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EDITORIAL

Osteoporotic fracture and parathyroid hormone

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Abstract

Osteoporosis and age-related bone loss is associated with changes in bone remodeling characterized by decreased bone formation relative to bone resorption, resulting in bone fragility and increased risk of fractures. Stimulating the function of bone-forming osteoblasts, is the preferred pharmacological intervention for osteoporosis. Recombinant parathyroid hormone (PTH), PTH(1-34), is an anabolic agent with proven benefits to bone strength and has been characterized as a potential therapy for skeletal repair. In spite of PTH's clinical use, safety is a major consideration for long-term treatment. Studies have demonstrated that intermittent PTH treatment enhances and accelerates the skeletal repair process *via* a number of mechanisms. Recent research into the molecular mechanism of PTH action on bone tissue has led to the development of PTH analogs to control osteoporotic fractures. This review summarizes a number of advances made in the field of PTH and bone fracture to combat these injuries in humans and in animal models. The ultimate goal of providing an alternative to PTH, currently the sole anabolic therapy in clinical use, to promote bone formation and improve bone strength in the aging population is yet to be achieved.

Key words: Osteoporosis; Fracture repair; Parathyroid hormone; Parathyroid hormone-1 receptor; Emerging therapies

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INTRODUCTION

Osteoporosis is a progressive disorder of aging bone in both men and women, and osteoporotic fractures have become a major public health threat in recent years[1,2]. In spite of widespread research, The lack of reliable and effective drugs to cure osteoporosis related fragility fractures remains an important global issue. Long considered a disease of post-menopausal women, osteoporosis is increasingly being recognized among the growing population of elderly men. New treatments and updates are constantly being recognized for treating osteoporosis in women[3,4]. Although only thirty percent of hip fractures occur in men, the mortality rate during initial hospitalization and the first year after fractures twice as high in men as in women. Nevertheless, osteoporosis in men is underdiagnosed and undertreated, and is an increasingly important clinical issue[5,6]. Osteoporosis in men is a heterogeneous clinical entity. While most men experience bone loss with aging, some develop osteoporosis at a relatively young age, often for unexplained reasons (idiopathic

osteoporosis). Declining sex steroid levels and other hormonal changes probably contribute to age-related bone loss, as do impairments in osteoblast number and/or activity[7]. Also, fragility fractures are common in men and are associated with a significant burden in terms of morbidity, mortality and economic cost to the community[7-9].

Intermittent treatment with teriparatide [recombinant human parathyroid hormone (hPTH-(1-34)], the only anabolic hormone, offers the potential to improve skeletal microarchitecture, and is a treatment modality for women with post-menopausal osteoporosis and men at high risk for fractures. Despite its clinical use, PTH has been reported to be associated with incidence of osteosarcoma, and safety is a major consideration for long-term use[10,11]. The molecular mechanisms underlying PTH's action to evoke increased bone mass are not fully understood. Further elucidation is required using more controlled study designs, to develop an understanding the pathophysiology of bone loss, optimize patient care and to yield novel therapeutic strategies for potentiating bone anabolic agents.

OSTEOPOROSIS

"Osteo" means bone, and "porosis" means porous. Osteoporotic bones become more porous with less solid and less dense bone masses. Bone is an active tissue where new bone is being made continuously by osteoblasts, the bone forming cells, and old bone is removed by osteoclasts, the bone resorbing cells, *via* a process known as remodeling. In childhood, more bone is built than removed, and so the bones grow in both mass and size. In older age, osteoporosis results from increased bone resorption and decreased bone formation. The cells that build new bone do not keep up with those that remove bone. The total amount of bone mass then decreases, and osteoporosis may develop as a result. This condition finally makes bone thinner, weaker and more fragile, ultimately leading to loss of their structural and functional protein framework.

The human body also needs enough calcium, phosphorus and hormones, including estrogen in women and testosterone in men, to maintain healthy bone. Sufficient vitamin D is required to allow absorption of calcium from food, which is incorporated into bones to maintain their normal function. Osteoporosis exists in both primary or a secondary forms. Primary osteoporosis is the more common form and is due to the typical age-related loss of bone from skeleton. It is classified as type 1 or postmenopausal osteoporosis. Estrogen deficiency is thought to underlie this form of osteoporosis, rendering the skeleton more sensitive to PTH, and resulting in increased calcium resorption from bone. This in turn decreases PTH secretion, 1,25-dihydroxyvitamin D production, and calcium absorption. This ultimately causes loss of trabecular bone, leading to vertebral crush fractures and Colles' fractures. Primary osteoporosis type 2 or senile osteoporosis occurs in women or men of more than 70 years of age and is usually associated with decreased bone formation along with decreased ability of the kidney to produce $1,25(OH)_2D_3$. Type 3 or secondary osteoporosis results from the presence of other diseases or conditions that predispose to bone loss and occurs equally in men and women and at any age. This type of osteoporosis is associated with a variety of conditions, including hormonal imbalances (e.g. Cushing's syndrome); cancer (notably multiple myeloma); gastrointestinal disorders (especially inflammatory bowel disease which causes mal-absorption); drug use [e.g. corticosteroids, cancer chemotherapy, anticonvulsants, heparin, barbiturates, valporic acid, gonadotropin-releasing hormone, excessive use of aluminum-containing antacids]; chronic renal failure; hyperthyroidism; hypogonadism in men; immobilization; osteogenesis imperfecta and related disorders; inflammatory arthritis (particularly rheumatoid arthritis); and poor nutrition (including malnutrition due to eating disorders)[12-14]. Thus, osteoporosis is classified as a systematic skeletal disease characterized by low bone strength and increased fracture risk[15]. In this disease spine, hip, wrist and other associated bone joints fracture very easily, leading to serious health problems.

OSTEOPOROTIC FRACTURES

Globally more than 30 million people are affected by osteoporosis with about 1.5-2 million osteoporotic fragility fractures happening in every year[16-18]. This includes more than 700 000 vertebral fractures and over 300 000 hip fractures[19]. The mortality rate following a hip fracture in osteoporotic patients is about 10%-20% within the first year, and less than 50% of survivors regain their pre-fracture level of mobility and independence[16]. Furthermore, mortality within 90 d of an osteoporotic fracture in individuals who are older than 65 years is substantially higher than might be expected, and for a subset of these fractures the risk for early lethality increases approximately sevenfold[20]. In the United States alone, osteoporotic fracture cost exceeds US $17 billion per year[21]. The first critical step in reducing the burden of osteoporotic fractures is to identify individuals at high risk of fracture by skeletal health evaluation and to then determine the appropriate pharmacological therapy, applying anabolic or anti-resorptive medication to reduce fracture risk[22,23]. Over the last decade, the prevention of osteoporotic fractures has been limited to the use of anti-resorptive[24] and anabolic drugs, which have proven to be insufficient for decreasing the mortality and morbidity in this patient population.

THERAPEUTIC OPENING FOR FRACTURE REPAIR

The fracture repairing process is biologically controlled and optimized. In approximately 5% to 10% of the 7.9 million fractures sustained annually it is difficult to achieve union[25]. Hence, there is a compelling need to

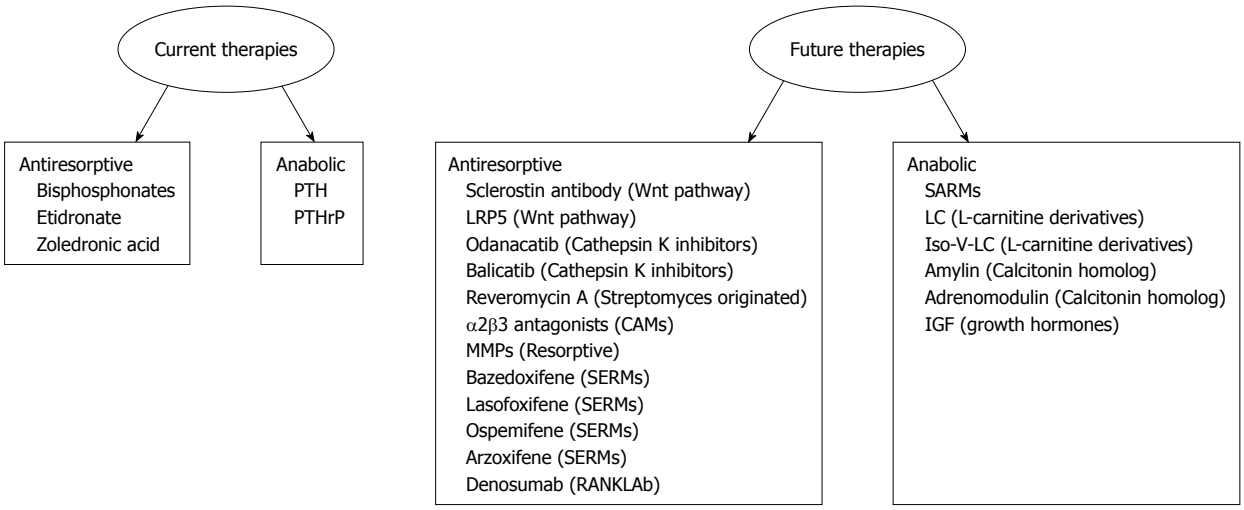

Figure 1 Current and future therapies for osteoporotic fractures[107-109]. SERMs: Selective estrogen receptor modulators; RANKL: Ab-receptor activator of nuclear factor ḰB antibody; Wnt: Wingless signaling pathway; CAM: Cell adhesion molecules; IGF: Insulin growth factor, LC: L-carnitine; Iso-V-LC: Isovaleryl-L-carnitine; MMP: Matrix metalloproteinase; PTH: Parathyroid hormone; LRP: LDL receptor related protein receptor; SARM: Selective androgen receptor modulators.

find novel and effective therapies to enhance fracture repair process. Advances in the understanding of the molecular and cellular signaling pathways of bone biology have led to the development of current and emerging therapeutic agents which are summarized in Figure 1.

The known anabolic effects of PTH on bone formation has led to the development of a human recombinant peptide, teriparatide (1-34 hPTH), corresponding to the first 34 amino acids of PTH. Teriparatide is a drug currently approved for treating patients with osteoporosis who are at high risk for future fracture. Studies have confirmed a striking increase in trabecular bone mass and also showed that an important part of teriparatide's action is to increase cortical bone. A formal trial in postmenopausal women with osteoporosis was conducted by Eli Lilly and Company in the United States. The unexpected occurrence of osteosarcomas in Fisher 344 rats treated long-term with teriparatide provoked an abrupt cessation of this trial. However, ambiguity concerning the relevance of this rat finding to human disease, combined with significant anti-fracture efficacy, led to FDA approval of teriparatide for men and postmenopausal women with osteoporosis "at high risk for fracture" in 2002. Subsequently, teriparatide has been approved also for treatment of patients with glucocorticoid-associated osteoporosis, and papers indicating the utility of this agent for dental and orthopedic applications have begun to appear[26]. In the treatment of osteoporosis, teriparatide works as an anabolic agent stimulating bone formation throughout the skeleton, principally by enhancing osteoblast-derived bone formation relative to osteoclast-derived bone resorption, resulting in a net increase in bone mass. For patients with a fracture, a similar process of increased bone formation is required transiently at the fracture site for repair. Teriparatide has been investigated in animal models and in patients as a potential agent to enhance fracture repair. Interestingly, in conditions with impaired healing such as aging, estrogen withdrawal, and malnutrition fracture repair is expedited by PTH treatment. Subcutaneous injection of PTH once per day led to increased bone mass in patients with osteoporosis[27] and in ovariectomized monkeys[28]. The capability of PTH to augment bone formation is dependent upon the hormone being administered in a way that yields a transient peak blood level[29,30].

It was initially noted that PTH could increase bone mass in rats[31,32]. Using various animal models, several groups have shown that intermittent exposure to PTH stimulates osteoblast differentiation and function *in vivo*[33,34]. Evidence that teriparatide enhances chondrogenesis has generated interest in using the agent for articular cartilage repair. Bukata *et al*[35] and Aleksyniene *et al*[36] found that treatment with PTH during distraction osteogenesis resulted in substantially higher mineralized tissue volume, mineral content, and bending strength. This suggests that treatment with PTH may benefit new bone formation during distraction osteogenesis and could form the basis for clinical application of this therapy in humans.

Knowledge of the effects of intermittent PTH treatment on newly regenerating bone after distraction osteogenesis is very limited. Seebach *et al*[37] reported enhanced mechanical strength and density of new bone after distraction osteogenesis in rats. However, no information is available on the effects of intermittent PTH treatment on distraction osteogenesis in larger animals. Recent experiments with rats have demonstrated that treatment with PTH increases mechanical strength and callus formation in normal healing fractures[38-42]. Furthermore, an increased density of regenerated bone and enhanced fixation of steel implants in rats have been shown after PTH treatment[43,44].

In a recent investigation, to evaluate the potential use as a therapeutic agent for osteoporotic fractures, Kim and Jahng examined the effects of intermittent administration of PTH on fracture healing in ovariectomized rats[45]. At 3 mo post-ovariectomy, bilateral tibial shaft fractures

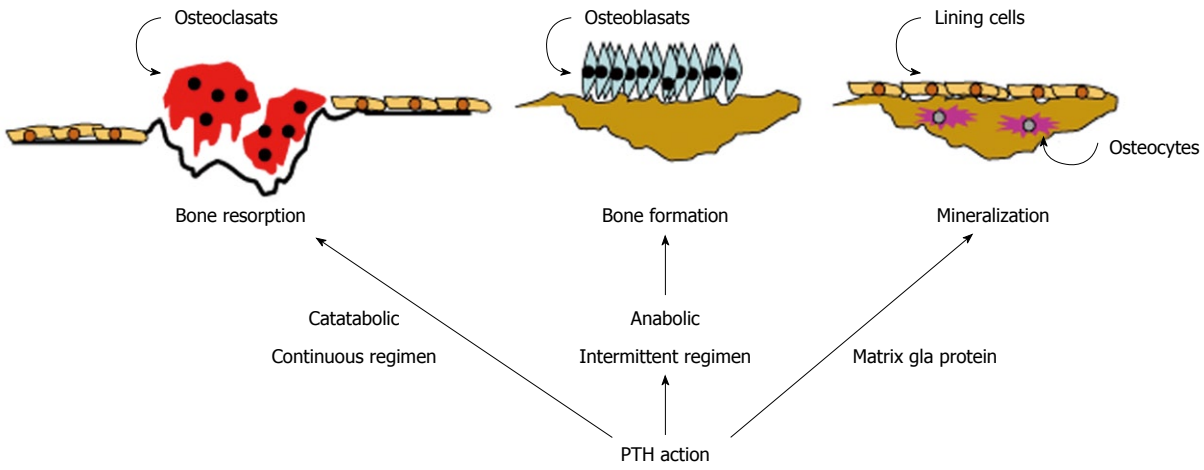

Figure 2 Effect of parathyroid hormone on bone cells.

were induced and stabilized by intramedullary nailing with Kirschner wires. Saline, 17-estradiol, or recombinant human PTH(1-84) was given once a day for 30 consecutive days during fracture healing. Fracture healing was assessed by morphometric and mechanical analysis of fracture callus. Intermittent PTH administration increased the morphometric and mechanical parameters in a dose-dependent manner. 17-estradiol, a bone-resorption inhibiting agent, showed no benefits in terms of fracture healing in ovariectomized rats. Verhaar *et al*[46] reported that exogenous PTH analogs, given as daily subcutaneous injections, stimulate bone formation, increase bone mass and bone strength, and improve calcium balance.

Traditionally PTH was thought to be catabolic to the human skeleton as severe osteoporosis and osteitis fibrosacystica may complicate long standing hyperparathyroidism. In 1932 Selye reported the ability of PTH to stimulate osteogenesis[32]. Subsequently, the anabolic effects of PTH have been examined in greater detail[30,47-52]. PTH was initially developed as a drug to treat postmenopausal osteoporotic women, enhancing bone mineral density[29], cortical thickness and trabecular bone volume[53,54] compared to placebo controls. In addition to its anabolic effects on bone turnover[29,47,55] teriparatide was shown in clinical trials to significantly reduce the risk of vertebral and non-vertebral fractures in osteoporotic women[29,56]. In randomized clinical trials PTH was shown to be useful in preventing fracture in osteoporotic subjects[50,57-59]. It is now well accepted that intermittent administration of PTH and PTH-related peptide (PTHrP) has net anabolic effects on bone[47,52,60,61].

Although it is now well established that PTH is a multifunctional molecule with a unique ability to affect the bone metabolism, the biological complexity of bone repair often makes it difficult to specify what events have failed during the repair process. Currently, several PTH analogs are being developed and are under evaluation. In general, PTH analogs are well tolerated and have an acceptable safety profile. They can be used for the prevention and treatment of fractures in postmenopausal women with severe osteoporosis. Thus PTH analogs reduce the risk of vertebral (PTH 1-34 and PTH 1-84) and non-vertebral fractures (only PTH 1-34). In men and women with glucocorticosteroid-induced osteoporosis, PTH 1-34 has been shown to reduce the risk of vertebral fractures[46]. In recent years β-arrestin-based agonists of PTH-1 receptor (PTH1R) have drawn much attention for promoting bone formation independent of G-protein activation[62,63].

MOLECULAR REGULATION OF PTH AND PTHrP IN BONE

It is well established that PTH, secreted from the parathyroid glands, is involved in calcium homeostasis and is a critical mediator of skeletal development and remodeling[64]. There are several reports of the beneficial use of PTH for treating osteoporosis. However, prolonged use of PTH leads to hypercalciurea, hypercalcemia and osteosarcoma[65], thus limiting the safe use of this peptide hormone. Therefore dissecting the molecular mechanisms of PTH actions is essential as this may uncover novel therapeutic targets for the prevention and reversal of osteoporosis and bone-related diseases and allow minimization of the adverse effects of PTH.

Although a large number of *in-vitro, in-vivo* and human studies have been performed, the mechanisms involved in PTH regulation of osteoblast function is poorly understood and only partly characterized. PTH binds to cells of the osteoblast lineage[66,67] and produces both anabolic and catabolic effects (Figure 2). The fact that PTH has dual effects depending on its administration method raises important questions about its mechanisms of action in bone formation and resorption. It was hypothesized that the anabolic and catabolic effects of PTH and PTHrP on osteoblasts occur through activation of signaling cascades different from PTH1R[64]. The PTH and PTHrP signal *via* PTH1R which is a G protein-coupled receptor with 7 transmembrane spanning domains. The receptor is encoded by a multi-exon gene, characterized in human, rat and mouse, with potential for alternate

splicing and alternate promoter usage[68]. Understanding the physiological roles, molecular and cellular actions of PTH and PTHrP began when PTH1R was first cloned in 1990s[69,70]. PTH1R signaling cascades involve adenylate cyclase/protein kinase A, phospholipase C/protein kinase C, and mitogen activated protein kinases, and lead to various biological effects including both anabolic and catabolic actions in bone[71-75]. Recently, Guo *et al*[76] further established that phospholipase C signaling *via* the PTH receptor is essential for normal bone response to PTH. Other studies suggested that FGF2 is equally important for the anabolic action of PTH on bone[77] and a crosstalk between skeletogenesis and FGF receptor was recently highlighted[78]. Among other mechanisms, PTH anabolic action with or without the involvement of Bcl2 has been described[79,80].

Increased bone formation is largely due to a rise in osteoblast number as a result of increased proliferation and differentiation of osteoblasts *in vitro* and *in vivo*[52,73,74,81-87], decrease in osteoblast apoptosis[88,89], and activation of bone lining cells[48,90]. A mechanism involving cell-cell contact in PTH-induced osteoblast proliferation has also been suggested[91]. Numerous targets of PTH and PTHrP as mediators of bone tissue regeneration have been suggested[71]. These include local cytokines and growth factors[92,93], transcription factors[94-96], and several genes such as MMP-13, a matrix metalloproteinase/collagenase[97,98], IL-6[99], IL-18[100], macrophage-colony stimulating factor[101], ephrinB2[102], and osteoblast cell cycle regulatory proteins[72,74,103,104].

Intermittent PTH 1-34 treatment stimulates bone formation, but the molecular mechanisms mediating this effect have not previously been studied in humans. A very recent study hypothesized that an inhibition of BMP signaling by PTH may, over time, limit the availability of mature osteoblasts on bone surfaces and thereby contribute to the observed decline in the anabolic response to PTH[105]. Several critical steps in the actions of PTH beyond receptor activation have been identified and more are yet to be discovered.

CONCLUSION

Fractures usually repair without incident. When fractures associated with osteoporotic bones do not repair in a timely fashion, the result is painful and detrimental to the patient's quality of life. Treatment, in such cases, is time-consuming and expensive for the health care system [106]. Bone repair after orthopedic fracture is a complicated process. PTH is the first bone anabolic drug approved for the treatment of osteoporosis and associated fractures. Intriguingly, a number of animal studies suggest that PTH could be beneficial in the treatment of fractures and could potentially offer a new treatment option for induction of fracture repair in humans. Furthermore, repair of fractures associated with conditions of impaired healing such as aging, estrogen withdrawal, and malnutrition can be expedited by PTH treatment. Although recent advances in molecular bone research using a variety of *in vivo* and *in vitro* models have increased our understanding of the role of PTH in osteoporotic the fracture repair process, pharmacological intervention using PTH cannot at present be considered a "gold standard". Many future therapies are currently under investigation for the management of fractures associated to osteoporosis.

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