Short-term, high-dose parathyroid hormone-related protein as a skeletal anabolic agent for the treatment of postmenopausal osteoporosis.** *J Clin Endocrinol Metab*, 2003, **88**:569-575.
  33. Wuster C, Rosen C: **Growth hormone, insulin-like growth factors. Potential applications and limitations in the management of osteoporosis.** In *Osteoporosis*. 2nd edition. Edited by Marcus R, Feldman D, Kelsey J. San Francisco, CA: Academic Press; 2001: 747-767.
  34. Rosen, T, Wilhelmsen L, Landin-Wilhelmsen K, Lappas G, Bengtsson B-A: **Increased fracture frequency in adult patients with hypopituitarism and GH deficiency.** *Eur J Endocrinol* 1997, **137**:240-245.
  35. Wuster C, Abs R, Bengtsson B-A, Bennmarker H, Feldt-Rasmussen U, Herrberg-Stahl E, Monsom JP, Westberg B, Wilton, P: **The incidence of growth hormone deficiency, growth hormone replacement therapy, and other aspects of hypopituitarism on fracture rate and bone mineral density.** *J Bone Miner Res* 2001, **16**:398-405.
  36. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenkler RA, Cohn L, Rudman IW, Mattson DE: **Effects of human growth hormone in men over 60 years old.** *N Engl J Med* 1990, **323**:1-6.
  37. Yakar S, Rosen CJ: **From mouse to man: redefining the role of insulin-like growth factor-I in the acquisition of bone mass.** *Proc Soc Exp Biol Med* 2003, **228**:245-252.
  38. Hankinson SE, Willet WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M: **Circulating concentrations of insulin-like growth factor-I and risk of breast cancer.** *Lancet* 1998, **351**:1393-1396.
  39. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ: **Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3.** *J Natl Cancer Inst* 1999, **91**:620-625.
  40. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M: **Plasma insulin-like growth factor-I and prostate cancer risk: A prospective study.** *Science* 1998, **279**:563-566.
  41. Landin-Wilhelmsen K, Nilsson A, Bosaeus I, Bengtsson, B: **Growth hormone increases bone mineral content in postmenopausal osteoporosis: a randomized placebo-controlled trial.** *J Bone Miner Res* 2003, **18**:393-405.
  42. Reginster JY: **Strontium ranelate in osteoporosis.** *Curr Pharm Des* 2002, **8**:1907-1916.
  43. Marie PJ, Hott M, Modrowski D, De Pollack C, Guillemin J, Deloffre P, Tsouderos Y: **An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats.** *J Bone Miner Res* 1993, **8**:607-615.
  44. Reginster JY, Deroisy R, Dougados M, Jupsin I, Colette J, Roux C: **Prevention of early postmenopausal bone loss by strontium ranelate: the randomized, two-year, double-masked, dose-ranging, placebo-controlled PREVOS trial.** *Osteoporos Int* 2002, **13**:925-931.
  45. Reginster JY, Hoszowski K, Roces Varela A, Balogh A, Clements M, Fiore C, Cormier C, Schmidt WE, Jensen JB, Prince R, Raeman F, Rizzoli R, Meunier PJ: **Strontium ranelate: a new effective antiosteoporotic treatment reducing the incidence of vertebral and non vertebral fractures in postmenopausal women with osteoporosis.** In *International Osteoporosis Society meeting*. June 2003; Osaka, Japan, in press.
  46. Meunier PJ, Reginster JY: **Design and methodology of the phase 3 trials for the clinical development of strontium ranelate in the treatment of women with postmenopausal osteoporosis.** *Osteoporos Int* 2003, **Suppl 3**:66-76.
  47. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G: **Stimulation of bone formation in vitro and in rodents by statins.** *Science* 1999, **286**:1546-1549.
  48. Garrett IR, Gutierrez G, Chen D, et al.: **Statins stimulate bone formation by enhancing eNOS expression [abstract].** *J Bone Miner Res* 2001, **16**:S141.
  49. van't Hof RJ, Ralston SH: **Nitric oxide and bone.** *Immunology* 2001, **103**:113-118.
  50. Ohnaka K, Shimoda S, Nawata H, Shimokawa H, Kaibuchi K, Iwamoto Y, Takayanagi R: **Pitavastatin-enhanced BMP-2 and osteocalcin expression by inhibition of Rho-associated kinase in human osteoblasts.** *Biochem Biophys Res Commun* 2001, **287**:337-342.
  51. Wang GJ, Chung KC, Shen WJ: **Lipid-clearing agents in steroid-induced osteoporosis.** *J Formos Med Assoc* 1995, **94**:589-592.
  52. Cosman F, Nieves J, Zion M, et al.: **Effects of short-term cerivastatin on bone turnover [abstract].** *J Bone Miner Res* 2001, **16**:S29.
  53. Bauer: *Arch Int Med*, in press.
  54. Bauer DC: **HMG CoA reductase inhibitors and the skeleton: a comprehensive review.** *Osteoporos Int* 2003, **4**:273-282.
  55. Reid IR, Hague W, Emberson J, Baker J, Tonkin A, Hunt D, MacMahon S, Sharpe N: **Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. Long-term intervention with Pravastatin in Ischaemic Disease.** *Lancet* 2001, **357**:509-512.
  56. LaCroix AZ, Cauley JA, Pettinger M, Hsia J, Bauer DC, McGowan J, Chen Z, Lewis CE, McNeeley G, Passaro MD, Jackson RD: **Statin use, clinical fracture, and bone mineral density in postmenopausal women: Results from the women's health initiative observational study.** *Ann Int Med* 2003, **139**:97-104.
  57. Locklin RM, Oreffo ROC, Triffitt JT: **Effects of TGF $\beta$  and bFGF on the differentiation of human bone marrow stromal fibroblasts.** *Cell Biol Int* 1999, **23**:185-194.
  58. Saadeh PB, Mehrara BJ, Steinbrech DS, Dudziak ME, Greenwald JA, Luchs JS, Spector JA, Ueno H, Gittes GK, Longaker MT: **Transforming growth factor-B1 modulates the expression of vascular endothelial growth factor by osteoblasts.** *Am J Physiol* 1999, **277**:C628-C637.
  59. Nagai H, Tsukuda R, Mayahara H: **Effects of basic fibroblast growth factor (bFGF) on bone formation in growing rats.** *Bone* 1995, **16**:367-373.
  60. Pun S, Florio CL, Wronski TJ: **Anabolic effects of basic fibroblast growth factor in the tibial diaphysis of ovariectomized rats.** *Bone* 2000, **27**:197-202.
  61. Wronski TJ, Ratkus AM, Thomsen JS, Vulcan Q, Mosekilde L: **Sequential treatment with basic fibroblast growth factor and parathyroid hormone restores lost cancellous bone mass and strength in the proximal tibia of aged ovariectomized rats.** *J Bone Miner Res* 2001 **16**:1399-1407.
  62. Lane NE, Kumer J, Yao W, Breunig T, Wronski T, Modin G, Kinney JH: **Basic fibroblast growth factor forms new trabeculae that physically connect with pre-existing trabeculae, and this new bone is maintained with an anti-resorptive agent and enhanced with an anabolic agent in an osteopenic rat model.** *Osteoporos Int* 2003, **14**:374-352.
  63. Street J, Bao, M, deGuzman L, Bunting S, Peale Jr. FV, Ferrara N, Steinmetz H, Hoeffel J, Cleland JL, Daugherty A, van Bruggen N,

Redmond HP, Carano RAD, Filvaroff EH: **Vascular endothelial growth factor stimulates bone repair by promoting angiogenesis and bone turnover.** *Proc Natl Acad Sci USA* 2002 **99**: 9656-9661.

64. Wang EA, Israel DI, Kelly S, Luxenberg DP: **Bone morphogenetic protein-2 causes commitment and differentiation in C3h10T1/2 and 3T3 cells.** *Growth Factors* 1993 **9**:57-71.

65. Ahrens M, Ankenbauer T, Schroder D, Hollnagel A, Mayer H, Gross G: **Expression of human bone morphogenetic proteins -2 or -4 in murine mesenchymal progenitor C3H10T1/2 cells induces differentiation into distinct mesenchymal cell lineages.** *DNA Cell Biol* 1993 **12**:871-880.

66. Komori T, Yagi H, Nomura S, Yamaguchi A, Sasaki K, Deguchi K, Shimizu Y, Bronson RT, Gao YH, Inada M, Sato M, Okamoto R, Kitamura Y, Yoshiki S., Kishimoto T: **Targeted disruption of Cbfa1 results in a complete lack of bone formation owing to maturational arrest of osteoblasts.** *Cell* 1997, **89**:755-764.

67. Onishi T, Ishidou Y, Nagamine T, Yone K, Imamura T, Kato M, Sampath TK, ten Dijke P, Sakou T: **Distinct and overlapping patterns of localization of bone morphogenetic protein (BMP) family members and a BMP type II receptor during fracture healing in rats.** *Bone* 1998, **22**:605-612.

68. Welch RD, Jones AI, Bucholz RW, Reinert CM, Tjia JS, Pierce WA, Wozney JM, Li XJ: **Effect of recombinant human bone morphogenetic protein-2 on fracture healing in a goat tibial fracture model.** *J Bone Miner Res* 1998, **13**:1483-1490.

69. Bouxsein ML, Turek TJ, Blake CA, D'Augusta D, Li X, Stevens M, Seeherman HJ, Wozney JM: **Recombinant human bone morphogenetic protein-2 accelerates healing in a rabbit ulnar osteotomy model.** *J Bone Joint Surg* 2001, **83-A**:1219-1230.

70. Govender S, Csimma C, Genant HK, Valentin-Opran A: **Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures.** *J Bone Joint Surg* 2002, **84-A**:2123-2134.

71. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA: **Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2.** *Spine* 2002, **27**:2396-2408.

72. BMP 2-Genetics Institute/ Medtronic-Sofamor Danek/Integra. Bone morphogenetic protein 2-Genetics Institute/ Medtronic-Sofamor Danek/Integra, INFUSE Bone Graft, recombinant human bone morphogenetic protein 2-Genetics Institute/Medtronic-Sofamor Danek/Integra, RhBMP 2-Genetics Institute/Medtronic-Sofamor Danek/Integra. *BioDrugs* 2002, **16**:376-377.

73. Barnes GL, Kostenuik PJ, Gerstenfeld LC, Einhorn TA: **Growth factor regulation of fracture repair.** *J Bone Miner Res* 1999, **14**: 1805-1815.

74. Reddi AH: **Bone morphogenetic proteins: from basic science to clinical applications.** *J Bone Joint Surg Am* 2001, **Suppl 1 (Pt 1)**:S1-6.

75. Geesink RG, Hoefnagels NH, Bulstra SK: **Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect.** *J Bone Joint Surg Br* 1999 **81**:710-718.

76. Friedlaender GE, Perry CR, Cole JD, Cook SD, Cierny G, Muschler GF, Zych GA, Calhoun JH, LaForte AJ, Yin S: **Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions.** *J Bone Joint Surg Am* 2001, **Suppl 1 (Pt 2)**:S151-S158.

77. Cook SD, Dalton JE, Tan EH, Whitecloud TS 3rd, Rueger DC: **In vivo evaluation of recombinant human osteogenic protein (rhOP-1) implants as a bone graft substitute for spinal fusions.** *Spine* 1994, **19**:1655-1663.

78. Margolin MD, Cogan AG, Taylor M, Buck D, McAllister TN, Toth C, McAllister BS: **Maxillary sinus augmentation in the non-human primate: a comparative radiographic and histologic study between recombinant human osteogenic protein-1 and natural bone mineral.** *J Periodontol* 1998, **69**:911-919.

79. Riggs BL, Hodgson SF, O'Fallon WM, Chao EY, Wahner HW, Muhs JM, Cedel SL, Melton LJ 3rd: **Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis.** *N Engl J Med* 1990 **322**:802-809.

80. Kleerekoper M, Peterson EL, Nelson DA, Phillips E, Schork MA, Tilley BC, Parfitt AM: **A randomized trial of sodium fluoride as a treatment for postmenopausal osteoporosis.** *Osteoporos Int* 1991, **1**:155-161.

81. Pak CY, Sakharee K, Adams-Huet B, Piziak V, Peterson RD, Poindexter JR: **Treatment of postmenopausal osteoporosis**

**with slow-release sodium fluoride: final report of a randomized controlled trial.** *Ann Intern Med* 1999, **123**:401-408.

82. Ringe JD, Rovati LC: **Treatment of osteoporosis in men with fluoride alone or in combination with bisphosphonates.** *Calcif Tissue Int* 2001, **69**:252-255.

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