Anabolic Therapy With Teriparatide
Indications Beyond Osteoporosis

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Outline

- Teriparatide pharmacological properties
- Fracture healing in animal models
- Fracture healing and non-unions in humans
- Atypical fractures due to bisphosphonates use
- Other potential uses
- Cautions and contraindications
- Conclusions and future research
Teriparatide

currently approved for treating patients with osteoporosis

everishing osteoblast derived bone formation
Teriparatide

- represents the **1-34** amino acid segment of the full-length 84 amino acid parathyroid hormone (PTH) molecule

- high levels of PTH or continuous infusions favor bone resorption and calcium release intermittent PTH stimulation, favors bone formation

- leads to bone formation on all bone surfaces, including trabeculae, endosteal and periosteal bone.
Teriparatide

- Increase trabecular connectivity and cortical thickness improving the microarchitectural strength of bone
- Bone turnover markers also rise during treatment (anabolic window)
- Teriparatide therapy has been associated with expansion of the osteoblast and preosteoblast progenitor cell populations
Animal models

- several recent studies using rat diaphyseal fracture models demonstrate that teriparatide:
  - accelerated healing
  - larger callus volume,
  - more rapid remodelling
  - improved biomechanical properties

- PTH enhances fracture healing in a dose-dependent manner

- the remodeling process in rat bones is not similar to humans
Intermittent Parathyroid Hormone (1–34) Treatment Increases Callus Formation and Mechanical Strength of Healing Rat Fractures

TROELS T. ANDREASSEN, CHARLOTTE EJERSTED, and HANS OXLUND

60–200 μg/kg per day

Intermittent administration of a high dose of PTH(1–34) is able to enhance callus volume and the mechanical strength of fractures after both 20 and 40 days of healing.

A lower PTH(1–34) dose, does not influence healing of fractures after the first 20 days; but after 40 days of healing this dose causes a substantial increase in callus volume and mechanical strength.
Low dose of teriparatide, at 5 μg/kg and 30 μg/kg per day, in a rat closed femur fracture model.

At day 21, the fracture calluses of 30-μg treated animals showed marked increases in volume, stiffness, torsional strength, density, and cartilage volume.

Similar effects were seen in the 5-μg treated animals by day 35.
3 groups: control (CNT, n=6), low-dose 0.75 μg/kg, and high-dose 7.5 μg/kg

2 t/week for 3 weeks and the fracture fixed with plate intermittent PTH for another 26 weeks

PTH accelerates the natural fracture healing process by shrinking callus size and increasing degree of mineralization
In the PTH-treated group: the regenerate callus had:

- **ultimate load** 33% higher,
- **absorbed energy** 100% higher,
- **BMC** 60% higher,
- **callus tissue volume** 179% higher than for the control group.

Treatment with PTH during distraction osteogenesis resulted in substantially higher mineralized tissue volume, mineral content, and bending strength.
Intermittent PTH_{1-34} does not increase union rates in open rat femoral fractures and exhibits attenuated anabolic effects compared to closed fractures

Magnus Tägil, Michelle M. McDonald, Alyson Morse, Lauren Peacock, Kathy Mikulec, Negin Amanat, Craig Godfrey, David G. Little

clinical situation of open and high-energy fractures.

6 weeks after fracture (administration of 50 μg/kg PTH)

significant increases in callus size and strength were found at closed fractures, but failed to increase the rate of union in the open fracture model
Fracture healing in humans

The Role of Recombinant PTH in Human Fracture Healing: A Systematic Review

Dafang Zhang, BA.* † Anish Potty, MD. ‡ § Parth Vyas, MD. ‡ § and Joseph Lane, MD. ‡ §

3 articles reporting results from a randomized controlled trial

13 articles reporting cases (2 correspondences)

There continues to be anecdotal evidence for the use of recombinant PTH to enhance fracture healing

(J Orthop Trauma 2014;28:57–62)
Teriparatide for Acceleration of Fracture Repair in Humans: A Prospective, Randomized, Double-Blind Study of 102 Postmenopausal Women With Distal Radial Fractures*

Per Aspenberg,1 Harry K Genant,2,3 Torsten Johansson,1 Antonio J Nino,4 Kyoungah See,4 Kelly Krohn,4 Pedro A Garcia-Hernández,5 Christopher P Recknor,6 Thomas A Einhorn,7 Gail P Dalsky,4 Bruce H Mitlak,4 Anke Fierlinger,3 and Mark C Lakshmanan4

102 postmenopausal women 45-85 years fracture of the distal radius 3 groups: teriparatide (20 or 40 µg/d) or placebo for 8 weeks.

Primary end point was time to healing defined as radiologic bridging between 3 out of 4 cortices.

The median time was 9.1 weeks in the placebo-treated group, 7.4 weeks in the group treated with 20 µg of teriparatide, and 8.8 weeks in the group treated with 40 µg of teriparatide.
1637 postmenopausal women with prior vertebral fractures

20 or 40 μg of parathyroid hormone (1-34) or placebo, administered subcutaneously

New vertebral fractures occurred in 14% in the placebo group and in 5% and 4% of the women in the 20-μg and 40-μg groups

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.
65 patients: DEXA, radiographs, and CT scan for pelvic fractures

21: once-daily injection of 100 μg of PTH 1-84 starting

44: control group.

CT scan every month until union

mean time to fracture healing 7.8 weeks

compared with 12.6 weeks for the control group
Teriparatide 20 mcg daily, was started on the 31st post-operative day. After only 1 month radiograph showed obvious dense callus formation and the patient became fully ambulatory
Atrophic humeral shaft nonunion treated with teriparatide (rh PTH 1-34): A case report

Ángel Oteo-Álvaro, MD, Enrique Moreno, MD


5 months
3 months PTH
6 months PTH
Atrophic femoral nonunion successfully treated with teriparatide

S. Giannotti · V. Bottai · G. Dell’Osso ·
G. de Paola · E. Pini · G. Guido

7 months

3 months PTH treatment
88 year old, rheumatoid arthritis, oral cortisone for more than 15 years
once-weekly injection of 56.5 μg chemically synthesized TPTD, complete
union of the fracture was obtained at 23 months
Successful treatment of nonunion with teriparatide after failed ankle arthrodesis for Charcot arthropathy

K. Tamai · K. Takamatsu · K. Kazuki

25-year-old woman with severe Type I diabetes mellitus that resulted in nonunion after multiple arthrodesis operations for Charcot arthropathy

3 months therapy with teriparatide
Teriparatide, a nonsurgical solution for femoral nonunion?
A report of three cases

Y.-K. Lee • Y.-C. Ha • K.-H. Koo
1 month after treatment with teriparatide, the lumbar pain improved, and after 2 months, the patient was able to walk using a T-cane.
**Atypical fractures**

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<th>Table 1</th>
<th>ASBMR criteria for the diagnosis of atypical femoral fractures.³</th>
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<td><strong>Principal features</strong></td>
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<td>1. Located in any part of the femur, from the distal portion of the minor trochanter to the proximal portion of the supracondylar prominence.</td>
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<td>2. Associated to minimal trauma, such as a fall whilst standing or at less height, or without previous trauma</td>
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<td>3. Short oblique or transversal configuration</td>
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<td>4. Without comminution</td>
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<td>5. Complete fractures extend through both corticals and may be associated to a medial spicula; incomplete fractures only affect the lateral cortical</td>
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**Secondary features**

1. Localised periosteal reaction of the lateral cortical
2. Generalised thickness increase of the cortical of the diaphysis
3. Prodromal symptoms with dull or constant pain in the thigh or inguinal region
4. Bilateral fractures and symptoms
5. Delay in consolidation
6. Associated disease (for example, vitamin D deficit, RA, hypophosphatasia)
7. Use of drugs (for example, bisphosphonates, glucocorticoids, PPI)

PPI: proton pump inhibitors; RA: rheumatoid arthritis.
14 pt, all reported 4–10 years exposure to bisphosphonates, 5 received teriparatide therapy 20 μg daily for 6 months

High resolution peripheral micro-computed tomography (HRpQCT) scans of the distal radius and distal tibia were analysed for their cortical bone tissue mineralisation density

2–3 fold increase in bone remodelling markers (p=0.01) and fracture healing
Other uses of teriparatide

- Dental indications
- Allograft osteointegration
- Overload-induced implant osteointegration
- Chondro-regenerative therapy
40 patients with chronic periodontitis had periodontal surgery and daily injections of teriparatide (20 μg) or placebo (follow-up 1 year)

Radiographic linear resolution of osseous defects was significantly greater after teriparatide therapy than after placebo beginning at 6 months, with a mean linear gain in bone at 1 year of 29% as compared with 3% (P<0.001). Clinical improvement was greater in patients taking teriparatide
Risk factors include:
old age, cancer (multiple myeloma), steroid use, poor oral hygiene, recent dental trauma

ONJ prevalence is associated with the duration of bisphosphonate use
Teriparatide, a Chondro-Regenerative Therapy for Injury-Induced Osteoarthritis

Erik R. Sampson¹, Matthew J. Hilton¹, Ye Tian¹, Di Chen¹, Edward M. Schwarz¹, Robert A. Mooney², Susan V. Bukata¹, Regis J. O’Keefe¹, Hani Awad³, J. Edward Puzas¹, Randy N. Rosier¹,†, and Michael J. Zuscik¹,†

Teriparatide either acutely or 8 weeks after meniscal/ligamentous injury in mice. Knee joints were harvested at 4, 8, or 12 weeks post-op

Immediate administration increased proteoglycan content and inhibited articular cartilage degeneration, whereas delayed treatment induced a regenerative effect.

The chondro-protective and chondro-regenerative effects correlated with decreased levels of type × collagen, Runx2, matrix metalloproteinase-13 and the c-terminal aggrecan cleavage product NITEGE.
40 μg/kg, teriparatide in critical femoral defects (4 mm) in mice. Evaluation at 4 and 6 weeks using micro CT, histology, and torsion testing

Significant 2-fold increase in normalized callus volume and Union Ratio compared to saline treated controls at 6-weeks.

Teriparatide treatment significantly increased the torsional rigidity and yield torque
In the late stage of overload-induced bone loss around implant, the gap between the overloaded implant and bone is occupied by fibrous tissue which is scar tissue without the potential to differentiate into bone (irreversible phase), similar to fracture nonunion.

Therefore, it may be able to reverse bone loss around implant and promote re-osseointegration with the use of teriparatide.
Hypercalcemia and hypercalciuria most common
Nausea, vomiting, and headaches (40 μg PTH)
Increased incidence of elevated uric acid

Caution when co-administered with digoxin,
high-dose hydrochlorothiazide (>25 mg/day), or
intravenous furosemide, (transient hypercalcemia
(2%) and hypercalciuria (37%).

Risk for osteosarcoma
Conclusions

Most of the evidence is obtained in animal studies and very few studies have been done in humans.

More clinical studies are warranted and these studies should include dose–response studies, studies in different patient populations/risk groups, and studies of different fractures as well as in both load-bearing and non–load-bearing bones.

As the anabolic effect of PTH is further enhanced, when bone is subjected to mechanical stimulation, fractures of load-bearing bones might be more susceptible to PTH treatment.
Teriparatide is an effective stimulator of bone remodeling for osteoporosis and shows assurance as a growth factor for fracture healing and bone fusion.

One of its primary effects is the stimulation of the chondrocyte lineage of cells; this role looks very promising for treating osteoarthritis.

Additional orthopedic uses, including the stimulation of healing for fracture non-unions, stimulation of bone ingrowth for porous stem orthopedic joint replacements and as a pharmacotherapy for management of loosened hip prosthesis yet remains to be fully investigated.