

OSTEOANABOLIC AGENTS: STATE OF THE ART AND POTENTIAL FOR ORTHOPEDIC SURGERY

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INTRODUCTION

Progress in development of safe and effective osteoanabolic agents has been made in the area of osteoporotic bone loss but may have other applications for orthopedic surgery. Skeletal aging is explained as the inexorable loss of bone mass that results from an imbalance between bone formation and resorption that may increase the risk of fracture. Approaches to prevention start in childhood with optimizing the accretion of peak bone mass by appropriate exercise and nutrition. In adults, in addition to proper exercise, nutrition, and avoidance of skeletal toxins like smoking, pharmacological tactics have been devised to diminish the rate of bone resorption with agents such as estrogen, calcitonin, raloxifene, and bisphosphonates. Past trials with osteoanabolic agents like fluoride, growth hormone, and insulin-like growth factor (IGF) have been disappointing because of unacceptable side effects and narrow range of effective doses. There are ongoing strategies to improve the advantage-to-disadvantage profiles of such agents, and to evaluate their potential for other indications, such as accelerating fracture healing or incorporation of prostheses.

THE PARATHYROID HORMONE (PTH) PARADOX

Recent FDA approval of teriparatide (a fragment of parathyroid hormone identified as PTH(1-34) for management of osteoporosis has renewed interest in anabolic actions of different forms of PTH. PTH has been recognized as a hormone that stimulates osteoclast differentiation and bone-resorbing activity. This apparent contradiction is resolved by information about the mechanisms of PTH's anabolic actions.

The intact form of PTH is a peptide with 84 amino acid residues, designated as PTH(1-84). Primary hyperparathyroidism presents with hypercalcemia due to excess secretion of PTH by benign adenoma(s) in the parathyroid gland and historically was associated with radiographic evidence of subperiosteal

bone resorption of the distal phalanges, loss of the lamina dura of the teeth, tapering of distal clavicles, "salt-and-pepper" appearance of the skull, bone cysts, and giant cell tumors in the long bones or gingiva. It is treated by surgical removal of the adenoma(s). In the United States, overt hyperparathyroid bone disease is now seen in less than 5% of patients with primary hyperparathyroidism, but primary hyperparathyroidism itself is a common endocrine disease with incidence of 1 in 500 to 1 in 1000. Only diabetes mellitus and hyperthyroidism are more common endocrine diseases.

In 1932, Selye showed that administration to rats of continuous high doses of PTH resulted in bone loss, whereas intermittent low doses of PTH or some of its fragments resulted in increased bone mass (1). Clinical and experimental research with the latter led to the development of new anabolic therapies capable of increasing the production of bone matrix by osteoblasts and reversing microarchitectural deterioration, resulting in major improvements in both bone quality and bone quantity. Teriparatide, a recombinant human parathyroid hormone consisting of the first 34 of 84 amino acids in human parathyroid hormone, was shown to reduce significantly the risk of both vertebral and non-vertebral fractures in postmenopausal women (2) and in men (3). There are still many unanswered questions regarding PTH treatment of osteoporosis, including the optimal duration of treatment, optimal dosing regimen, mechanism of resistance to its effect after 18-24 months, and the effect of subsequent rechallenge.

CENTRAL ROLE OF THE SKELETAL IGF SYSTEM

Adult bone homeostasis is characterized by a balance between bone formation by osteoblasts and bone resorption by osteoclasts, a process called bone remodeling. Remodeling is regulated by many factors including circulating, i.e. systemic, factors as well as local factors produced and acting within the bone microenvironment. Skeletal insulin-like growth factors (IGFs, a.k.a. somatomedins) are important local factors that stimulate bone formation and that serve as intermediary factors by which systemic agents promote bone formation.

IGFs are part of an axis whereby hypothalamic Growth Hormone Releasing Factor (GHRH) stimulates release of pituitary Growth Hormone (GH, a. k. a. somatotropin). Circulating GH exerts many effects on remote organs, the liver being one of its major target organs. GH induces both hepatic and skeletal production of IGF. IGFs bind to specific receptors on the surface of osteoblasts and result in DNA or matrix synthesis depending on receptor density and differentiation stage of the

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osteoblast. Activity of IGFs can be modulated by high-affinity IGF-Binding Proteins (IGF-BPs), which are produced by bone cells and co-regulated with IGFs. The BPs can be activating or inactivating, in some cases depending upon the phosphorylation state of the protein. In turn, IGF-BP effects can be modified by specific proteases that catalyze their proteolysis. Thus, IGF bioavailability is a complex result of many interactions and can explain temporal and spatial specificity of bone responses to manipulations or treatments.

ROLE OF NUTRITION AND IGF IN SKELETAL HEALTH

Many factors influence the extent of bone formation in an individual, especially nutritional ones. Adequate intake of protein is essential for skeletal growth and maintenance, but excess intake of animal proteins, such as found in Western diets, is associated with osteoporosis. Acid-forming proteins from animal foods cause hypercalciuria and drain the bone of stored mineral. This is an explanation for some vegetarian diets being more protective of bone health. Calcium is required for bone growth and maintenance, but adequate levels are not achieved with typical American diets. Current best estimates for the average calcium requirement are in the range of 1000 mg/day for mature adults and rising to 1200-1400 mg/day by age 75 years. Intestinal absorption of calcium averages approximately 30% and decreases with age. Calcium absorption is inhibited by phosphates, found in abundance in cola softdrinks and in many processed foods. Americans often exceed the phosphate recommendation of 700 mg/day for adults. High intake of sodium leads to increased urinary calcium excretion. Thus, for skeletal health, it is necessary to achieve the proper intake of protein and the proper proportions of calcium and phosphate, and of sodium and potassium in the diet. This is especially difficult for elders to achieve. In addition, dietary micronutrients like vitamin D, vitamin C, vitamin K, magnesium, boron, and other trace minerals have essential roles in bone tissues.

The rate of complications after fracture can be increased by nutritional insufficiencies. The IGF system appears to be directly involved in the mechanisms leading to osteoporotic fracture and to its complications. Studies show low serum concentrations of IGF-I in patients with osteoporotic fractures. Baseline IGF-I levels are associated with length of stay in rehabilitation hospitals. The effects of protein repletion have been investigated in elderly undernourished patients with a recent hip fracture. In several studies, clinical outcomes, including shorter rehabilitation hospital stay, were significantly improved by nasogastric, parenteral, or oral supplementations that rectified protein intake. In the presence of adequate calcium and vitamin D, protein supplements increase serum IGF levels. Evidence shows the importance of nutritional support to prevent and to heal osteoporotic fractures.

THE SOMATOPAUSE

Growth Hormone and IGFs are needed to support skeletal growth of children. Deficiency in children results in short stature. Increased secretion of GH by pituitary tumors leads to gigantism before puberty and to acromegaly after puberty. With aging, there is a decline in serum levels of both GH and

IGFs, a process termed the somatopause. Because GH deficiency is associated with low bone mass that is enhanced with GH therapy, interest rose for replenishing GH and/or IGF to prevent age-associated bone loss and musculoskeletal fragility. An early study reported that administration of GH to healthy elderly men resulted in reduced adiposity and increases in lean body mass and strength (4). Unfortunately, the small 1.6% increase in lumbar bone mineral density was not sustained. For unknown reasons, some subjects appeared to be GH-resistant. Even more troubling is the high incidence of side effects in many trials with recombinant GH, including glucose intolerance (i.e. diabetes mellitus), edema, carpal tunnel syndrome, gynecomastia, orthostatic hypotension, and weight gain. Use of GH-releasing analogs is not associated with significant side-effects, but further studies are needed to show efficacy on bone mass.

There are potential benefits to using recombinant IGF-I rather than GH in the treatment of osteoporosis: direct action on bone formation, avoidance of GH resistance, and reduction in side effects. Nevertheless, a recent study on the relationship between serum IGF-I concentration and the incidence of side effects of therapy with recombinant human growth hormone (rhGH) and recombinant human insulin-like growth factor-I (rhIGF-I) revealed that for both agents, the magnitude of the initial increase in the serum IGF-I concentration was a powerful risk factor for severe orthostatic hypotension, diffuse myalgias, and drug-induced hepatitis (5).

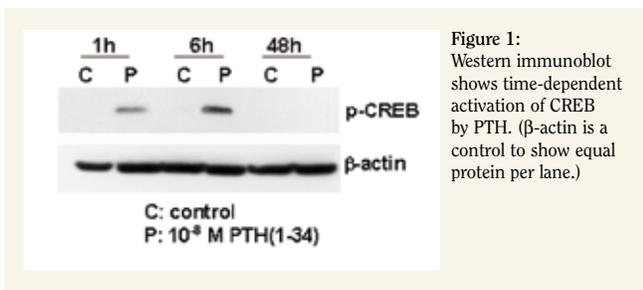
In vivo, IGF-I is transported in blood with a protein, IGF binding protein-3 (IGFBP-3). Because of animal studies showing that administration of the complex of IGF-I/IGFBP-3 had improved safety and efficacy compared with IGF-I alone, the complex was given to severely osteoporotic elderly women for 8 weeks following surgical management of hip fracture (6). All subjects lost hip bone density after hip fracture, but at 3 and 6 months the treated group regained lost bone while the placebo group continued to lose even more. In addition, post-surgical muscle strength and function ability were improved only in the treated group. There were no differences in side effects or clinical abnormalities. Other trials with stable complexes of IGF-I and IGFBP-3 are ongoing to assess long-term safety and efficacy in different populations.

ANABOLIC EFFECTS OF PARATHYROID HORMONE (PTH) VIA SKELETAL IGFs

Another strategy to enhance IGF-I action specifically in bone is exemplified by administration of an agent such as PTH. Animal studies with intermittent PTH demonstrated significant increases in cancellous bone mass and with no changes or slight decreases in cortical bone. PTH was unable to increase bone formation in IGF-I-deficient mice (7). It is also clear from *in vitro* studies that PTH induces IGF-I expression and secretion in osteoblasts (8). Given the issues of safety with administration of GH or IGF-I, it is possible that PTH acts at least in part by increasing local production of IGF-I or serum complexes of IGF and its modulating binding proteins, rather than by increasing serum levels of free IGF.

EFFECTS OF PARATHYROID HORMONE (PTH) ON HUMAN BONE MARROW CELLS (9)

We treated marrow-derived adherent stromal cells (MSCs, a.k.a. mesenchymal stem cells) obtained from subjects undergoing hip replacement with osteogenic supplements (10 nM dexamethasone, 5 mM glycerophosphate, and 170 μ M ascorbic phosphate) \pm 10 nM PTH(1-34). Osteoblast differentiation was assessed by measurement of alkaline phosphatase, an early marker of the osteoblast phenotype. In cultures from a 42-year-old woman, for example, PTH significantly stimulated alkaline phosphatase (780 \pm 49 nmole/min/g compared with control, 601 \pm 80, $p=0.03$). One of the signaling pathways that PTH stimulates in its target cells results in the phosphorylation of CREB (cAMP-responsive element binding protein). We assessed that mechanism with Western immunoblot of phosphorylated CREB in protein extracts of the same MSCs at intervals following treatment with 10nM PTH(1-34). These assays provides evidence for increased osteoblastogenesis and signaling by PTH in human MSCs and indicates the suitability of this cell culture system to assess osteoanabolic effects of PTH and other agents.



OSTEOANABOLIC THERAPIES AND ORTHOPEDIC SURGERY

Currently, anabolic PTH therapy is available only by daily injection of the peptide and is approved for treatment of osteoporosis. Research is targeted to the development of effective oral, buccal, sublingual, transdermal, nasal and pulmonary inhalation formulations.

Once easier delivery forms are available, there may be new enthusiasm for applying osteoanabolic therapies for other orthopedic indications such as impaired fracture healing or joint reconstruction. A number of rat studies, such as (10) and (11), suggest that PTH may enhance fracture healing, but more needs to be known for situations in which repair is compromised and whether the magnitude of stimulation is of clinical significance.

Studies indicate a dramatic drop in serum IGF-I in elders after a hip fracture (12). Whether this drop is a result of chronic malnourishment prior to surgery, of the injury itself, of the surgery, and/or of hospitalization, the theoretical possibility that short-term PTH treatment could have beneficial effects on healing needs further exploration.

DISADVANTAGES OF OSTEOANABOLIC THERAPY

As with other powerful anabolic therapies, there are concerns about overstimulation with chronic therapy for osteoporosis. Long-term carcinogenicity studies in rats revealed that up to 53% of rats that received hPTH (1-34) for 2 years developed osteosarcoma. That is the basis for the FDA requiring a black box warning in the package insert and limiting use for osteoporosis in humans to 2 years. It is generally believed that osteosarcoma is a low risk in humans because of little literature on osteosarcoma in primary hyperparathyroidism (although new reports have appeared since the approval of teriparatide), no osteosarcomas in the thousands of patients treated with teriparatide, the known susceptibility of Fischer 344 rats to osteosarcoma, and the very high doses given to the rats. Hypercalcemia and hypercalciuria are associated with PTH(1-34) (requiring patients to minimize calcium intake), but may be avoided with other PTH analogs. For all these reasons, teriparatide is recommended mainly for patients with severe osteoporosis who are refractory to other forms of anti-osteoporotic therapy. Cost is also an issue; teriparatide (Forteo[®]) costs \$600 per month.

Some immunological responses have been reported. Some tested patients developed antibodies to the peptide and some developed generalized urticarial reactions or local irritation at the injection site. It appears that skeletal responsiveness to teriparatide diminishes after 1.5 years of treatment, but the basis is not known.

Second generation forms of anabolic PTH are being developed to avoid these issues. In blood there are many fragments of PTH besides the 84-amino acid form. It had been believed that they were inactive degradation products, but recent studies indicate distinct and specific activities of many of them. These are being evaluated and derivatized for enhanced potential for osteoanabolic effects without side-effects.

SUMMARY

Research with osteoanabolic agents has eliminated many candidate compounds because of unacceptable side effects and narrow range of effective doses. Increased understanding of the important regulatory role of skeletal IGF raises interest in treatments that work through that mechanism but in a highly controlled manner. Information gained from clinical use of PTH for osteoporosis may have applications for short-term therapy for other orthopedic applications such as fracture healing and joint reconstruction.

Questions remain about patient selection, avoidance of antibody production, and strategies for administration by other than subcutaneous injection. More information is needed about the apparent selectivity of PTH for trabecular bone. Although there are concerns about long-term use of teriparatide, it is likely that short-term use of other PTH derivatives in orthopedic settings will have lower risk for complications.

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