Parathyroid Hormone

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22.1 Introduction

Parathyroid hormone (PTH) secreted by the parathyroid glands plays various important roles in calcium homeostasis and in bone remodeling. The secretion of PTH is regulated by extracellular calcium levels and other humoral factors including vitamin D.

PTH induces its biological effects by regulation of gene expression. The human gene encoding for PTH is located on chromosome 11 [1]. Several genetic factors have been identified that are associated with osteoporosis by influencing bone mineral density (BMD), bone turnover, calcium homeostasis, and susceptibility to osteoporotic fractures [2]. Some PTH polymorphisms have been identified showing an association with osteoporosis, fracture risk and fracture healing [3]. Polymorphisms in genes encoding for PTH may contribute to genetic regulation of BMD and thus the susceptibility to fracture risk [3].

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PTH stimulates the proliferation of osteoprogenitor cells, synthesis of alkaline phosphatase, and bone matrix proteins that contribute to hard callus formation and increases strength at the site of fractured bone. During remodeling, PTH promotes osteoclastogenesis restoring the original shape, structure, and mechanical strength of the bone.

22.2 Parathyroid Hormone Physiology

PTH consists of 84 amino acids, whereas the PTH-related peptide (PTHrP) consists of 141 amino acids. Eight of the first 13 amino acids of the PTHrP are identical to those in PTH; others have a large degree of structural homology [1]. Hypercalcemia associated with malignancy has been attributed to a pathological secretion of PTHrP [2, 3].

PTH maintains the physiological extracellular calcium levels utilizing three different mechanisms: regulation of the gastrointestinal calcium absorption, regulation of the renal reabsorption of calcium and phosphate, and regulation of the osteoclastic bone resorption. These activities of PTH reside within the 1–34 N-terminal fragment [2].

A chronic hyperparathyroidism produces hypercalcemia with subsequent osteoporosis and kidney stones and can be primary or secondary to vitamin D deficiency. Hypoparathyroidism is rare and leads to abnormally low blood levels of ionized calcium and elevated levels of phosphorus.

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A paradox effect of PTH, which is in contrast to the known effects of hyperparathyroidism has been described. Osteoanabolic effects have been shown with low-dose intermittent administration of PTH or its fragments. In animal models of post-ovariectomy osteopenia, intermittent PTH therapy increases trabecular osteoblastic activity and increases BMD [2]. Also in humans, the intermittent administration of recombinant human PTH has been shown to stimulate bone formation to a higher extent than bone resorption. This effect is now used in the management of osteoporosis [4].

Secretion of PTH is regulated by extracellular calcium levels and other humoral factors including vitamin D [5]. PTH regulates gene expression and induces biological effects both directly and indirectly. PTH stimulates proliferation and differentiation of osteoblasts and osteoclasts and promotes the synthesis of osteocalcin, fibronectin, and α-1 collagen. PTH also increases trabecular bone mass and skeletal responses to weight bearing and to treatment with estrogen, calcitonin, and vitamin D. As some of these factors may change with age, a modulation of bone metabolism by altered PTH secretion may occur [5]. Furthermore, serum levels of PTH increase with age and are thought to participate in involutional osteoporosis. The age-associated rise in serum PTH is likely related to vitamin D deficiency [6].

The PTHrP is another protein in the PTH pathway, which plays an important role in the skeletal development during the early bone growth through the regulation of chondrocyte proliferation and differentiation [7].

The human gene encoding for PTH is located on chromosome 11. The parathyroid hormone-like hormone gene (PTHLH) encoding for PTHrP is located on chromosome 12, whereas the genes encoding for the PTH-receptor 1 (PTHR1) and PTHR2 are located on chromosomes 3 and 2, respectively [1].

22.3 Genetic Variations of PTH with Bone Mineral Density and Fracture Risk

Decreased BMD is an index of osteopenia, osteoporosis, reduced bone strength, and increased risk of fracture. Association analyses of polymorphisms of candidate genes can suggest markers for genetic risk of osteoporosis. There is a number of papers dealing with PTH gene polymorphism and BMD [1, 5, 8, 9]. Also twin and family studies show that genetic factors influence BMD and hence the risk for osteoporosis [10–14]. Thus, genetic factors are associated with osteoporosis by influencing BMD, bone turnover, calcium homeostasis, and susceptibility to osteoporotic fractures. Polymorphisms in genes encoding PTH may contribute to genetic regulation of BMD and thus susceptibility to fracture risk [15]. Alterations in the PTH gene have associations with fracture risk. Tenne et al. showed that variations in the PTH gene contributed to fracture risk in elderly women [1].

22.4 PTH—The Paradox Effect

In the 1980s and 1990s, studies demonstrated that intermittent treatment with PTH increases osteoblast number and bone formation in growing and adult rats and also increases trabecular bone [4, 16]. The cellular mechanism for this increase in osteoblast number was investigated in 16-month-old female rats. PTH treatment resulted in dramatic increases of osteoblast numbers (626%), and steady state mRNA levels of osteocalcin (946%) and type 1 collagen (>1000%). Similar changes were observed in PTH-treated ovariectomized rats. As the PTH-induced increases of osteoblast numbers did not require proliferation of progenitor cells, we carried out an additional experiment in adult ovariectomized rats to determine the onset of PTH action. Incorporation of [3H]proline in the distal femoral epiphysis of PTH-treated adult ovariectomized rats was increased within 24 h. The authors concluded that the rapid PTH-induced rise in bone formation did not require cell proliferation and was most likely due to activation of preexisting bone lining cells to osteoblasts [17].

In a clinical pivotal trial, the effects of once-daily injections of PTH 1–34 on fractures were tested. 1637 postmenopausal women with prior vertebral fractures were randomly assigned to receive whether 20 or 40 μg of PTH 1–34 or placebo, administered subcutaneously daily. Vertebral radiographs were obtained at base line

and at the end of the study (median duration of observation: 21 months) and serial measurements of bone mass by dual-energy X-ray absorptiometry (DXA) were performed. The results showed that new vertebral fractures occurred in 14% of the women in the placebo group and in 5 and 4%, respectively, of the women in the 20 and 40 μg PTH groups; the respective relative risks of fracture in the 20 and 40 μg groups, as compared with the placebo group, were 0.35 and 0.31 (with a 95% confidence intervals, 0.22–0.55 and 0.19–0.50). New nonvertebral fragility fractures occurred in 6% of the women in the placebo group and in 3% of those in each parathyroid hormone group (relative risk, 0.47 and 0.46, respectively, 95% confidence intervals, 0.25 to 0.88 and 0.25–0.861). As compared with placebo, the 20 and 40 μg doses of PTH increased BMD by 9 and 13% in the lumbar spine and by 3 and 6% more in the femoral neck; the 40 μg dose increased BMD in the shaft of the radius by 2%. Both doses increased total-body bone mineral by 2 to 4% over the placebo group. It was concluded that PTH 1–34 decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body BMD. The 40-μg dose increased BMD more than the 20 μg dose but had similar effects on the risk of fracture and was more likely to have side effects [18].

22.5 Fracture Healing

The role of PTH treatment in fracture healing is currently an intensive area of research. Studies showed that PTH promotes hard callus formation and increases bone osteoporosis at the site of the fracture [18, 19]. PTH influences fracture healing at various levels. These include increased expression of chondrogenic transcription factors resulting in increased chondrocyte differentiation, proliferation, and cartilage formation in the callus [20]. PTH also stimulates the proliferation of osteoprogenitor cells and production of alkaline phosphatase and bone matrix proteins that contribute to hard callus formation. During the remodeling process, PTH promotes osteoclastogenesis by restoring the original shape, structure, and mechanical strength of the bone [2].

22.6 Experimental Studies

The effect of the intermittent application of PTH 1–34 on fracture healing was initially studied in experimental settings in rats by two groups. Andreassen et al. studied the effect of 60 μg/kg and 200 μg/kg PTH 1–34 on callus formation and mechanical strength in a rat tibia shaft fracture model at 20 and 40 days of healing. Control animals with fractures were given vehicle. The 200 μg/kg dose of PTH 1–34 increased the ultimate load by 175% and the external callus volume by 72% after 40 days of healing time. The 60 μg/kg dose of PTH 1–34 increased the ultimate load by 132% and the external callus volume of fractures by 42% after 40 days of healing time. The callus bone mineral content (BMC) increased in all groups. After 40 days, callus BMC in the 200 μg/kg PTH 1–34 group was 108% and callus BMC in the 60 μg/kg PTH 1–34 group was 76% of the control group [21]. Holzer et al. studied the effects of PTH 1–34 in 20 3-month-old male rats that had closed mid-diaphyseal femur fractures and stabilization with retrograde intra-medullary pin. Ten rats received placebo in form of daily subcutaneous injection of 0.9% saline, whereas the other ten rats got a daily subcutaneous injection of 80 μg/kg PTH 1–34. Twenty-one days after fracture, the rats were euthanized, the femurs were removed and subjected to biomechanical testing, bone densitometry (DXA, peripheral quantitative computed tomography (pQCT)), and histologic examination. The treatment group showed significant increases in callus area and mechanical strength. Results of DXA and pQCT indicated an increase in density, although these BMD changes did not achieve statistical significance. Histological examination of the calluses showed an increase in the amount of new bone formed. No differences were observed in the weights of the animals or the sizes of the bones [22]. Both groups concluded that the use of PTH would potentially stimulate fracture healing and should be further tested clinically.

The effect of RS-66271, a PTHrP analogue, on fracture healing has also been studied in rabbits receiving corticosteroids [23]. In rabbit ulnae, a 1-mm defect was created surgically and healing of fractures was delayed by daily injections of

prednisone 2 months before surgery and continued throughout the healing process. Daily injection of RS-66271, starting 1 day after surgery, resulted in union of 9 of 10 ulnae after 6 weeks. In the control group (saline), two bones healed at the same time point. Ulnae of the treatment group showed increased callus size, radiodensity and stiffness compared to controls.

Various experimental studies tried to identify the potential mechanism of PTH on the healing of fractures. Nakajima et al. confirmed the beneficial effect of 10 μ/kg PTH 1–34 in fracture healing in a rat femoral shaft fracture model. Furthermore, they found an increased number of proliferating osteoprogenitor cells at the second day after fracture. mRNA analysis showed increased expression of type I collagen, alkaline phosphatase, osteocalcin and osteonectin suggesting that PTH 1–34 stimulates the proliferation of mesenchymal stem cells and their differentiation into matrix-producing osteoblasts [24].

Alkhiary et al. produced fractures of the femoral diaphysis in 270 rats. Subsequently, the rats were treated with either 5 or 30 μg/kg of PTH 1–34 or vehicle. After 3 weeks, femoral fractures in the group with 30 μg/kg PTH 1–34 showed increased callus formation compared to controls in plain X-rays. Cartilage volume, torsional strength, stiffness, BMC and BMD were maintained at 3 months after fracture [20].

Similar results were seen in the same fracture model by Nakazawa et al. At week two after fracture, there was an increased callus formation in the treatment group (daily subcutaneous injections of PTH 1–34) compared to controls. However, this difference was not seen at week 3 and 4. Furthermore, the cartilage transcription factor sox-9 was up-regulated in the treatment group suggesting a role of PTH 1–34 in the early chondrogenesis and an acceleration of endochondral bone formation [25].

Komatsubara et al. identified an accelerated bone remodeling from woven to lamellar bone due to PTH 1–34 use in the rat femur fracture model compared to controls. Furthermore, increased percentage of cortical bone formation and ultimate load to failure was noticed in the 30 μg/kg PTH 1–34 treated rats compared to controls after 3 months [26].

22.7 Clinical Studies

Data obtained from animal studies cannot predict results in humans, but based on the preclinical findings of accelerated fracture healing in almost all studies, the expectations that PTH may also stimulate bone healing in humans are very high. Up to date, there are only few published reports studying the effects of PTH on healing of fractures in humans. It is already known that PTH accelerates the natural fracture healing process and provides a faster remodeling as it was described through a more rapid shrinkage of the callus and a simultaneous increase of the degree of mineralization of the fracture callus. However, in this study, the observed effects did not result in any significant improvement in mechanical strength at 26 weeks [27].

22.8 Delayed-Unions and Non-Unions

There are some case reports published that support a beneficial role of PTH use on the delayed-unions or non-unions after fractures. A report by Oteo-Alvaro et al. showed healing of a non-union of a traumatic right diaphyseal humerus fracture that underwent intramedullary osteosynthesis. At 6 months postoperative, no radiological signs of healing were seen. Subsequently, daily injections of PTH 1–34 were initiated. At 3 months, bone bridging and after 5 months of PTH 1–34 therapy, healing was seen [28].

Furthermore, Lee et al. showed a potential effect of PTH 1–34 in a series of three cases with non-unions after osteosynthesis in femoral fractures. Daily injections of 20 μg PTH 1–34 were administered for a 3–9-month period resulting in healing without any further need of surgery [29].

22.9 Fracture Healing in Osteoporotic Fractures

The first prospective clinical study of PTH 1–34 was performed in 102 postmenopausal women who had sustained a dorsally angulated distal

radial fracture (Colles' fracture), which needed a closed reduction, but not surgery [30]. The study was a multi-center, randomized, prospective, double-blinded, placebo-controlled clinical trial. The patients received either daily injections with 20 or 40 μg of PTH 1–34 or placebo within 1 week from the day of fracture and continued for 8 weeks in addition to 1000 mg elemental calcium and 800 IU Vitamin D per day. Healing was assessed by both X-rays and CT imaging and defined as healing of 3 of 4 cortices in X-rays. Radiographs and CT scans were assessed by a central quality assurance and reading service. Functional assessments included the self-administered Patient-Rated Wrist Evaluation (PRWE) questionnaire and assessment of grip strength via a Jamar dynamometer. The time to healing was significantly accelerated in the PTH 1–34 20 μg group compared to placebo (7.4 vs. 9.1 weeks). Pain and grip strength were not significantly different. In a subgroup analysis of 27 women from one of this study centers, a dose-dependent improvement in the quality of early callus formation in X-rays at 5 weeks was found [31].

Peichl et al. studied the effect PTH 1–84 on the healing course of osteoporotic pubic fractures. Included patients ($n = 65$) were above the age of 70 years, had osteoporosis and a stable unilateral pubic fracture with no need of surgery. Every third patient received a daily subcutaneous injection of PTH 1–84, which is roughly equivalent to 40 μg of PTH 1–34. However, due to differences in pharmacokinetics and actions between the forms of PTH, the anabolic effect of 100 μg of PTH 1–84 is more comparable to 20 μg of PTH 1–34. Fracture healing was assessed by CT and analysed blinded to treatment allocation. The primary endpoint was percentage of fracture healing at 8 weeks. Furthermore, patients had functional assessment at 8 weeks after fracture by the use of the timed "up and go" test and pain assessment using the visual analogue scale (VAS) every fourth week. Median time to cortical bridging was 7.8 weeks in the PTH group compared to 12.6 weeks in the control group. Healing at 8 weeks follow-up was 100% in the PTH group compared to 9.1% in the controls. Furthermore, patients in the intervention group had significant improvement in functional outcome (pain and mobility) compared to control [19].

Furthermore, the effect of PTH 1–34 on fracture healing of proximal humerus fractures was studied. The main inclusion criterion was a fracture suitable for non-surgical treatment or fixation with osteosutures. Fourty postmenopausal women with a proximal humerus fracture that were suitable for non-operative treatment or fixation with osteosutures were included in this single-center study. Patients were randomized to receive either daily injections with 20 μg PTH 1–34 for 4 weeks or no injection in the control treatment. Initially, pain at rest and during activity was assessed by VAS and prefracture function by using the DASH score. It was repeated at 7 weeks and again at 3 months postfracture. Fracture healing was evaluated by two radiologists by blind qualitative scoring of the callus at 7 weeks. Callus formation was classified as "normal" or "better". Thirty-nine patients completed the follow-up. Radiographically, a correlation of "better" in the PTH 1–34 group and "normal" in the control group was seen. However, there were no statistically significant differences in pain, in use of strong analgesics, or in function between the groups at the follow-up examinations [32].

Another single-center prospective randomized comparative pilot study has been initiated to study the effect of a 6-week course of 20 μg daily subcutaneous injections of PTH 1–34 on the functional recovery after trochanteric hip fractures in elderly patients [33]. Functional outcome will be assessed at 6 and 12 weeks using the Short Physical Performance Battery. The trial is finished by now and results are to be expected soon.

22.10 Stress Fractures

The acceleration of fracture healing by PTH 1–34 has also been described in two cases of metatarsal stress fractures in a 35-year-old patient and a 40-year-old patient. After 4 weeks of daily subcutaneous injections of PTH 1–34, callus formation was observed in X-rays. Furthermore, patients were free of pain [34].

22.11 Atypical Fractures Associated with Bisphosphonate Therapy

Chiang et al. conducted a small prospective study in 14 patients that were long-term bisphosphonate users (4–10 years) and experienced an atypical femoral fracture. Twenty micrograms of PTH 1–34 was administered daily subcutaneously in 5 of these patients for 6 months, whereas the other had no treatment with PTH 1–34. In the PTH 1–34 group, fracture union was seen in two and two further patients were free of pain. All of the treated patients showed increased bone remodelling markers. In the group that did not receive any PTH 1–34 treatment ($n = 9$), six patients had nonunion and persisting pain and one had pain and poor signs of healing [35].

Conclusions

The relationship between PTH and bone was acknowledged almost 100 years ago. Up to the 1980s and 1990s, it was thought that PTH has primarily a negative effect on bone as seen in diseases like chronic hyperparathyroidism. Later on, the so-called "paradox" effect of PTH was described and could be proven both experimentally and clinically. So, for more than 12 years, PTH is well established as an anabolic treatment in osteoporosis to reduce the future fracture risk in patients at high risk and with severe osteoporosis. Its main indication can be seen in the secondary prevention of fractures.

Although widely appreciated among orthopedic surgeons, who use PTH in patients with osteoporosis, the use of PTH 1–34 or PTH 1–84 to accelerate fracture healing is off-label. Several attempts to show a stimulating effect of PTH on fracture healing in clinical trials failed due to various methodological problems. Up to now, reports on PTH effects on fracture healing are limited to case reports, small case series and few prospective studies. Additional results from well-designed and executed clinical studies are needed to clarify the potential effect of PTH on fracture healing in humans.

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