PTH 1-84: bone rebuilding as a target for the therapy of severe osteoporosis

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Summary

Osteoporotic fractures, especially in elderly people, represent a health concern as they are associated with increased morbidity and mortality together with an increased economic burden for the society. During the past 20 years a great effort has been done in order to reduce the risk of fracture and many drugs are now available for this purpose, but osteoporosis is still regarded as an inevitable consequences of the aging process. Osteoporotic fractures occur most frequently in the spine and hip and with lower frequency in the wrist, pelvis, and upper arm. They are associated with significant morbidity and those of the hip and spine are also associated with excess mortality. The correct diagnosis and the adequate treatment of osteoporosis can reduce fracture risk. Together with well known anti-resorptive agents (like bisphosphonates, oestrogen and selective oestrogen receptor modulators) in the past few years anabolic therapy with parathyroid hormone (PTH) has become available for the treatment of severe osteoporosis. Human recombinant intact parathyroid hormone (PTH 1-84) and human recombinant PTH peptide 1-34 (Teriparatide) belong to this group of agents.

This paper will review PTH actions together with the anabolic effect of PTH 1-84 both in reducing fracture risk and in promoting fracture healing. Although in primary hyperparathyroidism bone catabolism prevails on bone anabolism, PTH remains a potent stimulator of osteoblasts and its anabolic properties can be seen when it is given at a low dosage and intermittently. Intermittent PTH can stimulate bone formation to a greater extent and earlier than bone resorption, thus creating the so called "anabolic window".

The TOP study demonstrated that PTH 1-84 is able to reduce the risk of a new fracture in patients with prevalent vertebral fractures, but the same effect was also seen on the incidence of the first fracture in women without fractures at baseline. Moreover PTH produced a continuous increase of bone mineral density, particularly in the cancellous bone. A positive effect of PTH has been described also on fracture healing, consisting both by a shortened time for fracture repair and by an improving of all the parameters of callus formation and development. Although most of the evidence has been obtained in animals some recent studies in humans confirmed, at least in part, these findings. In elderly patients with osteoporosis and fractures PTH treatment may reduce the healing time, improve clinical outcomes and reduce the time of immobilization together with the risk of complications.

KEY WORDS: human recombinant intact parathyroid hormone; PTH 1–84; osteoporotic fractures; fracture risk reduction; fracture healing.

Introduction

As human lifespan is increasing, particularly in industrialized countries, osteoporosis has become a major clinical issue. Osteoporotic fractures, especially in elderly people, represent a health concern as they are associated with increased morbidity and mortality (1). In addition these fractures increase the economic burden due to high surgical costs, long hospitalization and rehabilitation and loss of independence (1, 2). Therefore a great effort has been done in order to reduce the risk of fracture and many drugs are now available for this purpose.

Osteoporosis is characterized both by a reduction of bone mass and a disruption of bone architecture, resulting in increased bone fragility and increased fracture risk (1).

The first description of osteoporosis can be brought back up to the French pathologist Jean Georges Lobstein who in 1929 noticed that some patients' bones were "riddled with larger than normal holes" and that this process increased with increasing age. Even though a widely accepted conceptual description of osteoporosis, based on the measurement of bone mineral density (BMD), was formulated almost 20 years ago (3) this disease is still regarded as an inevitable consequences of the aging process. On the contrary it must be kept in mind that osteoporosis is a well-defined disease that affects more than 75 million people in the United States, Europe and Japan (1) and that its consequences reside in the fractures that may arise. A fractures occurring after a low trauma is commonly considered as osteoporotic. The "low energy" that can cause these kind of fractures may variously be defined as a fall from a standing height or less, or trauma that in a healthy individual would not give rise to fracture (4). Osteoporotic fractures occur most frequently in the spine and hip and with lower frequency in the wrist, pelvis, and upper arm. They are associated with significant morbidity and those of the hip and spine are also associated with excess mortality, with mortality rates of 24% in the first year after hip fracture (5, 6).

Patients who sustain a fracture have an increased risk of further fractures; for example 19% of women with a vertebral fracture will experience a new one within 12 months of the first (7). In Switzerland the annual costs of hospitalization for osteoporotic fractures are almost 3.0 times greater than those for other serious and chronic diseases such as chronic obstructive pulmonary disease, stroke and myocardial infarction (8). Osteoporosis affects approximately 50% of all women over 50 years of age and approximately 20% of all men (9, 10) in the same age range. For women the lifetime risk of suffering a hip fracture is around 17% and it is greater than the risk of breast cancer (11). At the age of 50

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years, approximately 75% of people hospitalized for vertebral fractures have fractures that are attributable to low energy injuries, increasing to 100% by the age of 90 years (12).
The correct diagnosis and the adequate treatment of osteoporosis can reduce fracture risk but even with an accurate diagnosis, patients may not receive correct or appropriate pharmacological therapy (13-17). Together with well known anti-resorptive agents (like bisphosphonates, oestrogen and selective oestrogen receptor modulators) in the past few years anabolic therapy with parathyroid hormone (PTH) has become available for the treatment of severe osteoporosis. Human recombinant intact parathyroid hormone (PTH 1-84) and human recombinant PTH peptide 1-34 (Teriparatide) belong to this group of agents.
This paper will review PTH actions together with the anabolic effect of PTH 1-84 both in reducing fracture risk and in promoting fracture healing.

PTH actions

PTH is produced by the parathyroid glands as a result of serum calcium lowering. PTH restores blood calcium through three main actions (Figure 1): 1) release of calcium and phosphorus from bones by stimulation of osteoclastic activity; 2) decrease of calcium excretion in the kidney (while phosphorus excretion is increased); 3) rise of dietary calcium and phosphorus intestinal absorption trough increased calcitriol formation in the kidney (18).
As a matter of fact a continuous production of PTH increases bone loss, as in primary hyperparathyroidism where PTH enhances bone resorption via an activation of osteclastogenesis. Nonetheless there is evidence for a relative protection of trabecular bone, even in primary hyperparathyroidism (19-21). Although in this disease bone catabolism prevails on bone anabolism, PTH remains a potent stimulator of osteoblasts and its anabolic properties can be seen when it is given at a low dosage and intermittently. Intermittent PTH can stimulate bone formation to a greater extent and earlier than bone resorption, thus creating the so called “anabolic window” (Figure 2). In this temporal anabolic space more bone is formed than resorbed producing both an increase in bone volume and an improvement of microarchitecture with the result of enhancing bone strength (22).
The evidence of rapid new bone formation by intermittent PTH administration is clearly demonstrated by histomorphometric analysis conducted on bone biopsy specimens from humans and from ovariectomized rhesus monkeys (23, 24). Trabecular bone volume, connectivity, bone microarchitecture were increased after treatment as well as biomechanical properties of bone. PTH appears to increase bone volume by increasing the number of bone trabeculae, possibly after the division (tunneling) of thickened trabeculae (24). In rodent models, PTH enhances bone formation to a greater extent at periosteal than at endocortical sites, thus increasing the periosteal circumference that in turn is known to increase bone strength (25). In humans, the anabolic effects of PTH on cortical bone are lower than in rodents, while PTH action on cancellous bone appear to be as pronounced as in animal models (23, 24).

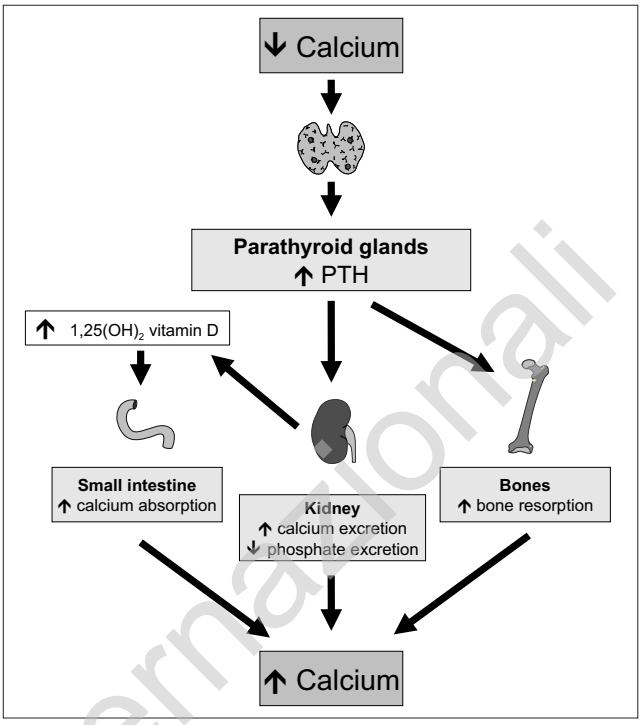

Figure 1 - PTH actions.

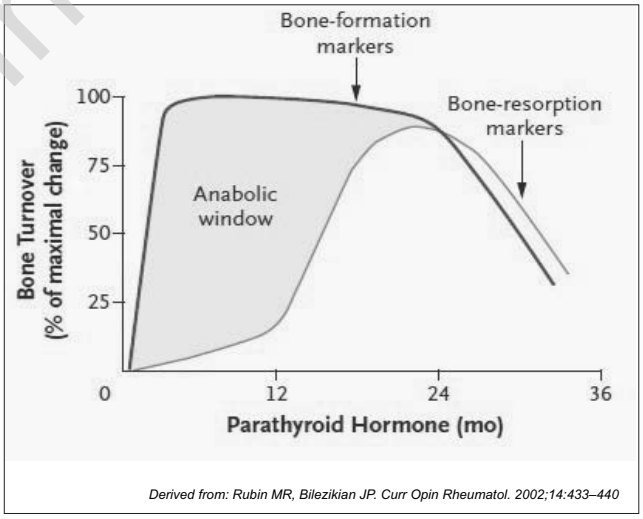

Figure 2 - The “anabolic window”.

Effects of PTH 1-84 on osteoporotic fractures and bone mineral density

The registration of PTH 1-84 for the therapy of severe osteoporosis has been based on the results of ‘‘Treatment of Osteoporosis’’ study (TOP study) (26). This 18 months, randomized, double-blind placebo-controlled study, investigated the effects of PTH 1-84 in 2532 postmenopausal women with osteoporosis. Patients were randomized to receive either 100 mcg of PTH 1-84 daily administered by subcutaneous injection plus placebo (700 mg/day of calcium + 400 IU/day of vitamin D), or placebo alone. The women enrolled were 45-54 years old with a BMD T-score ≤ -3 measured either at lumbar spine, total hip or femoral neck. Women with a BMD T-score ≤ -2.5 and one to four prevalent vertebral fractures were included as well. Finally women older than 55 years were enrolled if their BMD T-score was ≤ -2.5 in the absence of vertebral fractures or ≤ -2.0 with one to four prevalent vertebral fractures. The primary endpoints of the TOP study were both the incidence of new vertebral fractures and the worsening of pre-existing vertebral fractures. The secondary endpoint of the study were the incidence of nonvertebral fractures and the changes in BMD, biochemical markers of bone turnover, bone biopsies and safety data. Although PTH 1-84 is registered for the treatment of severe osteoporosis it is noteworthy that a large part of the women (81%) enrolled in the TOP study were not patients with a high risk of frac-

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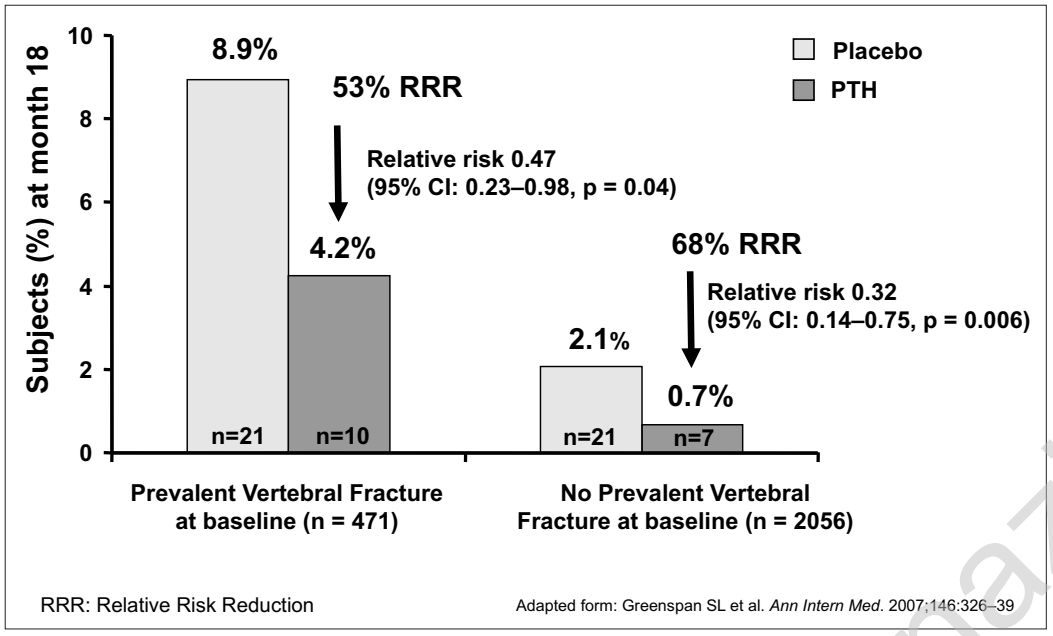

Figure 3 - TOP Study: Reduced risk of new vertebral fractures with/without fracture at baseline.

ture as evinced by the lack of a prevalent fracture. In this group of patients (i.e. without a vertebral fracture at baseline) a significant 68% reduction (p=0.006) in the relative risk of the first vertebral fracture after 18 months of treatment with PTH 1-84 was observed compared to placebo (RR: 0.32; CI: 0.14-0.75). In parathyroid hormone-treated women with a prevalent vertebral fracture at baseline, there was also a significant 53% reduction (p=0.04) in the risk of a new vertebral fracture compared to placebo group (RR: 0.47; CI: 0.23-0.98) (Figure 3). Among secondary endpoints no significant difference were reported between nonvertebral fractures in the treatment (5.6%) and placebo (5.8%) group. This result can be explained by the fact that the TOP study was not designed to detect nonvertebral fractures as the whole population enrolled showed a too low risk for this kind of fractures. As a matter of facts, when a high risk group was selected for a post-hoc analysis (231 patients with lumbar spine BMD T-scores ≤ -3 SD and at least one prevalent vertebral fracture) a trend (non-significant) towards reduced nonvertebral fracture was observed (PTH 1-84 = 6.3% vs. placebo = 10.9%) and this trend resembles the one reported by the Neer trial, with teriparatide (PTH 1-34 = 6.3% vs. placebo = 9.7%) (27).

A statistically significant increases in lumbar spine BMD was seen at months 6, 12 and 18 in the PTH group compared to placebo. At month 18 the total increase in lumbar spine BMD in the PTH group was 6.53% while it showed a 0.32% decrease in the placebo group. At hip and femoral neck level BMD decreased initially in women receiving PTH 1-84 (month 6), but increased thereafter and by month 18 BMD was significantly higher in treatment than in placebo group. On the contrary, the distal radius BMD decreased significantly in the treatment group compared to the placebo group, but this BMD reduction was overcome by the generally favorable changes occurred in bone geometry with the net result of preserving the indices of bone strength (28). In an open-label extension of the TOP study (OLES study), 781 women continued treatment with PTH 1-84 for an extra time of 6 months (29). The extended period of treatment resulted in further small increases in lumbar spine BMD beyond those seen in the TOP study although the increase was markedly smaller than in any of the previous six month periods. Also the total hip BMD continued to slightly increases with PTH 1-84 and the reduction in vertebral fracture risk was sustained with PTH 1-84 therapy in the OLES study (30).

Effects of PTH 1-84 on fracture healing

Two different PTH compounds (PTH 1-34 and PTH 1-84) are approved for the treatment of severe osteoporosis in Europe and both drugs have demonstrated a strong anabolic action on bone (31). PTH 1-34 (teriparatide) consists of the first thirty-four amino acids of the human parathormone (the ''active'' part of this hormone), while PTH 1-84 comprehends also the other fifty amino acids that represent the ''inactive'' part of the hormone. Although no head-to-head comparison studies have been carried out between PTH 1-34 and full-length native PTH 1-84 in terms of their effects on bone, the activity of PTH 1-34 is considered to be equivalent to that of PTH 1-84 (32). Therefore, from now on, we will use the term PTH referring both to PTH 1-34 and PTH 1-84.

A large number of fractures can be complicated by impaired healing and non-union as far as fracture healing is a complex process. The length of the entire process of fracture healing is dependent not only on the type of fracture but also on several internal and external condition, such as aging, co-morbidities, or medications (33). Impaired healing delays the rehabilitation process and affects both the quality of life (QOL) of the patients and the economic burden of the society. Although pharmacological treatment of delayed unions or non-unions in individuals with impaired bone healing as well as accelerated rate of healing in healthy individuals appears to be a promising therapy, in terms of QOL and costs, no approved treatment is available to date for this purpose (34).

Several experiments on otherwise healthy animals have demonstrated that PTH can accelerate fracture healing also under normal circumstances, where no other factors that may impair the healing process are present. Andreassen et al. (35) aimed to investigate the strength of bone at the fracture site in rats closed tibial fractures treated with two different regimens of PTH (60 and 200 mcg/Kg/day) or with vehicle. Also callus dimension (CD), external callus volume (CV), and bone mineral content (BMC) of callus were examined. Bone strength at the fracture site was increased by 75% in the high-dose group, while both dose groups showed increased fracture-site strength after 40 days and no difference in strength could be detected between the two doses. After 20 days for the high dose regimen and after 40 days for both treatment groups CD, CV and BMC of callus were respectively increased by 28%, 72% and 108% compared to vehicle treated animals.

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Table 1 - Differences in fracture healing and VAS score between PTH 1-84 treatment and placebo group.

	PTH 1-84 treatment group (n = 21)	Placebo group (n = 44)	P value
Rate of fracture healing			
Week 4	**4.8%**	**0%**	**0.145**
Week 8	**100%**	**9.1%**	**<0.001**
Week 12	**100%**	**68.2%**	**0.004**
Mean visual analog scale score for pain (VAS)			
basal	**7.6 ± 1.1**	**7.7 ± 1.1**	**0.743**
Week 8	**3.2 ± 7.7**	**6.5 ± 0.9**	**<0.001**

Adapted from: Peichl P et al. J Bone Joint Surg Am. 2011;93:1583-7

Four other studies on rats found similar results confirming a high efficacy of PTH treatment in accelerating the process of fracture healing (36-39).
All these experiments rose high expectation on PTH actions on fracture healing, but their clinical importance was diminished by the fact that the remodeling process in rat bones is not similar to that in humans. Animals more closely resembling human bone physiology are cynomolgus monkeys. It is believed that these animals possess a haversian remodeling system more similar to that of humans and therefore reflect the human fracture healing process better than the rat (40). A study on femur midshaft fractures healing in monkeys, treated with either vehicle, or two different dosage of PTH (0.75 mcg/Kg/twice weekly or 7.5 mcg/Kg/twice weekly) showed a dose-dependently accelerated fracture healing process, recognized by a smaller callus size, a higher degree of mineralization in the callus, as well as an increase in intrinsic material properties of the fractured femur (41). As metaphyseal fractures heal in a different manner than diaphyseal ones Tsiridis et al. (42) established a new model of metaphyseal bone healing in tibial osteotomy of rabbits treated with PTH or vehicle. Daily treatment with 10 or 40 mcg/kg/day for 28 days led to accelerated healing of the tibial osteotomy compared to vehicle treatment as measured by radiography-detected lines of the osteotomy. Moreover the Authors demonstrated that PTH is able to enhance healing of metaphyseal as well as diaphyseal bone.
All these experiments showed that PTH can accelerate the healing process in healthy animals, but their findings could be unsuitable in a clinical orthopedic setting where the utmost problem is the healing of osteoporotic fractures in older patients. Moreover these patients usually present co-morbidities and take several drugs that can slow down the healing process. In order to answer these questions several studies investigated the ability of PTH in enhancing fracture healing in old animals, as well as in ovariectomized or orchiectomized ones and in animal models of malnutrition (43-47). All the studies, even though at different extents, showed a positive effect of PTH in bone healing, confirming the data obtained in healthy animals.
The last problem is to demonstrate if all these results can be applied to human beings. Some case reports demonstrated PTH efficacy in accelerating the bone healing of human fractures (48, 49) and two recent studies addressed the question systematically. The first study (50) randomized 102 postmenopausal, women who had sustained a wrist fracture, to receive a 8 weeks treatment with teriparatide (20 mcg/day or 40 mcg/day) or placebo. The primary end point of the study was time to healing, defined as radiological bridging between three out of four cortices. In the group treated with 20 mcg/day of teriparatide the median time from fracture bridging was significantly lower (7.4 weeks) than placebo group (9.1 weeks). In the group treated with 40 mcg/day of teriparatide the healing time (8.8 weeks) did not significantly differed both from teriparatide 20 mcg/day or placebo. A possible explanation for the lack of effect shown by the higher teriparatide dosage could be the well known decrease in BMD of the radial cortex observed in patients treated with high doses of PTH (27).
The second study investigating fracture healing in humans was recently published by Peichl et al. (51). The Authors randomized 65 patients to receive either PTH 1-84 (100 mcg/day by subcutaneous injection) or placebo (1000 mg of calcium and 800 IU of vitamin D3). The primary endpoint of the study was to determine the effects of PTH 1-84 on the time of radiographic and clinical fracture-healing and reduction of pain in a group of patients with osteoporosis and pelvic fractures. This type of fractures are rarer than typical osteoporotic fractures (i.e. spine, hip and wrist), but they are of particular interest as they are characterized by delayed or impaired healing and by severe pain, both conditions complicating patient mobilization and pain management. In 8 weeks of treatment pelvic fractures were completely healed in 100% of treated patients versus only 9.1% of placebo group ($p < 0.001$). The visual analog scale score for pain significantly improved in the study group as compared with the control group ($p < 0.001$) at 8 weeks too (Table 1). The Authors concluded that in elderly patients with osteoporosis, PTH 1-84 accelerates fracture-healing in pelvic fractures and improves functional outcome.

Effects of PTH 1-84 on QoL

Regarding the improved QOL of patients on therapy with PTH 1-84, recently a prospective, open-label, single arm, multi-center study was published (52) with specific focus on the effects of treatment with PTH(1-84) on quality of life and reported pain in the patients with postmenopausal osteoporosis. The study period was 12 months and 112 patients (mean age: 72 years) were included. After the baseline visit, four follow-up visits were scheduled after 1, 3, 6 and 12 months. As primary efficacy endpoint, the authors considered the QUALEFFO-41 total score (Quality of Life Questionnaire of the European Foundation for Osteoporosis). This questionnaire was administered to the patients at baseline, after 6 months and at the end of the study (12 months). Comparing the scores registered after 12 months with baseline, the QUALEFFO-41 total score showed a significant improvement, from 49.8 (baseline) to 41.3 points (12 months, $p < 0.0001$, Wilcoxon test). The authors registered also a VAS score in order to capture the effects of PTH 1-84 on backpain at rest and on movement. As for QUALEFFO-41 scores, VAS values showed a significant improvement after 12 months with respect to baseline: the authors registered an improvement of about 20% ($p < 0.0001$, Wilcoxon test)

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for pain at rest, and about 36% vs baseline ($p < 0.0001$, Wilcoxon test) for the pain elicited on movement.
The treatment with PTH 1-84 caused also an improvement on mobility in these patients: compared with baseline, the time needed to perform this test improved of around 2 seconds on average.

Conclusions

In conclusion, PTH given intermittently exerts an anabolic action on bone that is greater and faster than its traditional catabolic action. Moreover it is clearly effective in reducing the relative risk of fracture in patient with severe osteoporosis and in increasing bone mineral density, particularly of cancellous bone.
A positive effect of PTH has been described also on fracture healing, consisting both by a shortened time for fracture repair and by an improving of all the parameters of callus formation and development. Although most of the evidence has been obtained in animals some recent studies in humans confirmed, at least in part, these findings. In elderly patients with osteoporosis and fractures PTH treatment may reduce the healing time, improve clinical outcomes and reduce the time of immobilization together with the risk of complications.
Treatment with PTH 1-84 is also associated with a significant improvement of quality of life and mobility with a subsequent decrease of the burden of osteoporotic symptoms for the patients.

References

1. Strom O, Borgström F, Kanis JA, et al. Osteoporosis: burden, health care provision and opportunities in the EU. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2011;6:59-155.
2. Adami S. Full length parathyroid hormone, PTH(1-84), for the treatment of severe osteoporosis in postmenopausal women. Curr Med Res Opin 2008;24:3259-74.
3. Anonymous. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94:646-50.
4. Melton LJ, 3rd, Thamer M, Ray NF, et al. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:16-23.
5. Magaziner J, Lydick E, Hawkes W, et al. Excess mortality attributable to hip fracture in white women aged 70 years and older. Am J Public Health 1997;87:1630-6.
6. Dreinhofer KE, Feron JM, Herrera A, et al. Orthopaedic surgeons and fragility fractures. A survey by the Bone and Joint Decade and the International Osteoporosis Foundation. J Bone Joint Surg Br 2004;86:958-61.
7. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA 2001;285:320-3.
8. Lippuner K, von Overbeck J, Perrelet R, et al. Incidence and direct medical costs of hospitalizations due to osteoporotic fractures in Switzerland. Osteoporos Int 1997;7:414-25.
9. Melton LJ, 3rd, Atkinson EJ, O'Connor MK, et al. Bone density and fracture risk in men. J Bone Miner Res 1998;13:1915-23.
10. Cooper C. The crippling consequences of fractures and their impact on quality of life. Am J Med 1997;103:12S-7S; discussion 7S-9S.
11. Sambrook P, Cooper C. Osteoporosis. Lancet 2006;367:2010-8.
12. Johnell O, Kanis JA, Jonsson B, et al. The burden of hospitalised fractures in Sweden. Osteoporos Int 2005;16:222-8.
13. Port L, Center J, Briffa NK, et al. Osteoporotic fracture: missed opportunity for intervention. Osteoporos Int 2003;14:780-4.
14. Panneman MJ, Lips P, Sen SS, Herings RM. Undertreatment with anti-osteoporotic drugs after hospitalization for fracture. Osteoporos Int 2004;15:120-4.
15. Hauselmann HJ, Rizzoli R. A comprehensive review of treatments for postmenopausal osteoporosis. Osteoporos Int 2003;14:2-12.
16. Gehlbach SH, Fournier M, Bigelow C. Recognition of osteoporosis by primary care physicians. Am J Public Health 2002;92:271-3.
17. Boonen S, Bischoff-Ferrari HA, Cooper C, et al. Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. Calcif Tissue Int 2006;78:257-70.
18. Pleiner-Duxneuner J, Zwettler E, Paschalis E, et al. Treatment of osteoporosis with parathyroid hormone and teriparatide. Calcif Tissue Int 2009;84:159-70.
19. Rubin MR, Bilezikian JP. New anabolic therapies in osteoporosis. Curr Opin Rheumatol 2002;14:433-40.
20. Roschger P, Dempster DW, Zhou H, et al. New observations on bone quality in mild primary hyperparathyroidism as determined by quantitative backscattered electron imaging. J Bone Miner Res 2007;22:717-23.
21. Dempster DW, Parisien M, Silverberg SJ, et al. On the mechanism of cancellous bone preservation in postmenopausal women with mild primary hyperparathyroidism. J Clin Endocrinol Metab 1999;84:1562-6.
22. Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med 2007;357:905-16.
23. Hodsman AB, Kisiel M, Adachi JD, et al. Histomorphometric evidence for increased bone turnover without change in cortical thickness or porosity after 2 years of cyclical hPTH(1-34) therapy in women with severe osteoporosis. Bone 2000;27:311-8.
24. Dempster DW, Cosman F, Kurland ES, et al. 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;16:1846-53.
25. Iida-Klein A, Lu SS, Cosman F, et al. Effects of cyclic vs. daily treatment with human parathyroid hormone (1-34) on murine bone structure and cellular activity. Bone 2007;40:391-8.
26. Greenspan SL, Bone HG, Ettinger MP, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med 2007;146:326-39.
27. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
28. Bogado CE, Zanchetta JR, Gordon CL. Treatment of osteoporotic postmenopausal women with parathyroid hormone (1-84) for 18 months decreases BMD but does not affect indices of bone strenght at distal radius. J Bone Miner Res 2006;21:S112.
29. Greenspan S, Hanley DA, Morris SA, Marriott TB. Bone turnover markers and BMD remain elevated in postmenopausal osteoporotic women through a full 24 months of treatment with human parathyroid hormone 1-84 (PTH). J Bone Miner Res 2006;21:114.
30. Roux C, Clausen J. Sustained effect of PTH (1-84) on the risk of vertebral fractures 12 months after cessation of therapy. Calcif Tissue Int 2007;80:S146.
31. Verhaar HJ, Lems WF. PTH-analogs: comparable or different? Arch Gerontol Geriatr 2009;49:e130-2.
32. Takahata M, Awad HA, O'Keefe RJ, et al. Endogenous tissue engineering: PTH therapy for skeletal repair. Cell Tissue Res 2011.
33. Gaston MS, Simpson AH. Inhibition of fracture healing. J Bone Joint Surg Br 2007;89:1553-60.
34. Ellegaard M, Jorgensen NR, Schwarz P. Parathyroid hormone and bone healing. Calcif Tissue Int 2010;87:1-13.
35. Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res 1999;14:960-8.
36. Komatsubara S, Mori S, Mashiba T, et al. Human parathyroid hormone (1-34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora. Bone 2005;36:678-87.
37. Holzer G, Majeska RJ, Lundy MW, et al. Parathyroid hormone enhances fracture healing. A preliminary report. Clin Orthop Relat Res 1999:258-63.
38. Andreassen TT, Willick GE, Morley P, Whitfield JF. Treatment with parathyroid hormone hPTH(1-34), hPTH(1-31), and monocyclic hPTH(1-31) enhances fracture strength and callus amount after withdrawal fracture strength and callus mechanical quality continue to increase. Calcif Tissue Int 2004;74:351-6.

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39. Alkhiary YM, Gerstenfeld LC, Krall E, et al. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). J Bone Joint Surg Am 2005;87:731-41.
40. Jee WS, Yao W. Overview: animal models of osteopenia and osteoporosis. J Musculoskelet Neuronal Interact 2001;1:193-207.
41. Manabe T, Mori S, Mashiba T, et al. Human parathyroid hormone (1-34) accelerates natural fracture healing process in the femoral osteotomy model of cynomolgus monkeys. Bone 2007;40:1475-82.
42. Tsiridis E, Morgan EF, Bancroft JM, et al. Effects of OP-1 and PTH in a new experimental model for the study of metaphyseal bone healing. J Orthop Res 2007;25:1193-203.
43. Shirota T, Tashiro M, Ohno K, Yamaguchi A. Effect of intermittent parathyroid hormone (1-34) treatment on the bone response after placement of titanium implants into the tibia of ovariectomized rats. J Oral Maxillofac Surg 2003;61:471-80.
44. Nozaka K, Miyakoshi N, Kasukawa Y, et al. Intermittent administration of human parathyroid hormone enhances bone formation and union at the site of cancellous bone osteotomy in normal and ovariectomized rats. Bone 2008;42:90-7.
45. Jahng JS, Kim HW. Effect of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. Orthopedics 2000;23:1089-94.
46. Gabet Y, Muller R, Levy J, et al. Parathyroid hormone 1-34 enhances titanium implant anchorage in low-density trabecular bone: a correlative micro-computed tomographic and biomechanical analysis. Bone 2006;39:276-82.
47. Andreassen TT, Fledelius C, Ejersted C, Oxlund H. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. Acta Orthop Scand 2001;72:304-7.
48. Yu CT, Wu JK, Chang CC, et al. Early callus formation in human hip fracture treated with internal fixation and teriparatide. J Rheumatol 2008;35:2082-3.
49. Resmini G, Iolascon G. 79-year-old post-menopausal woman with humerus fracture during teriparatide treatment. Aging Clin Exp Res 2007;19:30-1.
50. Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res 2010;25:404-14.
51. Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am 2011;93:1583-7.
52. Moricke R, Rettig K, Bethke TD. Use of Recombinant Human Parathyroid Hormone(1–84) in Patients with Postmenopausal Osteoporosis - A Prospective, Open-Label, Single-Arm, Multicentre, Observational Cohort Study of the Effects of Treatment on Quality of Life and Pain - the PROPOSE Study. Clin Drug Investig 2011;31(2):87-99.

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