



# Parathyroid hormone and its analogues — molecular mechanisms of action and efficacy in osteoporosis therapy

Parathormon i jego analogi — molekularne mechanizmy działania a skuteczność w leczeniu osteoporozy

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## Abstract

Most medical agents currently applied in osteoporosis therapy act by inhibiting bone resorption and reducing bone remodelling, i.e. they inhibit the process of bone mass loss by suppressing bone resorption processes. These drugs provide an ideal therapeutic option to prevent osteoporosis progression. They however have a rather limited usefulness when the disease has already reached its advanced stages with distinctive bone architecture lesions. The fracture risk reduction rate, achieved in the course of anti-resorptive therapy, is insufficient for patients with severe osteoporosis to stop the downward spiral of their quality of life (QoL) with a simultaneously increasing threat of premature death.

The activity of the N-terminal fragment of 1–34 human parathormone (teriparatide — 1–34 rhPTH), a parathyroid hormone (PTH) analogue obtained via genetic engineering, is expressed by increased bone metabolism, while promoting new bone tissue formation by stimulating the activity of osteoblasts more than that of osteoclasts. The anabolic activity of PTH includes both its direct effect on the osteoblast cell line, and its indirect actions exerted via its regulatory effects on selected growth factors, e.g. IGF-1 or sclerostin. However, the molecular mechanisms responsible for the actual anabolic effects of PTH remain mostly still unclear.

Clinical studies have demonstrated that therapeutic protocols with the application of PTH analogues provide an effective protection against all osteoporotic fracture types in post-menopausal women and in elderly men with advanced osteoporosis. Particular hopes are pinned on the possibility of applying PTH in the therapy of post-steroid osteoporosis, mainly to suppress bone formation, the most important pathological process in this regard.

The relatively short therapy period with a PTH analogue (24 months) should then be replaced and continued by anti-resorptive treatment. (*Pol J Endocrinol* 2011; 62 (1): 73–78)

**Key words:** osteoporosis, therapy, parathyroid hormone, teriparatide

## Streszczenie

Większość leków stosowanych obecnie w terapii osteoporozy wykazuje działanie przeciwresorpcyjne, czyli spowalnia utratę masy kostnej poprzez hamowanie resorpcji kostnej. Stanowią one idealne leczenie w celu zapobiegania postępowi osteoporozy, wykazują jednak ograniczoną przydatność, kiedy choroba jest zaawansowana, a architektura kości uszkodzona. Redukcja ryzyka złamań, uzyskiwana w trakcie leczenia antyresorpcyjnego, jest niewystarczająca dla chorych z ciężką osteoporozą, aby powstrzymać postępujący spadek jakości ich życia i rosnące zagrożenie przedwczesnym zgonem. Działanie otrzymywanego w technologii inżynierii genetycznej analogu PTH, rekombinowanego N-końcowego fragmentu 1–34 ludzkiego parathormonu (teryparatydu — 1–34 rhPTH) wyraża się nasileniem obrotu kostnego i promuje tworzenie nowej kości poprzez stymulowanie aktywności osteoblastów w większym stopniu niż aktywności osteoklastów. Anaboliczne działanie PTH obejmuje zarówno bezpośredni wpływ na linię komórkową osteoblasta, jak szereg działań pośrednich, poprzez regulacyjny wpływ PTH na wybrane czynniki wzrostowe, na przykład IGF-1 lub sklerostynę. Mechanizmy molekularne odpowiadające za rzeczywisty efekt anaboliczny PTH pozostają jednak w większości nieznane.

Badania kliniczne wykazały, że leczenie analogami PTH skutecznie zapobiega wszystkim typom złamań osteoporotycznych u kobiet po menopauzie i starszych mężczyzn z zaawansowaną osteoporozą. Szczególne nadzieje budzi możliwość zastosowania PTH w leczeniu osteoporozy posteroideowej, ze względu na wiodące w tej patologii zahamowanie kościotworzenia. Względnie krótkotrwałe leczenie analogiem PTH (24 miesiące) powinno być następnie kontynuowane leczeniem antyresorpcyjnym.

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**Słowa kluczowe:** osteoporoza, leczenie, parathormon, teriparatide



## Introduction

Fracture prevention is the number one target in osteoporosis therapy.

Most medical agents currently used for this purpose include anti-resorptive drugs, which slow down bone mass loss by suppressing bone resorption. This is the mechanism of action of biphosphates, oestrogens, selective oestrogen receptor modulators, calcitonin and denosumab, i.e. the registered medical agents approved for the treatment of osteoporosis [1]. Antiresorptive drugs (taking into account the actual limitations in hormonal replacement therapy resulting from the studies of the Women's Health Initiative and the Million Women Study), are an ideal way of preventing osteoporosis progression. However, they have limited usefulness in more advanced stages of the disease, when the quality of bone architecture is seriously compromised [2, 3].

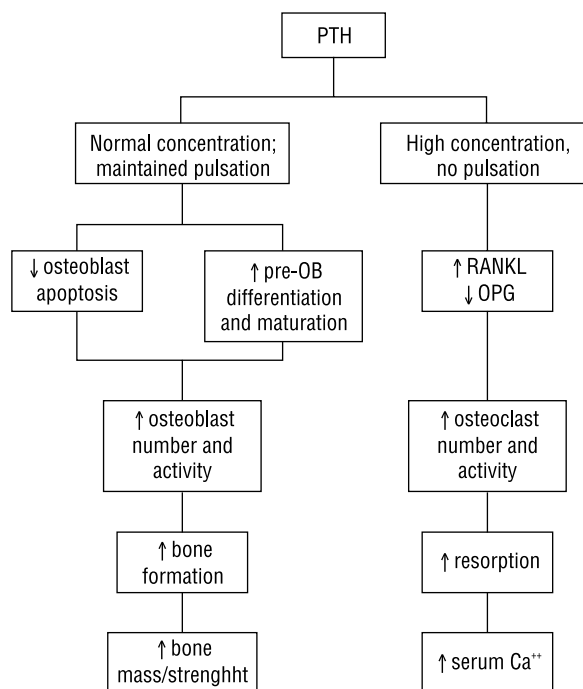
In all the published, randomised, placebo-controlled clinical studies, patients with osteoporosis who were treated with antiresorptive agents sustained new bone fractures significantly less frequently than placebo-administered patients, although some new fractures occurred in the actively treated group, though at a much lower level. In the Fracture Intervention Trial (FIT), over the course of a three-year observation, 8% of alendronate-treated patients sustained a new vertebral fracture (vs. 15% of placebo-receiving patients) [4, 5]. In the three-year Multiple Outcomes of Raloxifene Evaluation (MORE) study, new vertebral fractures were identified in 14.7% of raloxifene-treated patients vs. 21.2% of placebo-receiving subjects [6]. Patients with severe osteoporosis and numerous fractures of vertebral bodies are especially susceptible to subsequent osteoporotic fractures, regardless of applied antiresorptive therapy. In these patients, a 50% fracture risk reduction, obtained during antiresorptive treatment, is insufficient to halt the QoL (quality of life) drop that comes with the simultaneously growing risk of premature death [3].

An entirely new therapeutic strategy, based on bone reconstruction factors (including PTH analogues and strontium salts) would be a real breakthrough in the management of patients with severe osteoporosis.

The ability of anabolic factors to improve bone mineral density much more efficiently than antiresorptive agents would also suggest a higher fracture risk-reducing potential of the former substances [7–9].

## Parathormone analogues

Endogenous parathyroid hormone (PTH) is secreted by the four parathyroid glands, mainly as an 84-amino acid peptide [PTH (1–84)] [10]. PTH secretion is controlled by serum calcium concentration, by means of a nega-



**Figure 1.** PTH activity: anabolic or catabolic, depending on secretion rate and character

**Rycina 1.** Działanie PTH na tkankę kostną w zależności od stężenia i sposobu wydzielania

tive feedback mechanism via the membrane calcium receptor (CaR) [11]. In response to hypocalcaemia, PTH acts directly to increase renal tubular calcium reabsorption and indirectly to enhance intestinal calcium absorption via its stimulatory action on renal 1-cholecalciferol hydroxylase (thereby increasing circulating calcitriol). The normal physiological role of PTH on skeletal homeostasis, when secreted endogenously, is more complex, but probably serves to regulate bone remodelling rather than overall skeletal mass. Within the physiological range of concentrations, PTH stimulates the bone-forming activity of osteoblasts at the same level as the bone-losing activity of osteoclasts [12].

But because normal concentrations and the pulsative character of PTH secretion support the bone formation process, it is osteoclastic bone resorption, and free osseous calcium ion release into the extracellular fluid, which dominate in the situation of constantly elevated PTH concentration, something characteristic of both primary and secondary hyperparathyroidism (Fig. 1).

It is assumed that the primary biological activity of endogenous PTH (1–84) depends on the N-terminal fragment sequence, which is why the shortened, N-terminal, 34-amino acid hPTH analogue (1–34) (teriparatide) preserves the features of the entire molecule [13]. The majority of PTH actions, as well as of the actions of its evolutionary analogue, a parathormone-related pep-

ptide (PTHrP) [14], are mediated by PTH receptor type 1 (PTH-receptor-PTHrP), identifying and activated by the above-mentioned N-terminal sequence of amino acids [15]. The PTH receptor belongs to the class of membranous receptors, characterised by a heptahelical protein structure, associated with G protein and adenylyl cyclase. The PTH receptor is localised in the bone on the osteoblast surface only. The primary, physiological activity of PTH, i.e. normocalcaemia control by enhancing osteoclastic bone resorption and releasing the free calcium ion into the extracellular space, is then an indirect effect.

In pre-osteoblasts, PTH [16] amplifies the production of RANKL (Receptor Activator of NF $\kappa$ B Ligand) cytokine, belonging to the superfamily of tumour necrosis factors (TNF), while simultaneously decreasing the release of osteoprotegerin, a soluble, decoy receptor for RANKL (OPG) [17-19]. It increases the accessibility of RANKL for the functional RANK receptor on the surface of the monocyte/macrophage-osteoblast development line cells [20]. In this way, RANKL enhances the proliferation/differentiation/fusion/maturation and metabolic activity of osteoclasts, so leading to intensification of osteolysis.

Regarding osteoblasts, PTH simultaneously activates cAMP-dependent protein kinase and calcium-dependent C protein kinase, as well as MAP kinase and A and D phospholipase, all of them of key importance for osteoblast activity [21]. The PTH-receptor complex also undergoes internalisation and can thus exert significant gene transcription controlling activity [22].

However, the specific signal pathway responsible for the anabolic activity of PTH remains unknown, especially given that this particular activity is a combination of direct PTH effects on the cell line of osteoblasts and of indirect action via the controlling influence of PTH on selected bone growth factors and on the substances which are, for them, antagonistic. PTH demonstrates mitogenic activity towards osteoblasts, inhibiting their apoptosis [23]. In consequence, the number of osteoblasts is growing. Independently from growth hormone (GH) activity, PTH induces the synthesis of the insulin-like growth factor 1 (IGF-1), a strong bone anabolic factor, in bone tissue [21, 24-25]. At the same time, PTH suppresses the expression of sclerostin, an osteocyte-derived SOST protein, which blocks the activity of the Wnt-beta-catenin pathway responsible for promotion of many transcriptive processes, leading, in effect, to the increased number and activity of osteoblasts [21, 26].

The mechanism of PTH anabolic activity also includes the transitional phase of bone surface preparation, together with bone matrix metalloproteinase synthesis. Other PTH effects include modulation of locally

secreted paracrine factors (TGF- $\beta$ , transforming growth factor beta), enzymes and other substances (including prostaglandins), participating in cell replication processes and osteogenesis stimulation [27-30]. However, little is known about the role of the type 2 receptor for PTH [33], activated by the C-terminal section of PTH (1-84), as well as by C-terminal fragments of PTH, either directly released from the parathyroid glands or produced as a result of peripheral degradation. It seems that the C-terminal fragments of PTH enhance the apoptosis of osteocytes [34], while when in cultures they stimulate the synthesis of alkaline phosphatase and other osteoblast activity markers [34]. So it is possible that the therapeutic activity of the whole PTH molecule (1-84) may slightly differ from teriparatide activity [36]. While not dismissing the importance of that observation, it should, however, be emphasised that the molecular mechanism responsible for the actual anabolic effect of PTH remains unknown. Similarly, it is not entirely clear why an intermittent administration of small doses of either exogenous PTH or teriparatide should exert mainly anabolic activity and differ in its final effect from an exposure to long-term, elevated PTH concentrations with a dominating catabolism of the cortex bone [31, 32]. It seems that a single administration of a short-acting PTH preparation, or of its analogue, may imitate a single, normal secretion pulse of the endogenous hormone.

## Clinical application

Teriparatide, the N-terminal 1-34 fragment of the human parathormone (rhPTH (1-34), teriparatide), obtained via bioengineering and administered intermittently, has turned out to be a factor promoting new bone formation and bone weight increase much more effectively than anti-resorptive agents. Studies on animals, and preliminary results of clinical studies, have demonstrated that intermittent PTH treatment causes a significant increase in cancellous bone weight, but either does not influence the cortex core at all, or merely diminishes it slightly [37, 38].

The effects of teriparatide therapy on the risk of osteoporotic, vertebral and non-vertebral fractures in postmenopausal women were evaluated in the Fracture Prevention Trial, a clinical trial involving 1,637 postmenopausal women with confirmed osteoporosis [39]. After 18 months of therapy with daily subcutaneous teriparatide injections in 20 mg doses, a significant reduction in both new fractures (vertebral by 65% and non-vertebral by 54% vs. placebo) was demonstrated. Moreover, the treatment with teriparatide resulted in significant, dose-dependent bone mineral density (BMD) increase in the lumbar spine, the hip and the

whole skeleton vs. the control group ( $p < 0.001$  for all the values). As with the antiresorptive agents, the observed reduction in fracture risk may only partly be explained by the BMD increase. A certain reduction in the vertebral fracture risk was also observed in postmenopausal women treated with recombinant PTH (1–84). However, the high percentage of patients who did not complete the study was a serious obstacle to the statistical evaluation of the observations [40].

A favourable effect of treatment with PTH analogues on BMD has also been demonstrated in men with advanced osteoporosis. In a short-term observation of 437 men with low BMD values, an administration of recombinant human PTH (1–34) (teriparatide, 20–40 mg sc/d) for 2–15 months resulted in significant BMD increase in the lumbar spine and in the hip (though not in the radial bone or in the total body) and increased bone turnover. In that study, the therapy effects on fracture risk were not evaluated; but the similarity of those effects on BMD and BTM with the effects observed in clinical studies of women where the influence of the treatment on fracture incidence was assessed, clearly indicates the therapeutic usefulness of teriparatide in both sexes [41].

Histomorphometric studies of biopsied bone material, collected from teriparatide-treated subjects, have revealed not only increased bone trabecular volumes but also higher numbers of trabeculas and of intertrabecular connections, as well as improved cancellous bone architecture and increased cortical bone thickness [42, 43].

Moreover, it seems that PTH better stimulates osteogenesis on subperiosteal bone surface, which increases periosteal apposition [44]. It brings about favourable changes for bone geometry by increasing its dimensions, which, in consequence, leads to improved bone resistance to mechanical stress [45].

The study, initially scheduled for three years, was prematurely stopped (on average after 19 months of therapy). The cause of the early termination was osteosarcoma development in rats that had been administered supraphysiological doses of teriparatide for almost their whole lives [46, 47]. No development of any neoplastic bone changes was observed in other animal species (monkeys included), treated in the same way [48]. A single case of osteosarcoma described in a woman treated with teriparatide for almost a year vs. around 800,000 teriparatide-treated subjects, has to be interpreted as corresponding to the population risk of occurrence of this extremely rare neoplasm [49]. However, regarding the oncological concerns, the administration time period of PTH analogues has been reduced to 24 months (FDA, EMEA). Any oncological episode in the past, or Paget's disease, or previous skeleton irradiation, is an absolute contraindication to the administration of PTH

analogues; these agents are also contraindicated in children.

A possibility to apply PTH analogues in the therapy of glucocorticosteroid-induced osteoporosis (GIO) raises particular hopes for osteogenesis suppression, a leading disorder in this pathology [50]. In a clinical study, comparing head-to-head teriparatide with alendronate in women and men with GIO, a significantly higher increase in BMD, with a lower incidence of vertebral fractures, was noted in the group of patients administered PTH (1–34) for 18 months [51].

A relatively brief anabolic therapy (24 months) with PTH analogues raises an obvious question, namely what to do after the therapy. The results of observations made in the course of large clinical studies indicate a considerable bone mass loss after teriparatide treatment, both in women and men, unless antiresorptive agents are not immediately applied [52]. Also in a clinical study of treating postmenopausal osteoporosis with rhPTH (1–84), the favourable effects of therapy continuation were observed, with alendronate administered immediately after PTH withdrawal [53, 54].

Conclusions from the available data should be drawn with great caution, if at all, because of the lack of prospective studies, the rather small study population, and, especially, the lack of evaluation of the antiresorptive treatment, applied after the termination of PTH analogue therapy, on the incidence of fractures. It seems, however, that antiresorptive treatment preventing bone mass loss after teriparatide withdrawal should be recommended [55].

The necessity for daily subcutaneous injections of PTH analogues significantly diminished patients' acceptance of this therapy. An alternative may soon be provided by a novel teriparatide transdermal microneedle delivery system. This comprises a 5 cm<sup>2</sup> adhesive patch with TPTD coated on a 2 cm<sup>2</sup> titanium microneedle array with 1,300 microneedles of a 190 μm average length. The tips of the microneedles are coated with teriparatide. The recently published results of a clinical, phase-two study demonstrated not only a comparable effect (non-inferiority) of subcutaneously injected teriparatide on vertebral BMD and on the activity of bone metabolism markers, but also a higher BMD increase in the proximal femoral bone (superiority) in transcutaneously treated patients [56].

The introduction of PTH analogues to osteoporosis therapy seems to be particularly advantageous for patients at advanced stages of the disease, with high fracture risk. Teriparatide is now the only medical agent reconstructing bone tissue structure, regardless of the degree of its initial destruction.

On the other hand, the relative decrease of fracture incidence obtained in patients treated with teriparati-

de exceeds only very slightly the fracture risk reduction after modern anti-resorptive drugs.

Several questions arise, such as:

- would therapy split into shorter cycles (intermittent treatment) give a better therapeutic effect?
- would therapy longer than 18–24 months provide a more efficient outcome?
- would there be more positive results if the therapy was repeated after a certain time period (cyclic treatment)?

We do not have answers to these and other questions.

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