RESEARCH PAPER

Comparative study between bisphosphonates and PTH in Osteoporosis: A Systemic Review article

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Abstract: Osteoporosis is a metabolic bone disease that, on a cellular level, results from osteoclastic bone resorption not compensated by osteoblastic bone formation. This causes bones to become weak and fragile, thus increasing the risk of fractures. Traditional pathophysiological concepts of osteoporosis focused on endocrine mechanisms such as estrogen or vitamin D deficiency as well as secondary hyperparathyroidism. However, research over the last decades provided exiting new insights into mechanisms contributing to the onset of osteoporosis, which go far beyond this. Bisphosphonates and parathyroid hormone (PTH) represent the antiresorptive and anabolic classes of drugs for osteoporosis treatment. Bone mineral density (BMD) is an essential parameter for the evaluation of anti-osteoporotic drugs. The aim of this study was to evaluate the effects of PTH versus bisphosphonates on BMD for the treatment of osteoporosis.

Keywords: Osteoporosis, bisphosphonates, parathyroid hormone, teriparatide, bone mineral density, fracture risk, systematic review.

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Introduction:

Osteoporosis is a metabolic bone disease characterized by low bone mass and structural deterioration of bone tissue. It results from failure of osteoblasts to form sufficient new bone, from an excessive rate of osteoclastic bone resorption, or from the combination of both processes. The resultant bone fragility leads to an increased susceptibility to fractures, especially of the hip, spine and wrist. There is an increased mortality rate following both hip and vertebral fractures, and the presence of one fracture is a potent risk factor for future fractures. This leads to a decline in the quality of life and an associated loss of independence among the millions of individuals in the worldwide afflicted with the disease. There is an additional population at an increased risk for fractures due to a less severe loss of bone mass, known as osteopenia (1).

Antiresorptive agents, such as bisphosphonates, are the most widely used group of drugs for osteoporosis treatment [2,3,4] Bisphosphonates directly reduce the number of active osteoclasts by inhibiting their recruitment and also by inhibiting the osteoclast-stimulating activity of osteoblasts. bisphosphonate therapy normalizes bone turnover, reduces the number of bone remodeling units, restores the balance of bone remodeling, prevents bone loss and deterioration of

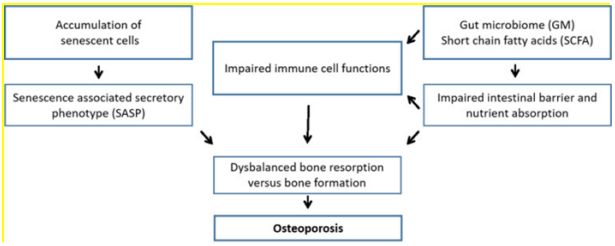
bone structure and reduces fracture risk in patients with osteoporosis [5].

Parathyroid hormone (PTH) is used clinically as an anabolic agent [6,], Two forms of recombinant human PTH have been evaluated: teriparatide, the 34-residue amino-terminal fragment of human PTH (1–34) and the intact 84-amino acid form of PTH (1–84), which is marketed as Protect. PTH directly increases osteoblast production rate and inhibits apoptosis of osteoblasts, thereby leading to a rapid increase in skeletal mass as well as improvement of bone micro-architecture and strength [7].

The combination therapy with antiresorptive and osteoanabolic drugs is based upon the hypothesis that if bone formation is stimulated by an osteoanabolic agent while bone resorption is inhibited by an antiresorptive agent (such as bisphosphonate), the combination might lead to better results than monotherapy with either agent alone. Several studies [8,9] have been designed to investigate the combination therapy with PTH analogues and bisphosphonates. Some studies [10] found combination therapy could improve the level of bone mineral density (BMD) than single therapy whereas others studies [11,12]] reported no differences between combination therapy and single therapy. To date, the conclusions among studies are still controversial.

Pathophysiology of Osteoporosis

Osteoporosis is a classic example of a multifactorial disease with a complex interplay of genetic, intrinsic, exogenous, and life style factors contributing to an individual's risk of the disease. Traditional pathophysiologic models frequently emphasized endocrine mechanisms, e.g. estrogen deficiency and secondary hyperparathyroidism in elderly due to estrogen deficiency, reduced dietary intake, and widely prevalent vitamin D deficiency, as the key determinants of postmenopausal osteoporosis (13). However, it has become clear in the last years that pathophysiological mechanisms contributing to the onset of osteoporosis go far beyond this. Selected mechanisms will be discussed in the following paragraphs



Biological causes of osteoporosis

In adults, the daily removal of small amounts of bone mineral, a process called resorption, is balanced by an equal deposition of new mineral in order to maintain bone strength. When this balance tips toward excessive resorption, bones weaken and over time can become brittle and prone to fracture (osteoporosis). This continual resorption and re-deposition of bone mineral, or bone remodeling, is intimately tied to the pathophysiology of osteoporosis. Understanding how bone remodeling is regulated is the key to the effective prevention and treatment of osteoporosis. Bones have evolved to be light yet strong. These properties are conferred to a large degree by architecture and geometry [14]. The long bones are tubular in shape, with a strong outer shell, or cortical layer, surrounding a spongier core called trabecular bone [15]. The combination makes these bones strong and light, but flexible enough to absorb the stress from high impact exercises without breaking. The vertebrae are similarly constructed, with a thick cortical layer surrounding sheet of trabecular bone. As a unit, each vertebra can compress when temporarily loaded and then return to their original size.

However, a skeleton is alive and must be able to grow, heal, and respond to its environment. This is where bone remodeling plays a crucial role. However, as we age, daily remodeling leads to a gradual resorption of the minerals on the inside of the cortical layer and in the bone cavity itself leads to an inexorable loss of trabecular bone and a widening of the bone cavity. This is partly compensated for by the gradual addition of extra layers of mineral to the outside of the cortical layer [16]. Continual remodeling, and its effect on bone microarchitecture have a huge impact on the pathophysiology of osteoporosis. For example, young adults with wider femurs might be at higher risk for hip fractures late in life because, on average, wider bones tend to have thinner cortical layers. The thinner this layer is, the more susceptible it will be to resorption later in life [17].

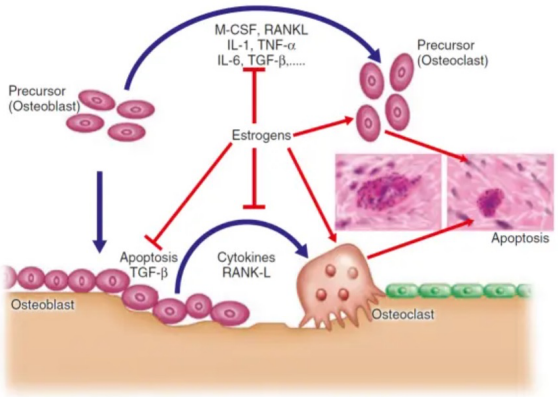
Factors influencing osteoclasts and osteoblasts

Hormones are possibly the most crucial modulators of bone formation. It is well established that oestrogen [18]. parathyroid hormone [19]. and to a lesser extent testosterone directly or indirectly via the conversion into oestrogen [20,21]. are essential for optimal bone development and maintenance. Of these, oestrogen is now believed to have the most direct effect on bone cells, interacting with specific proteins, or receptors, on the surface of osteoblasts and osteoclasts [22].

This interaction sets off a complex chain of events within the cells, increasing osteoblast activity while at the same time interfering with osteoblast-osteoclast communication – one of the ironies of bone remodelling is that the osteoblasts release factors that stimulate osteoclasts and drive bone resorption, as we shall see below.

Oestrogen effects are mediated through one specific type of cell surface receptor called the oestrogen receptor alpha (ERα), which binds and transports the hormone into the nucleus of the cell where the receptor-hormone complex acts as a switch to turn on specific genes. ERα receptors are found on the surface of osteoblasts, as is oestrogen receptor-related receptor alpha (ERRα), which may play an auxiliary role in regulating bone cells [23]. Recent studies also suggest that sex hormone binding globulin (SHBG), which facilitates entry of oestrogen into cells, may also play a supportive role [24].

Oestrogen, of course, is made and secreted into the bloodstream some distance from bone and it also has profound effects on other tissues, such as the uterus and breast. But there are other, locally produced signalling molecules that have profound effects on bone physiology.



Cytokine production under the control of estrogen in bone and bone remodeling

Role of Bisphosphonates in osteoporosis

Biological actions: The bisphosphonates have been shown to have various physicochemical effects on bone salt crystals and biological effects on bone mineralization and bone resorption.

Physicochemical effects: Bisphosphonates inhibit the formation and aggregation and slow down the dissolution of calcium phosphate crystals. These effects are related to the marked affinity of these compounds for solid-phase calcium phosphate, on the surface of

which they bind strongly. This property is the basis for the use of these compounds as skeletal markers in nuclear medicine and the basis for their selective pharmacological effects [26].

Mechanisms of action: While the effect on mineralization is due to the physicochemical inhibition of crystal growth, the action on bone resorption is mediated through mechanisms other than the physicochemical inhibition of crystal dissolution, as was initially postulated, namely by acting on the osteoclast. Four mechanisms appear to be probably involved: inhibition of osteoclast recruitment, inhibition of osteoclastic adhesion, shortening of the life span of osteoclasts due to earlier apoptosis, and inhibition of osteoclast activity. Very recently the cellular mechanism has been partially unraveled. It was found that nitrogen containing bisphosphonates can, by inhibiting farnesyl pyrophosphate synthase, decrease the formation of some compounds important for many cell functions, including cytoskeletal assembly and intracellular signaling, which leads eventually to apoptosis and death. In contrast, some non-nitrogen-containing bisphosphonates, such as clodronate, and etidronate, can be incorporated into the phosphate chain of ATP-containing compounds, which also impair cell function, leading to apoptosis and cell death. Thus, the bisphosphonates can be classified into two major groups with different modes of action but the same final effect [27].

Pharmacokinetics: The bisphosphonates appear to be absorbed, stored, and excreted unaltered in the body. Therefore, the bisphosphonates seem to be nonbiodegradable, at least with respect to their P-C-P bond. The bioavailability of an oral dose of a bisphosphonate both in animals and in humans lies between less than 1% and 10%. Absorption is substantially diminished when the drug is given with meals, especially in the presence of calcium and iron. Therefore, bisphosphonates should never be given at mealtimes and never together with milk or dairy products. Between 20% and 80% of the absorbed bisphosphonate is taken up very rapidly by bone, the remainder being rapidly excreted in the urine. This rapid uptake by bone means that the soft tissues are exposed to bisphosphonates for only short periods, explaining why practically only bone is affected in vivo. The areas of deposition are mostly those of bone formation and destruction. Once deposited in the skeleton and covered under new layers of bone, the bisphosphonates are released to a large extent only when the bone in which they were deposited is resorbed. The half-life in bone bisphosphonates is therefore very long, for humans it can be over 10 years. The renal clearance of bisphosphonates is high, at least in animals higher than that of inulin, indicating active secretion.[26]

Clinical use in osteoporosis: Bisphosphonates are today the most frequently used drug in metabolic bone disease. About ten are commercially available in the world, the conditions treated most frequently with these compounds being osteoporosis, Paget's disease and metastatic bone disease. This review deals only with osteoporosis. A more extended clinical and clinical information can be found in a book written for the practicing physician [27]. Role of PTH in osteoporosis

Physicochemical effects: Parathyroid hormone is an 84-amino acid polypeptide which is secreted by the parathyroid glands in response to decreases in calcium concentration. Its main actions are to increase renal tubular calcium reabsorption, to stimulate renal calcitriol, or 1,25 dihydroxy vitamin D, production thereby indirectly increasing intestinal calcium absorption, and to regulate bone remodeling [28]. Its ligand is the PTH - 1 receptor, a G protein-coupled

receptor expressed primarily in kidney and bone [29]. PTH results in an increase in the number of bone-forming cells by promoting osteoblast growth and decreasing osteoblast cell death or apoptosis [30]. Interestingly, PTH also stimulates osteoclast genesis. Mice that do not have osteoclasts do not respond to PTH, suggesting that osteoclast activity is required for PTH to have its full anabolic action [31]. Additionally, PTH regulates certain skeletal growth factors (such as IGF-1) and growth factor antagonists (such as sclerostin) to further promote the building of bone.

Parathyroid hormone stimulates both osteoclast-mediated bone resorption and osteoblast-mediated bone formation. This increased bone turnover is evidenced by marked increases in biochemical markers of both bone formation and resorption beginning soon after administration [32]. The predominant skeletal action of PTH depends on the pattern of administration [33]. Short-term or intermittent exposure to PTH, as occurs after a single subcutaneous injection, leads to a predominance of osteoblast-mediated bone formation. This bone formation occurs in cortical bone and to a lesser extent trabecular bone [34]. In contrast, continuous administration of PTH or persistently high PTH levels, as occurs in primary hyperparathyroidism, results in predominance of osteoclast-mediated bone resorption and consequent net bone loss [35,36]. The anabolic response to daily transient peak levels of PTH is the greatest during the first 6–12 months of therapy, the anabolic window, and subsequently tends to wane as bone resorption increases to match the increased bone formation [37]. The mechanisms determining whether PTH has anabolic or catabolic actions are not known as the skeletal effects of PTH are complex and not yet completely understood.

Parathyroid hormone related protein (PTHrP) is widely expressed in normal tissues throughout development, though it does not normally appear in the circulation except during lactation. PTH and PTHrP have significant homology in the N-terminal region, allowing them to bind to the same PTH - 1 receptor, though each protein favors a different conformational state, resulting in somewhat different downstream effects on calcium metabolism [38]. PTHrP acts as a paracrine and autocrine factor to regulate cellular growth, differentiation, development and cell death as well as epithelial calcium transport in cartilage, bone, mammary glands, and a variety of other tissues [39]. Studies in mice have demonstrated that PTHrP is required for normal bone development [40]. PTHrP also plays a role in mobilizing calcium during lactation [41].

Similar to PTH, continuous secretion of PTHrP causes a pathological state, humoral hypercalcemia of malignancy, which is characterized by hypercalcemia and increased bone resorption. Continuous infusion of both PTHrP and PTH result in elevated serum calcium levels, decreased renal calcium excretion, an increase in markers of bone resorption and a decrease in markers of bone formation . In contrast, intermittent administration of PTHrP has been found to increase bone mass in rodents [42] and in humans [43], and some data suggest that intermittent PTHrP may be more purely anabolic than PTH [44.].

Bisphosphonates versus PTH Analogs: After the introduction of PTH analogs researchers performed studies comparing bisphosphonates with PTH analogs to develop better treatment algorithms for enhancing osseous union in osteoporotic patients.[45] some of the studies compared the use of teriparatide versus bisphosphonates in osteoporotic patient [46]. Overall, there is supportive evidence that teriparatide use alone is associated with higher osseous fusion rates compared with the use of bisphosphonates alone

Combined Use of Bisphosphonates and PTH Analogs:

To obtain superior effects on the skeleton, combined use of an antiresorptive bisphosphonate with a bone-forming PTH analog was put forward as an appealing hypothesis. [47,48] Although evidence suggests potential advantages of using simultaneous combination therapies on hip BMD (Bone Mineral Density) over monotherapy alone, the effect of combination therapies on spine BMD, osteoporotic fracture incidence, and postoperative spinal fusion needs to be further studied.

Summary:

Osteoporosis presents a unique challenge for surgeons. Antiresorptive bisphosphonates and bone forming PTH analogs are two commonly used pharmacotherapeutics to minimize the risk of postoperative complications due to reduced bone quality in elderly osteoporotic patients. The use of bisphosphonates or PTH analogs alone has been shown to improve bone quality in osteoporosis. There is evidence that using PTH analogs alone is associated with higher osseous-union rates than the use of bisphosphonates. Although simultaneously inhibiting osteoclasts and stimulating osteoblasts may sound sensible, concurrent use of bisphosphonates and PTH analogs has not been proven to be more efficacious for treatment of osteoporosis than using either therapy alone. However, there may be potential benefits in sequential use of PTH analogs and bisphosphonates. We suggest that, unless there is any contraindication, every elderly osteoporotic patient should start PTH analogs at least four to six weeks and continue for a minimum of five months after surgery. It is advisable to switch to an antiresorptive bisphosphonate after discontinuation of PTH analogs to preserve the gain in BMD. Decisions on the extension of PTH analog treatment at six months after operation, the type of bisphosphonate to be initiated, and duration of treatment, must be taken on a case-by-case basis.

CONCLUSION:

Combination therapy in different conditions of naive or previous bisphosphonate treatment might have different outcomes. The use of combination therapy, however, may be an alternative option among osteoporotic patients with a history of bisphosphonate use. Combined teriparatide with denosumab appear to show the most substantial and clinically relevant skeletal benefits to osteoporotic patients. Although addition of PTH appears to be advantage than switching to PTH, any possible benefits of combination therapy must be weighed in relation to costs and inconveniency caused by taking two drugs as opposed to one. Finally, additional research is necessary to define optimal methods of developing sequential and/or cyclical combinations of PTH and antiresorptive agents. Long-term safety and efficacy of such combinations remain to be determined.

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Authors' contributions:

Dr. Devendra Sharma and Dr. Raj Kumar have designed the study, conducted various experiments, and written the manuscript. Dr. Aman Jyoti was responsible for patient recruitment and experiment guidance. Dr Raj Kumar is the research head and has contributed to manuscript preparation, editing the journal article. Mr. Deepak Neupane and Dr. Indra Prasad Adhikari have contributed to the writing of the journal article.

REFERENCES:

1. Black DM, Bouxsein ML, Palermo L, McGowan JA, Newitt DC, Rosen E, Majumdar S, Rosen CJ; PTH Once-Weekly Research (POWR) Group. Randomized trial of once-weekly parathyroid hormone (1-84) on bone mineral density and emodeling. J Clin Endocrinol Metab. 2008 Jun;93(6):2166-72. doi: 10.1210/jc.2007-2781. Epub 2008 Mar 18.
2. Cremers SC, Pillai G, Papapoulos SE. Pharmacokinetics/pharmacodynamics of bisphosphonates: use for optimisation of intermittent therapy for osteoporosis. Clin Pharmacokinet. 2005;44:551–570. doi: 10.2165/00003088-200544060-00001. [DOI] [PubMed] [Google Scholar][Ref list]
3. Mulder JE, Kolatkar NS, LeBoff MS. Drug insight: Existing and emerging therapies for osteoporosis. Nat Clin Pract Endocrinol Metab. 2006;2:670–680. doi: 10.1038/ncpendmet0325. [DOI] [PubMed] [Google Scholar][Ref list
4. Macedo JM, Macedo CR, Elkis H, De Oliveira IR. Meta-analysis about efficacy of anti-resorptive drugs in post-menopausal osteoporosis. J Clin Pharm Ther. 1998;23:345–352. doi: 10.1046/j.1365-2710.1998.00168.x. [DOI] [PubMed] [Google Scholar
5. Boonen S, Vanderschueren D, Venken K, Milisen K, Delforge M, et al. Recent developments in the management of postmenopausal osteoporosis with bisphosphonates: enhanced efficacy by enhanced compliance. J Intern Med. 2008;264:315–332. doi: 10.1111/j.1365-2796.2008.02010.x. [DOI] [PubMed] [Google Scholar][Ref list
6. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–1441. doi:10.1056/NEJM200105103441904. [DOI] [PubMed] [Google Scholar][Ref list
7. Lyritis GP, Georgoulas T, Zafeiris CP. Bone anabolic versus bone anticatabolic treatment of postmenopausal osteoporosis. Ann N Y Acad Sci. 2010;1205:277–283. doi: 10.1111/j.1749-6632.2010.05666.x. [DOI] [PubMed] [Google Scholar][Ref list
8. Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1–34)] in postmenopausal osteoporosis. J Bone Miner Res 2011; 26:503–511.
9. Walker MD, Cusano NE, Sliney J Jr, et al. Combination therapy with risedronate and teriparatide in male osteoporosis. Endocrine 2013; 44:237–246.
10. Cosman F, Nieves J, Zion M, et al. Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med 2005; 353:566–575.
11. Black DM, Greenspan SL, Ensrud KE, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 2003; 349:1207–1215
12. Finkelstein JS, Hayes A, Hunzelman JL, et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 2003; 349:12161226.http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/522/CN-00440522/frame.html.
13. Clarke BL, Khosla S. Physiology of bone loss. Radiol Clin North Am. 2010;48:483–495. doi: 10.1016/j.rcl.2010.02.014. [DOI] [PMC free article] [PubMed] [Google Scholar][Ref list
14. Martin, R.M. and P.H. Correa, Bone quality and osteoporosis therapy. Arq Bras Endocrinol Metabol, 2010. 54(2): p. 186-99.
15. Parfitt, A.M., Chapter 15 - Skeletal Heterogeneity and the Purposes of Bone Remodeling: Implications for the Understanding of Osteoporosis, in Osteoporosis (Second Edition), R. Marcus, D. Feldman, and J. Kelsey, Editors. 2001, Academic Press: San Diego. p. 433-447.
16. Seeman, E., From density to structure: growing up and growing old on the surfaces of

bone. J Bone Miner Res, 1997. 12(4): p. 509-21
17. Seeman, E. and P.D. Delmas, Bone quality--the material and structural basis of bone strength and fragility. N Engl J Med, 2006. 354(21): p. 2250-61
18. Lindsay, R., Prevention and treatment of osteoporosis. Lancet, 1993. 341(8848): p. 801-5
19. [Lips, P., Vitamin D physiology. Prog Biophys Mol Biol, 2006. 92(1): p. 4-8
20. Seeman, E., The structural basis of bone fragility in men. Bone, 1999. 25(1): p. 143-7.
21. Van Pottelbergh, I., et al., Perturbed sex steroid status in men with idiopathic osteoporosis and their sons. J Clin Endocrinol Metab, 2004. 89(10): p. 4949-53
22. Zallone, A., Direct and indirect estrogen actions on osteoblasts and osteoclasts. Ann N Y Acad Sci, 2006. 1068: p. 173-9
23. Bonnelye, E. and J.E. Aubin, Estrogen receptor-related receptor alpha: a mediator of estrogen response in bone. J Clin Endocrinol Metab, 2005. 90(5): p. 3115-21
24. Goderie-Plomp, H.W., et al., Endogenous sex hormones, sex hormone-binding globulin, and the risk of incident vertebral fractures in elderly men and women: the Rotterdam Study. J Clin Endocrinol Metab, 2004. 89(7): p. 3261-9.
25. Fleisch H. Bisphosphonates in osteoporosis. Eur Spine J. 2003;12 Suppl 2(Suppl 2):S142-S146. doi:10.1007/s00586-003-0622-z
26. Rogers MJ (2003) New insights into the molecular mechanisms of action of bisphosphonates. Curr Pharmaceut Design (in press) [DOI] [PubMed][Ref list
27. Fleisch H (2000) Bisphosphonates in bone disease—from the laboratory to the patient. Academic, San Diego
28. Hodsman AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 2005;26:688–703.
29. Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med. 2007;357:905–916.
30. Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med. 2007;357:905–916. doi: 10.1056/NEJMra067395. [DOI] [PubMed] [Google Scholar
31. Esbrit P, Alcaraz MJ. Current perspectives on parathyroid hormone (PTH) and PTH-related protein (PTHrP) as bone anabolic therapies. Biochem Pharmacol. 2013;85:1417–1423.
32. Hodsman AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 2005;26:688–703. doi: 10.1210/er.2004-0006.
33. Frolik CA, Black EC, Cain RL, et al. Anabolic and catabolic bone effects of human parathyroid hormone (1-34) are predicted by duration of hormone exposure. Bone. 2003;33:372–379.
34. Frost ML, Siddique M, Blake GM, et al. Differential effects of teriparatide on regional bone formation using (18)F-fluoride positron emission tomography. J Bone Miner Res. 2011;26:1002–1011.
35. Dobnig H, Turner RT. The effects of programmed administration of human parathyroid hormone fragment (1-34) on bone histomorphometry and serum chemistry in rats. Endocrinology. 1997;138:4607–4612. doi: 10.1210/endo.138.11.5505
36. Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. Bone. 2007;40:1434–1446. doi: 10.1016/j.bone.2007.03.017
37. Cipriani C, Irani D, Bilezikian JP. Safety of osteoanabolic therapy: a decade of experience. J Bone Miner Res. 2012;27:2419–2428. doi: 10.1002/jbmr.1800
38. Wysolmerski JJ. Parathyroid hormone-related protein: an update. J Clin Endocrinol Metab. 2012;97:2947–2956. This review article summarizes PTHrP functions throughout the body with particular focus on research from the past decade

39. Philbrick WM, Wysolmerski JJ, Galbraith S, et al. Defining the roles of parathyroid hormone-related protein in normal physiology. Physiol Rev. 1996;76:127–173. doi: 10.1152/physrev.1996.76.1.127.
40. Miao D, Li J, Xue Y, et al. Parathyroid hormone-related peptide is required for increased trabecular bone volume in parathyroid hormone-null mice. Endocrinology. 2004;145:3554–3562
41. Philbrick WM, Wysolmerski JJ, Galbraith S, et al. Defining the roles of parathyroid hormone-related protein in normal physiology. Physiol Rev. 1996;76:127–173. doi: 10.1152/physrev.1996.76.1.127
42. Philbrick WM, Wysolmerski JJ, Galbraith S, et al. Defining the roles of parathyroid hormone-related protein in normal physiology. Physiol Rev. 1996;76:127–173. doi: 10.1152/physrev.1996.76.1.127
43. Horwitz MJ, Tedesco MB, Gundberg C, et al. Short-term, high-dose parathyroid hormone-related protein as a skeletal anabolic agent for the treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2003;88:569–575.
44. Horwitz MJ, Tedesco MB, Garcia-Ocana A, et al. Parathyroid hormone-related protein for the treatment of postmenopausal osteoporosis: defining the maximal tolerable dose. J Clin Endocrinol Metab. 2010;95:1279–1287
45. Buerba RA, Sharma A, Ziino C et al. Bisphosphonate and Teriparatide Use in Thoracolumbar Spinal Fusion: A Systematic Review and Meta-analysis of Comparative Studies. Spine (Phila Pa 1976). 2018;43:E1014-E1023
46. Seki S, Hirano N, Kawaguchi Y et al. Teriparatide versus low-dose bisphosphonates before and after surgery for adult spinal deformity in female Japanese patients with osteoporosis. Eur Spine J 2017;26:2121-2127
47. Cosman F. Combination therapy for osteoporosis: a reappraisal. Bonekey Rep. 2014;3:518.,
48. Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. J Clin Endocrinol Metab 2010;95:1838-45