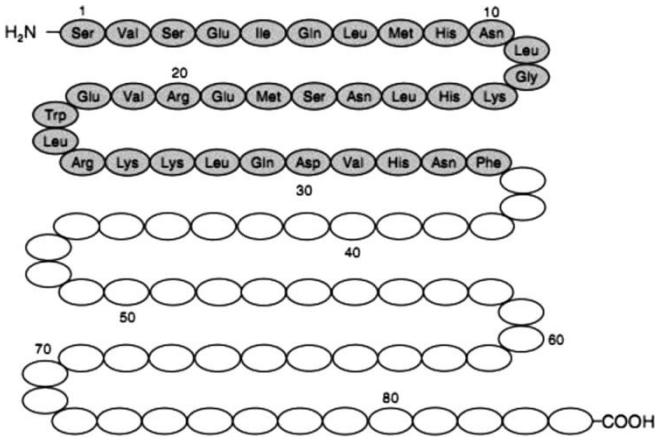
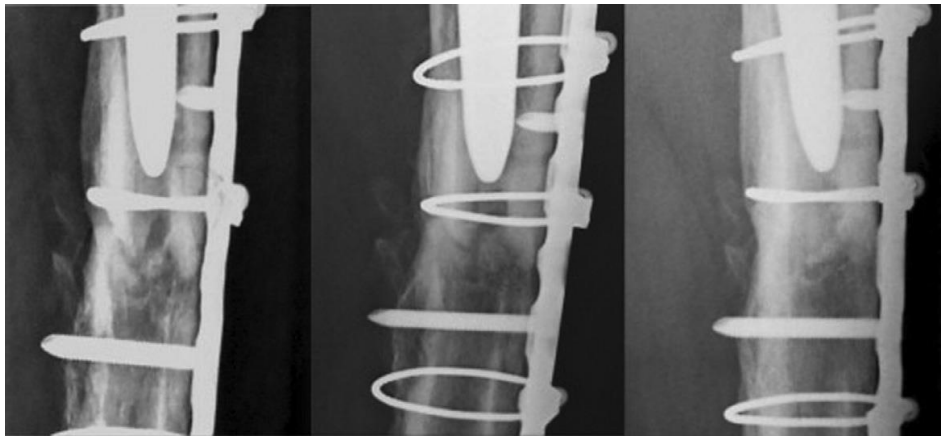
Anabolic Therapy With Teriparatide Indications Beyond Osteoporosis





Andreas Panagopoulos MD, PhD
Upper Limb & Sports Medicine Orthopaedic Surgeon
Assistant Professor, University of Patras

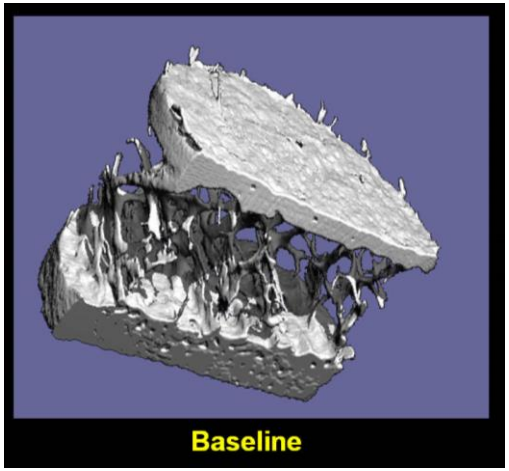
Outline

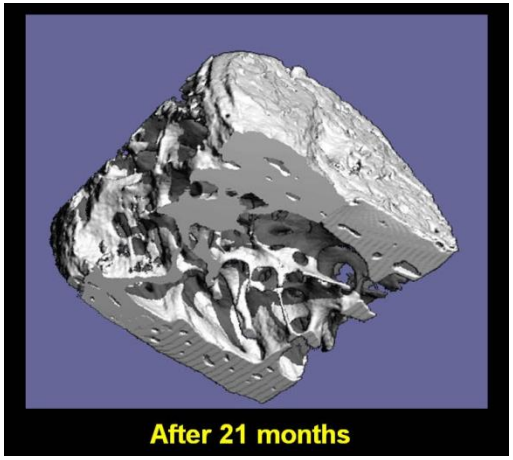
- Teriparatide pharmacological properties
- Fracture healing in animal models
- Fracture healing and non-unions in humans
- Atypical fractures due to bisphosphonates use
- Other potential uses
- Cautions and contraindications
- Conclusions and future research

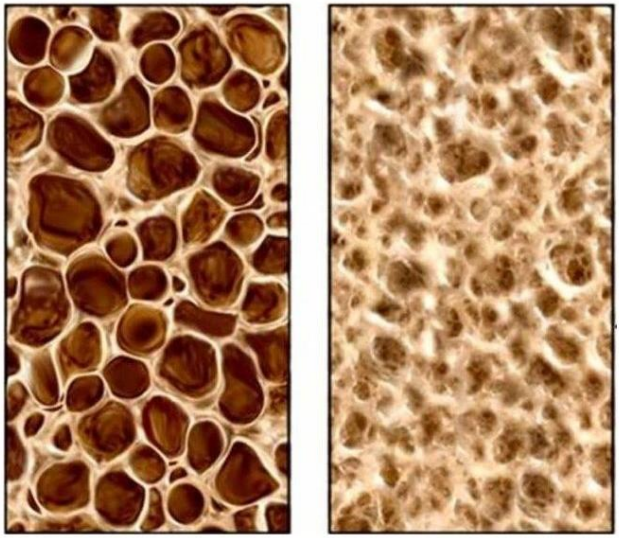
Teriparatide

currently approved for treating patients with osteoporosis

enhancing osteoblast derived bone formation

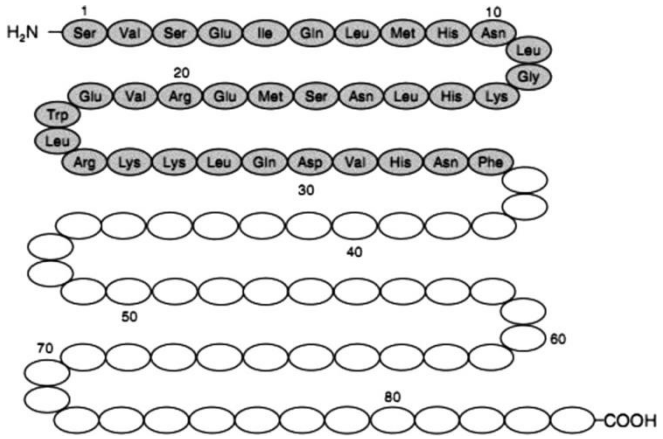






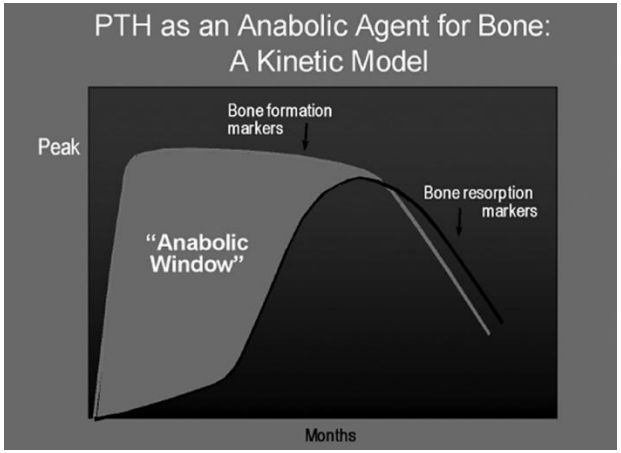
Teriparatide

- 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

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 14, Number 6, 1999
Blackwell Science, Inc.

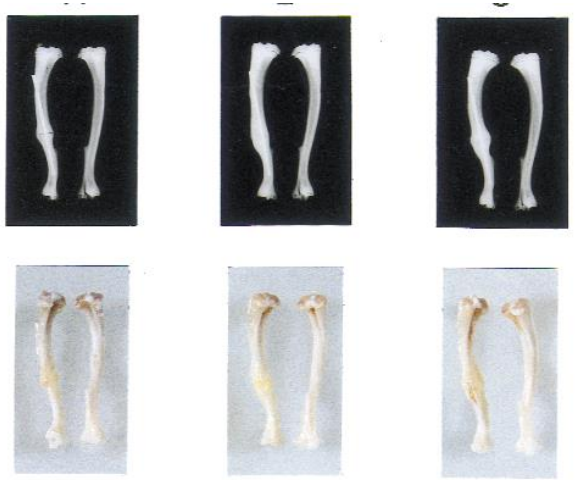
Intermittent Parathyroid Hormone (1–34) Treatment Increases Callus Formation and Mechanical Strength of Healing Rat Fractures

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



JBJS The Journal of Bone & Joint Surgery

Enhancement of Experimental Fracture-Healing by Systemic Administration of Recombinant Human Parathyroid Hormone (PTH 1-34)

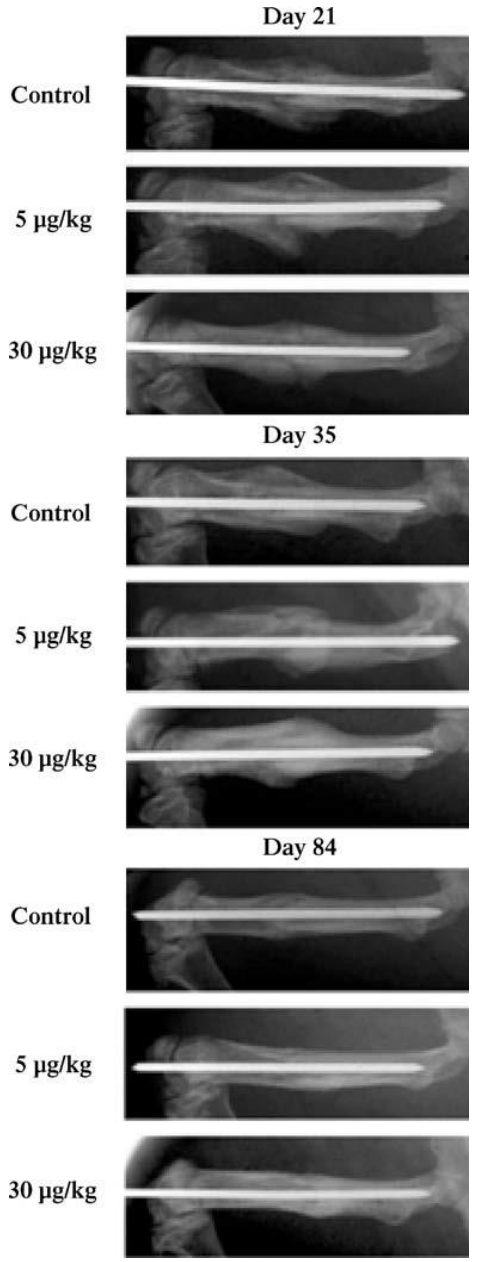
Yaser M. Alkhiary, BDS, MSD, DSD; Louis C. Gerstenfeld, PhD; Elizabeth Krall, PhD; Michael Westmore, PhD; Masahiko Sato, PhD; Bruce H. Mitlak, MD; Thomas A. Einhorn, MD

J Bone Joint Surg Am, 2005 Apr;87(4):731-741. http://dx.doi.org/10.2106/JBJS.D.02115

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.



ELSEVIER

Bone 40 (2007) 1475–1482

BONE

www.elsevier.com/locate/bone

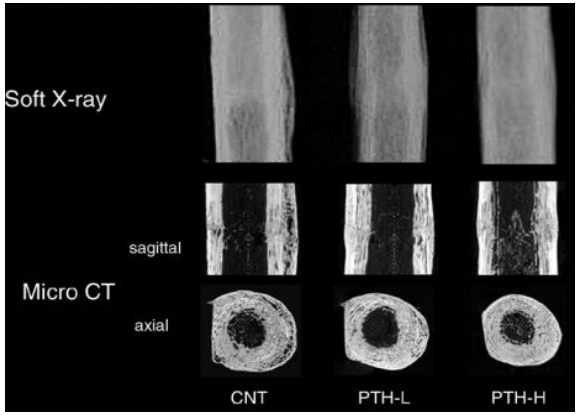
Human parathyroid hormone (1–34) accelerates natural fracture healing process in the femoral osteotomy model of cynomolgus monkeys

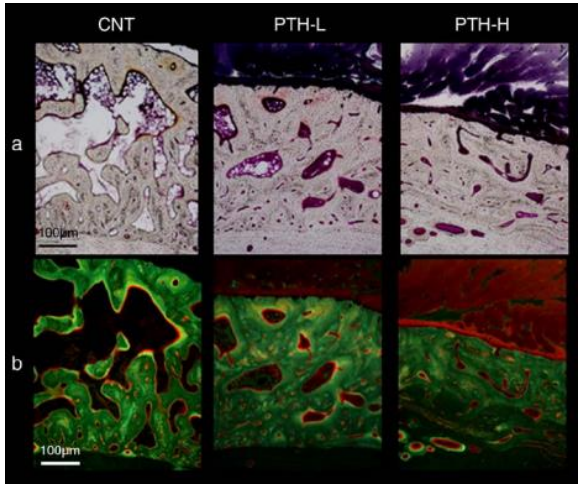
Takeshi Manabe [a], Satoshi Mori [a,*], Tasuku Mashiba [a], Yoshio Kaji [a], Ken Iwata [a], Satoshi Komatsubara [a], Azusa Seki [b], Yong-Xin Sun [a], Tetsuji Yamamoto [a]

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

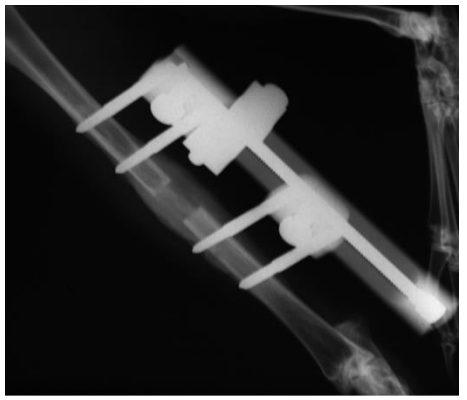
PTH accelerates the natural fracture healing process by shrinking callus size and increasing degree of mineralization



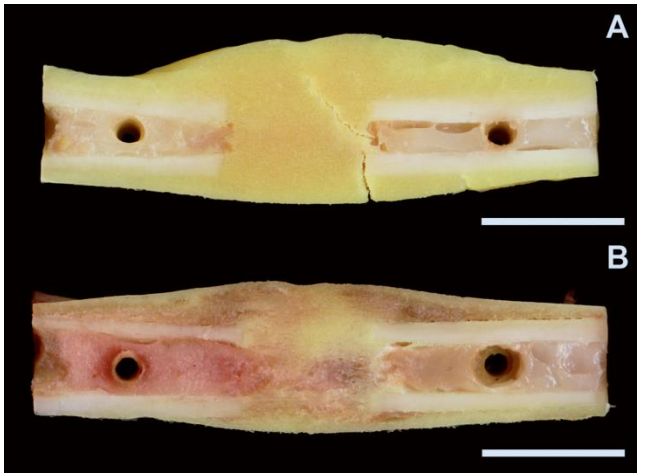


Parathyroid hormone PTH(1–34) increases the volume, mineral content, and mechanical properties of regenerated mineralizing tissue after distraction osteogenesis in rabbits

Ramune Aleksyniene[1], Jesper Skovhus Thomsen[2], Henrik Eckardt[3], Kristian G Bundgaard[4], Martin Lind[5], and Ivan Hvid[6]



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

Bone 46 (2010) 852–859

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

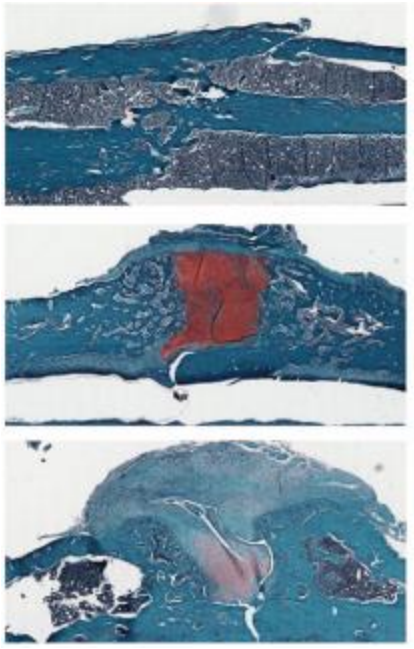
Intermittent $PTH_{(1-34)}$ does not increase union rates in open rat femoral fractures and exhibits attenuated anabolic effects compared to closed fractures

Magnus Tägil [a,c,*], Michelle M. McDonald [a], Alyson Morse [a], Lauren Peacock [a], Kathy Mikulec [a], Negin Amanat [a,b], Craig Godfrey [a], David G. Little [a,d]

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

REVIEW ARTICLE

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)

ORIGINAL ARTICLE

JBMR Vol. 25, No. 2, February 2010, pp 404–414

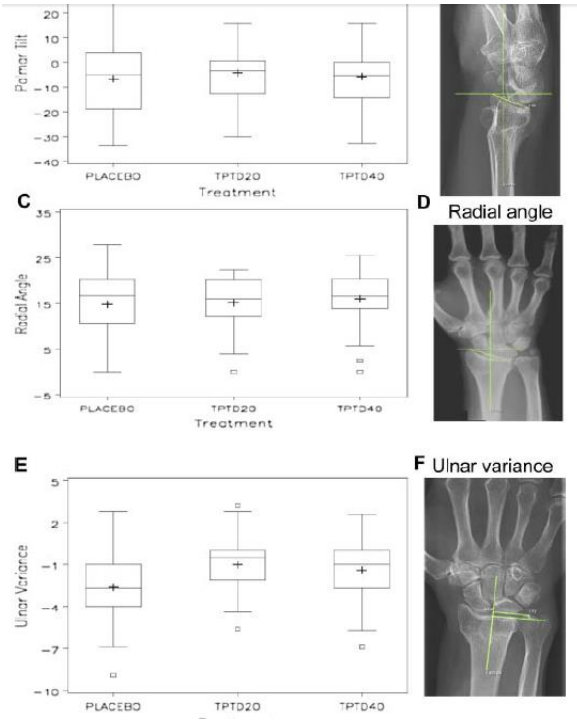
Teriparatide for Acceleration of Fracture Repair in Humans: A Prospective, Randomized, Double-Blind Study of 102 Postmenopausal Women With Distal Radial Fractures*

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

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.



The New England Journal of Medicine

EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

ROBERT M. NEER, CLAUDE D. ARNAUD, JOSE R. ZANCHETTA, RICHARD PRINCE, GREGORY A. GAICH, JEAN-YVES REGINSTER, ANTHONY B. HODSMAN, ERIK F. ERIKSEN, SOPHIA ISH-SHALOM, HARRY K. GENANT, OUHONG WANG, AND BRUCE H. MITLAK

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.

Parathyroid Hormone 1-84 Accelerates Fracture-Healing in Pubic Bones of Elderly Osteoporotic Women

Peter Peichl, MD; Lukas A. Holzer, MD; Richard Maier, MD; Gerold Holzer, MD

J Bone Joint Surg Am, 2011 Sep 07;93(17):1583-1587. http://dx.doi.org/10.2106/JBJS.J.01379

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

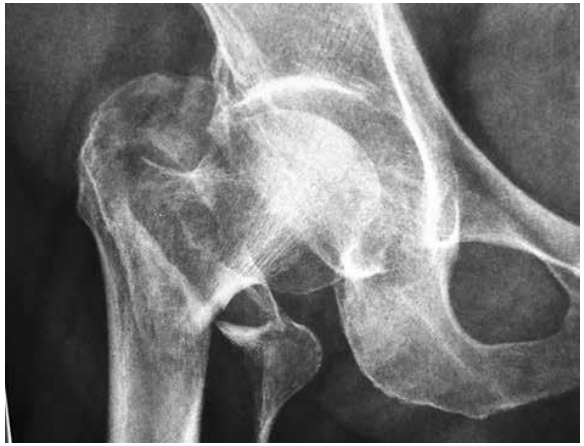
compared with 12.6 weeks for the control group

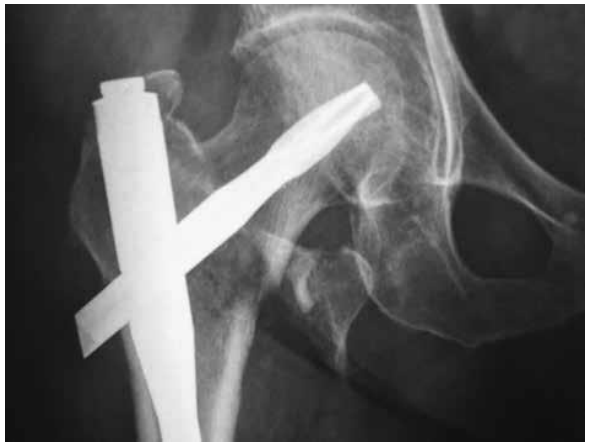
Accelerated fracture healing with teriparatide

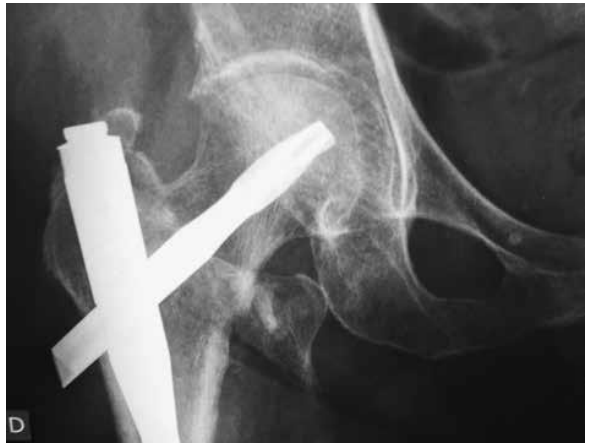
Arq Bras Endocrinol Metab. 2013;57(2):153-6

Consolidação de fratura acelerada com teriparatida

João Lindolfo C. Borges[1], Anderson Freitas[2], John P. Bilezikian[3]





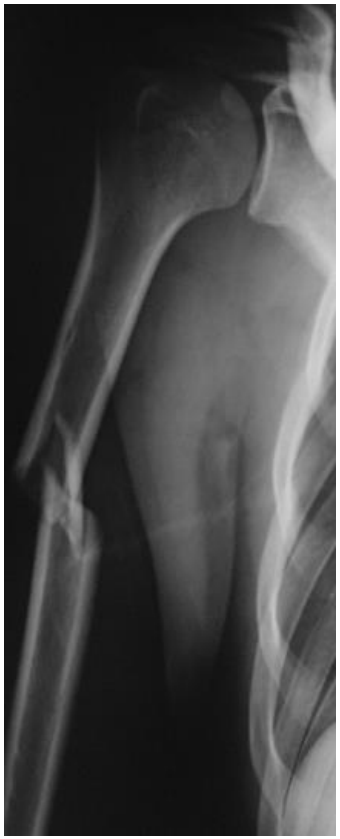


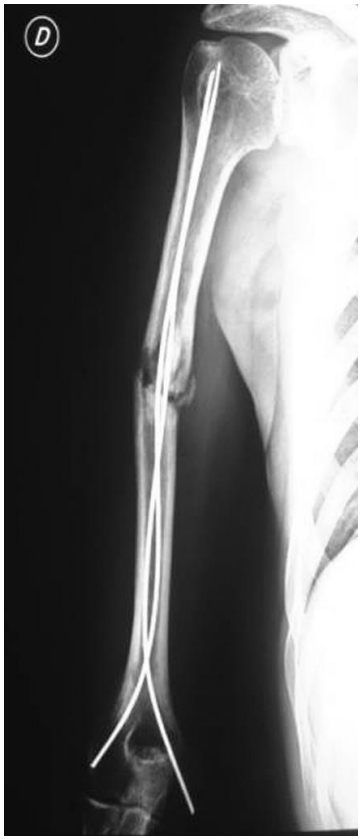
Teriparatide 20 mcg daily, was started on the 31st post-operative day. After only 1 month radiograph showed obvious dense callus formation and the patient became fully ambulatory

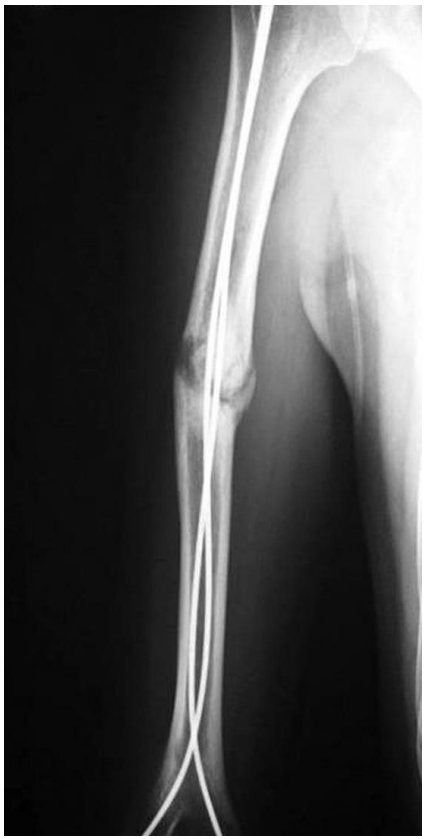
Atrophyc humeral shaft nonunion treated with teriparatide (rh PTH 1-34): A case report

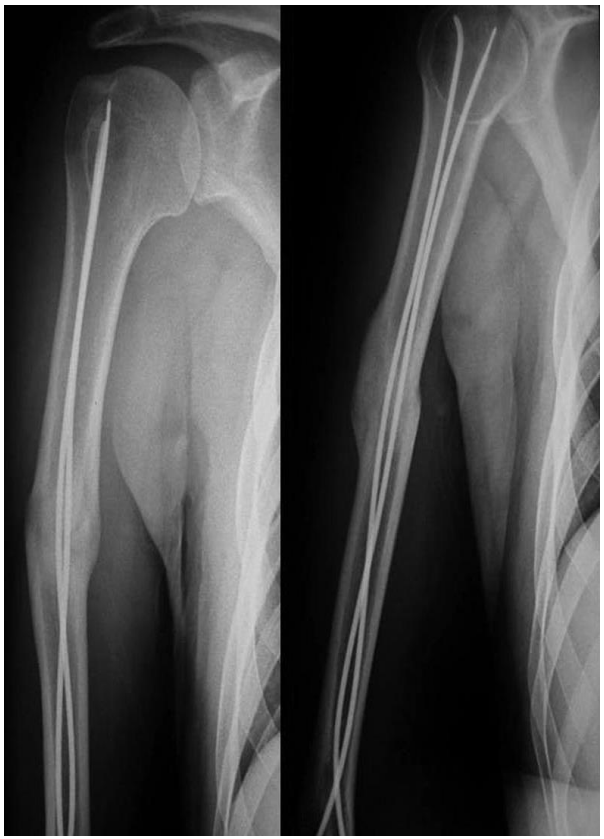
Ángel Oteo-Álvaro, MD[a,*], Enrique Moreno, MD[b]

J Shoulder Elbow Surg (2010) 19, e22-e28









5 months

3 months PTH

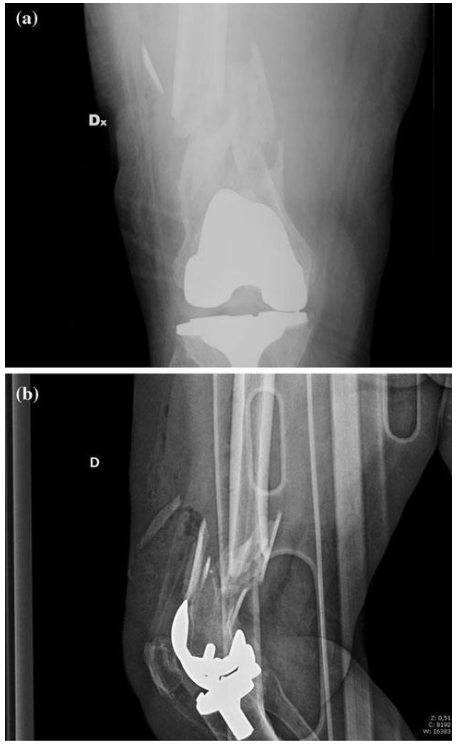
6 months PTH

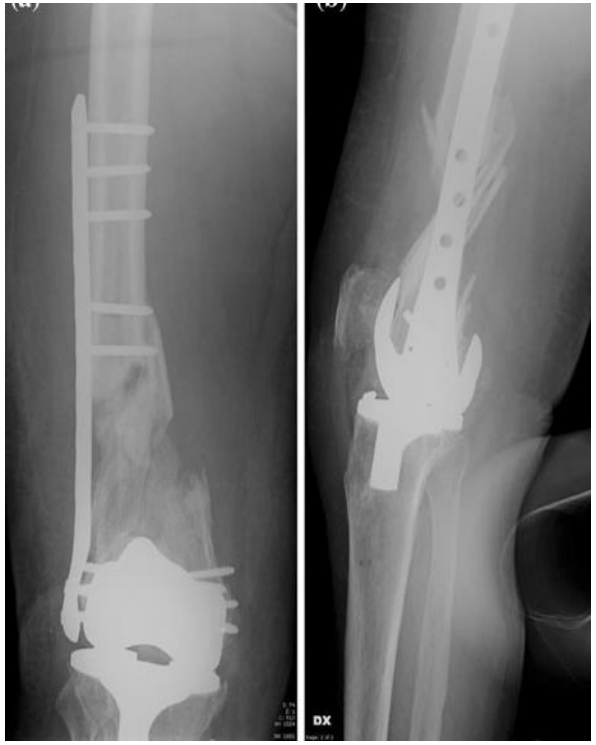
Eur J Orthop Surg Traumatol (2013) 23 (Suppl 2):S291–S294
DOI 10.1007/s00590-012-1143-4

UP-TO DATE REVIEW AND CASE REPORT

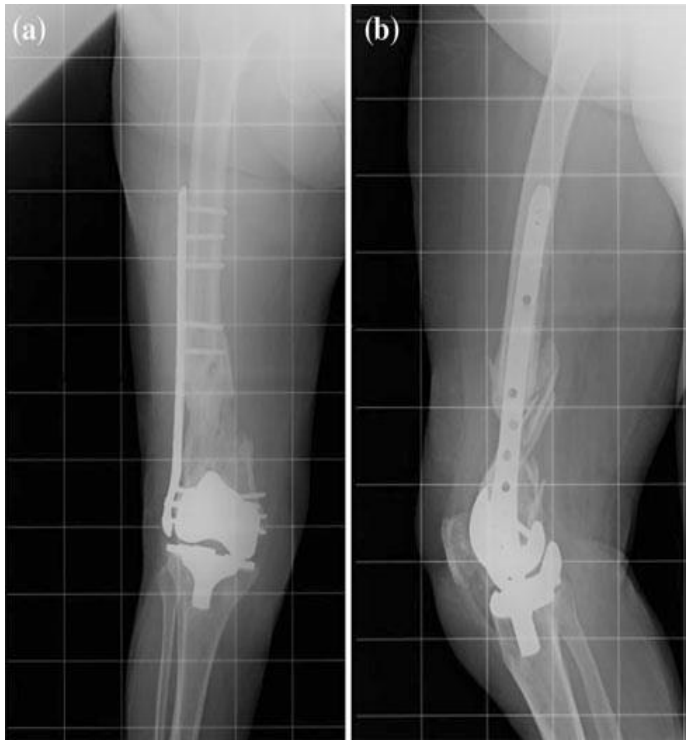
Atrophic femoral nonunion successfully treated with teriparatide

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





7 months



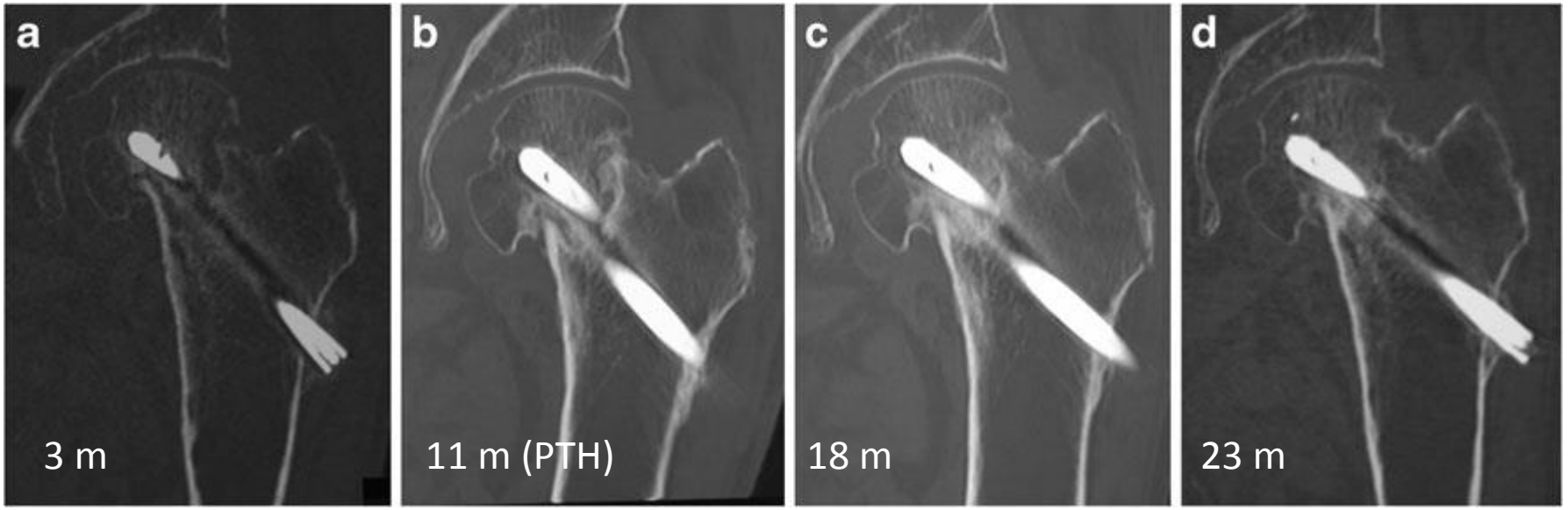
3 months PTH treatment

Arch Osteoporos (2013) 8:131
DOI 10.1007/s11657-013-0131-6

CASE REPORT

Effective treatment of a steroid-induced femoral neck fracture nonunion with a once-weekly administration of teriparatide in a rheumatoid patient: a case report

Yuichi Mitani



88 year old, rheumatoid arthritis, oral cortisone fore more than 15 years
once-weekly injection of 56.5 µg chemically synthesized TPTD, complete union of the fracture was obtained at 23 months

Osteoporos Int (2013) 24:2729–2732
DOI 10.1007/s00198-013-2367-9

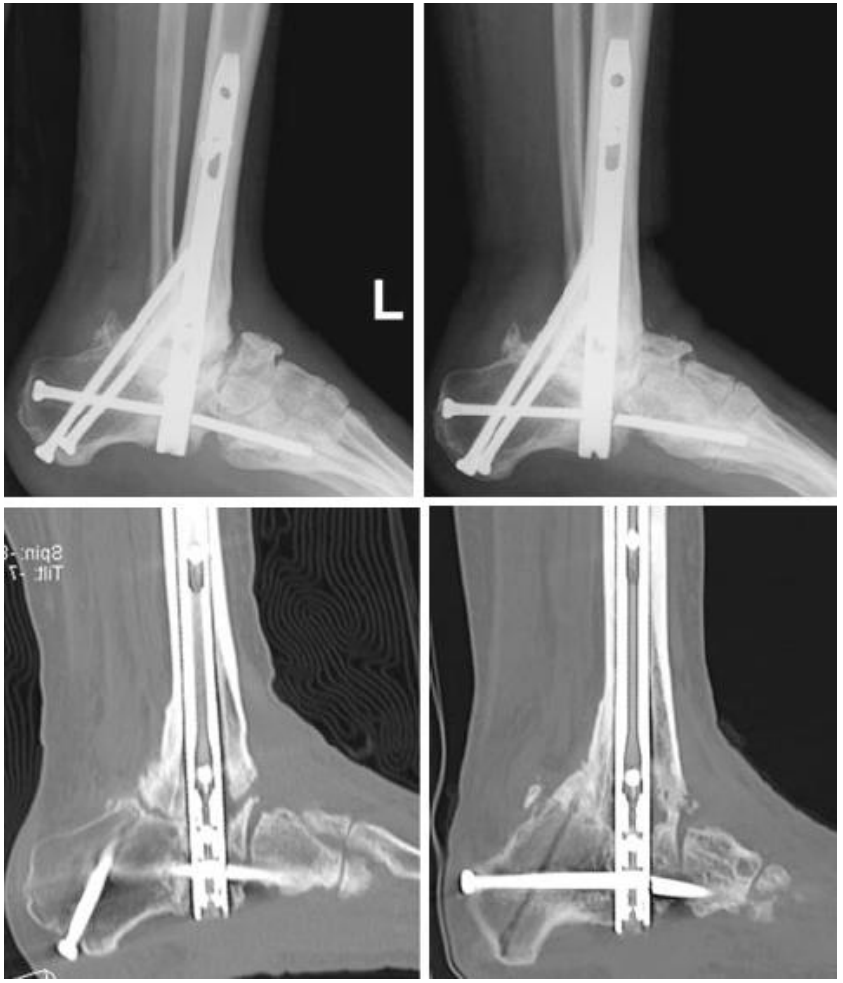
CASE REPORT

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

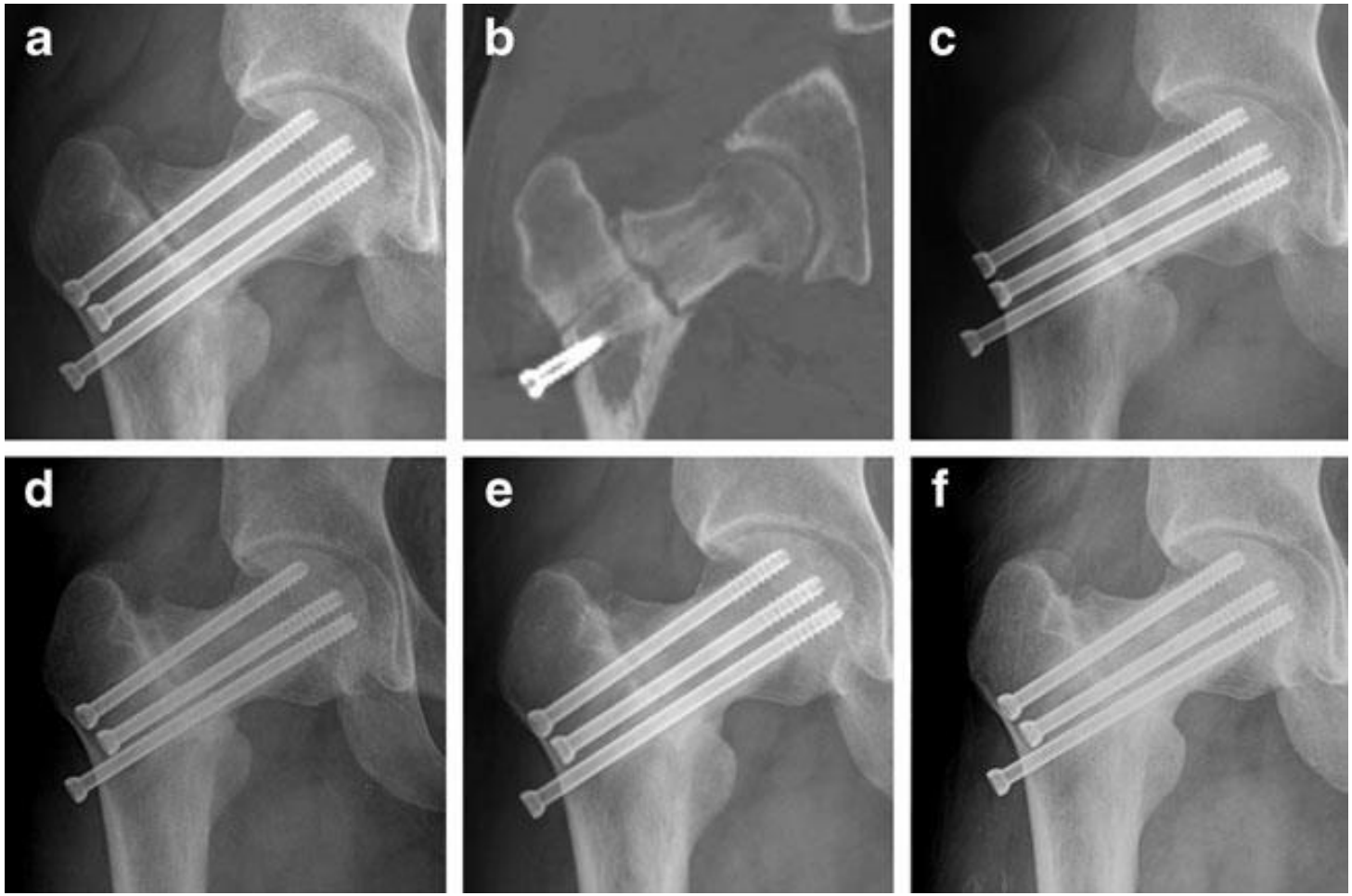


Osteoporos Int (2012) 23:2897–2900
DOI 10.1007/s00198-012-2172-x

CASE REPORT

Teriparatide, a nonsurgical solution for femoral nonunion? A report of three cases

Y.-K. Lee · Y.-C. Ha · K.-H. Koo



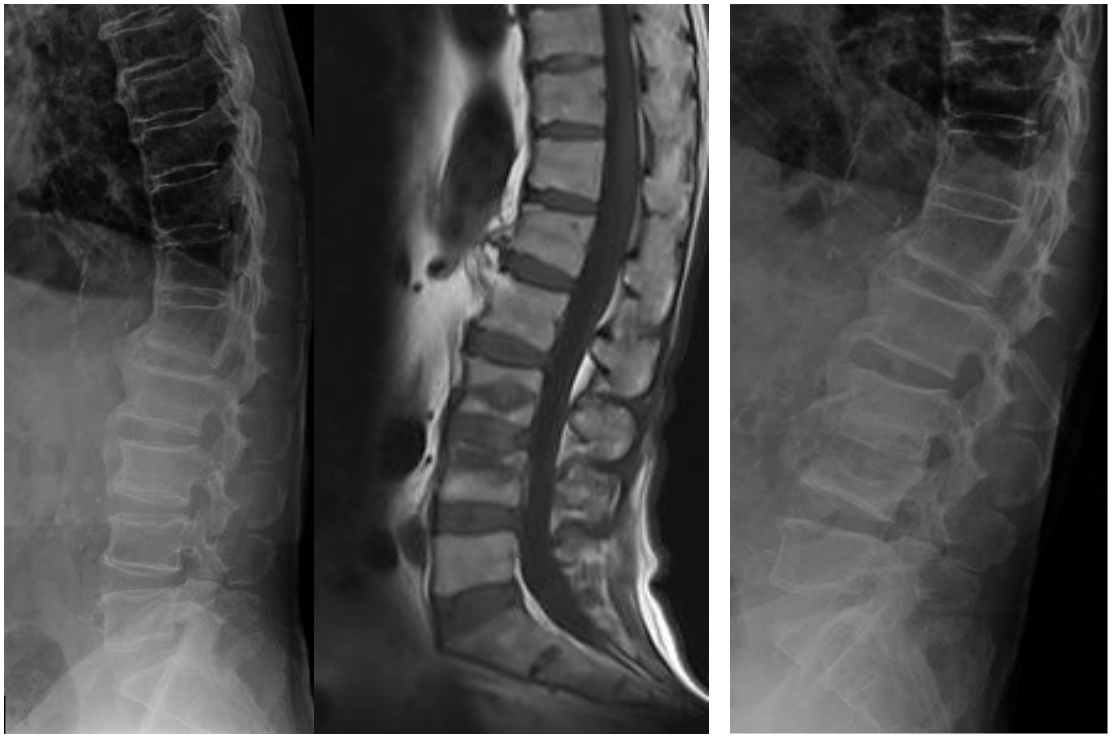
Open Journal of Orthopedics, 2013, 3, 278-282
http://dx.doi.org/10.4236/ojo.2013.36051 Published Online October 2013 (http://www.scirp.org/journal/ojo)

Scientific Research

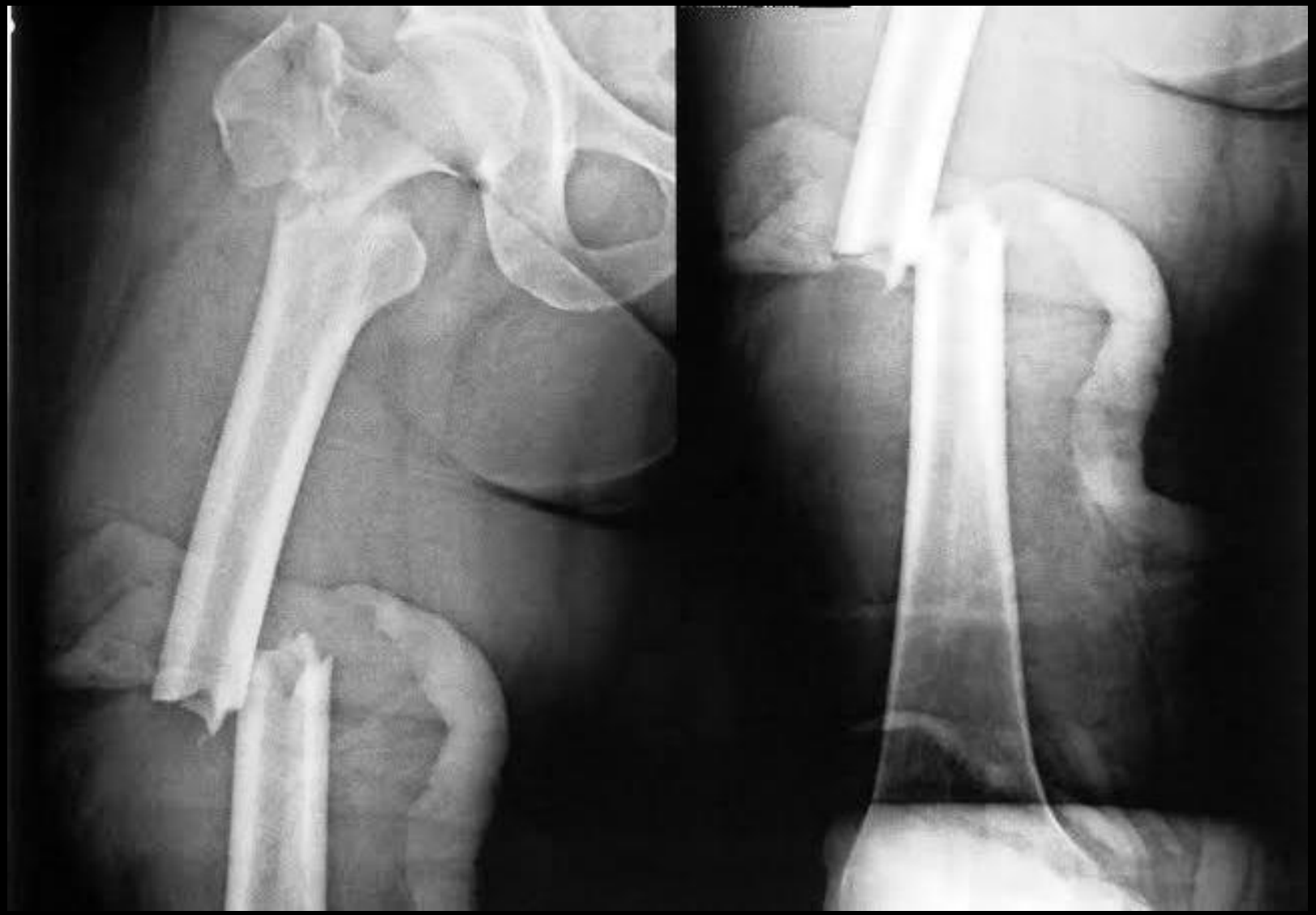
Successful Treatment of Spine Fracture for Diffuse Idiopathic Skeletal Hyperostosis with Teriparatide—A Report of Two Cases*

Yasuaki Iida, Hiroshi Takahashi#, Yuichiro Yokoyama, Yasuhiro Inoue, Daisuke Suzuki, Keiji Hasegawa, Shintaro Tsuge, Wataru Shishikura, Katsunori Fukutake, Ryo Takamatsu, Kazumasa Nakamura, Masayuki Sekiguchi, Akihito Wada

1 month after treatment with teriparatide, the lumbar pain improved, and after 2 months, the patient was able to walk using a T-cane.



6 months

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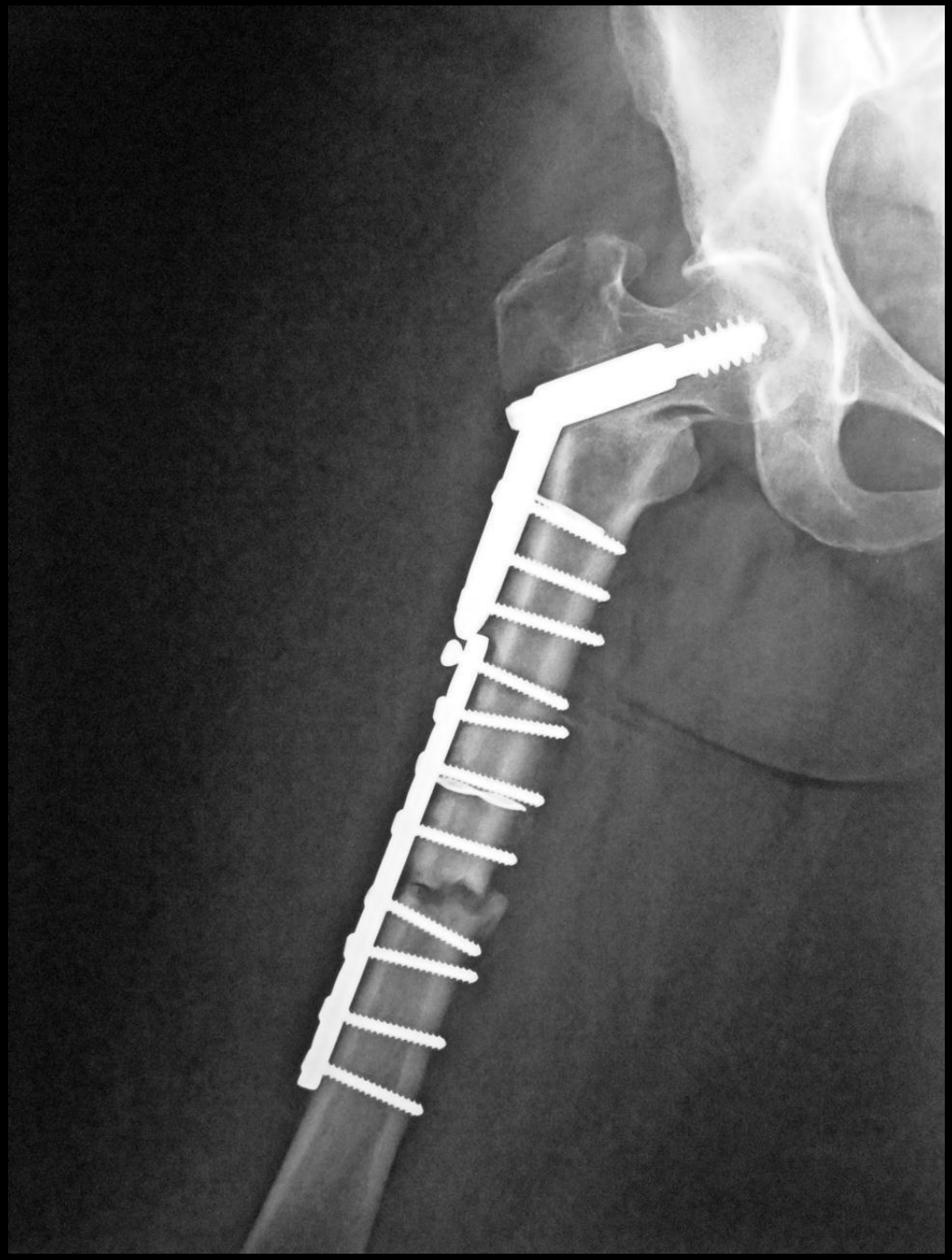

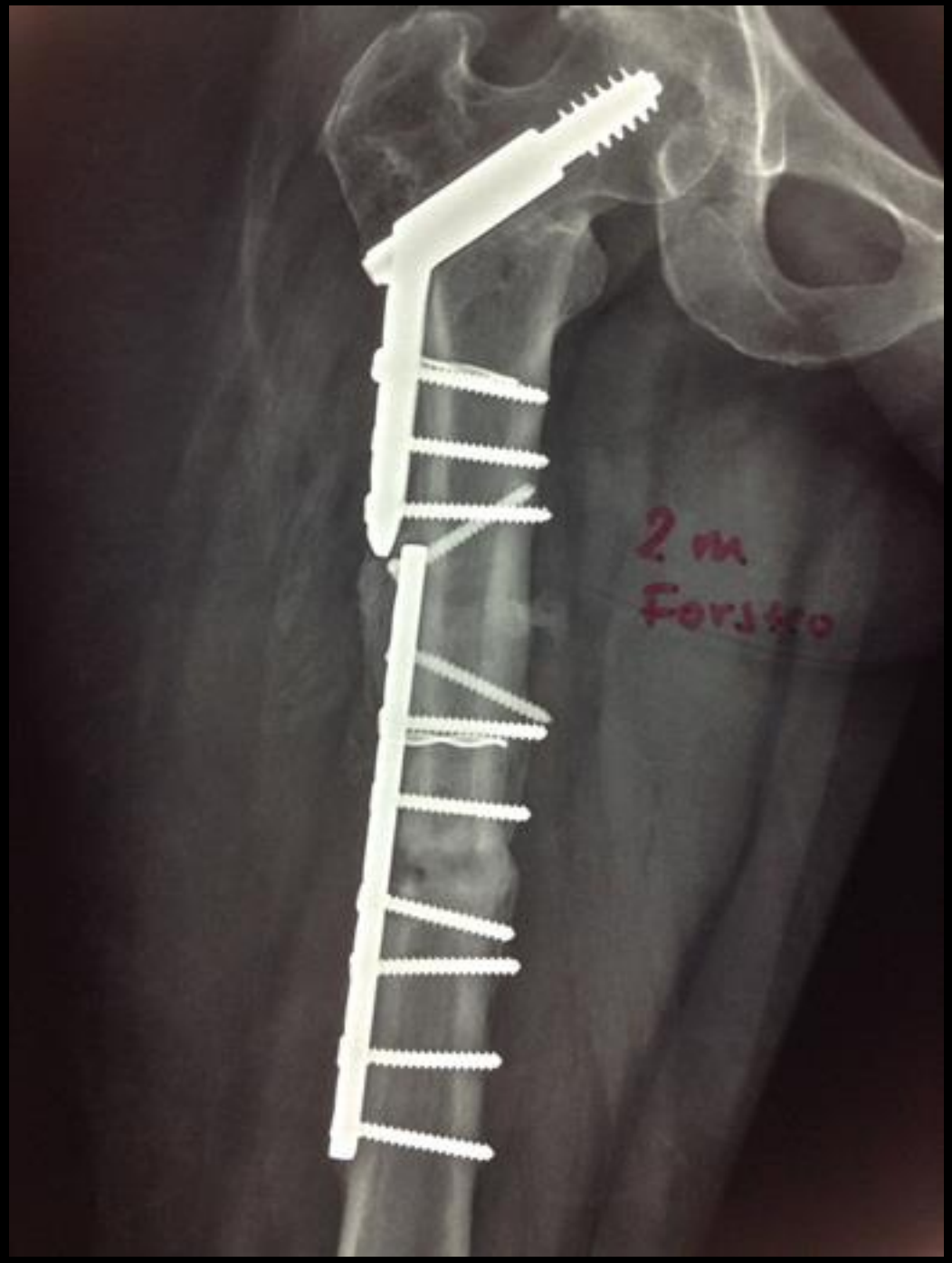
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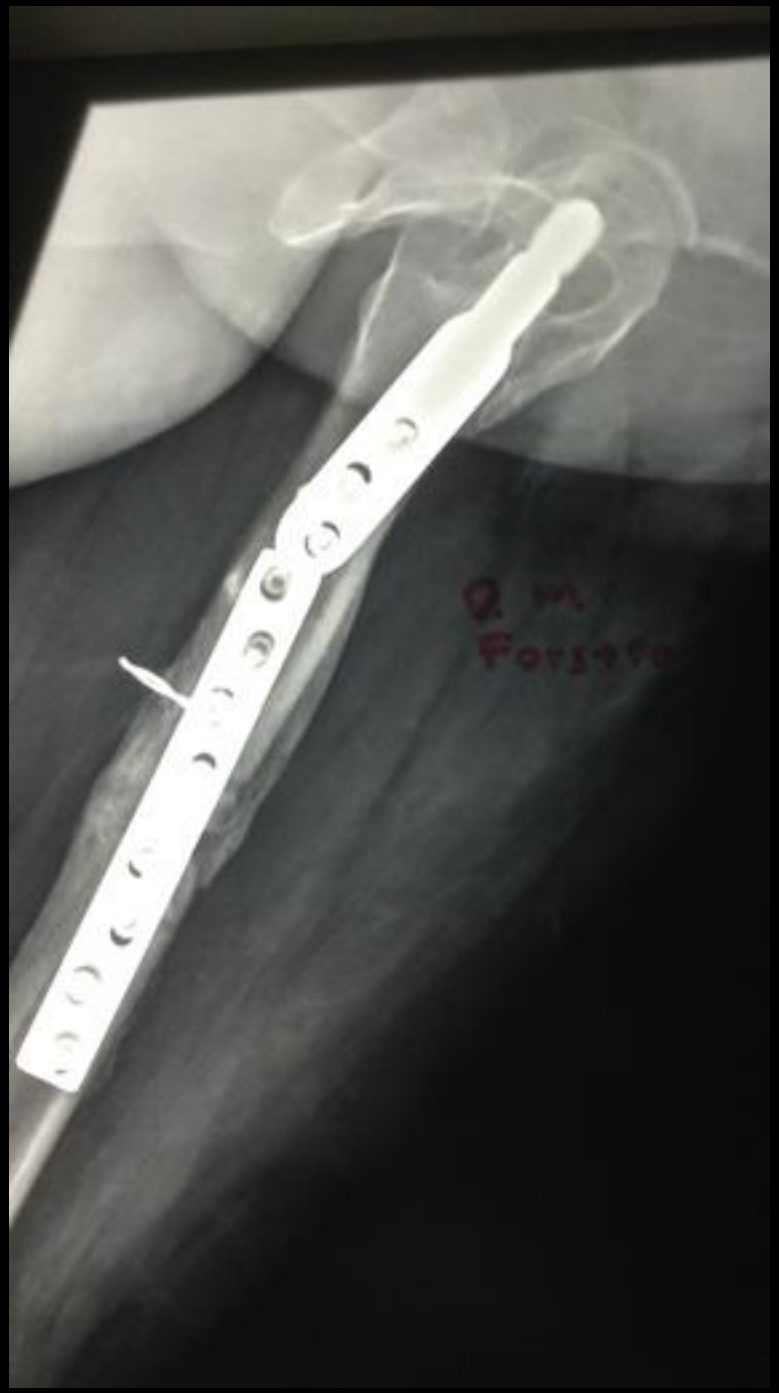

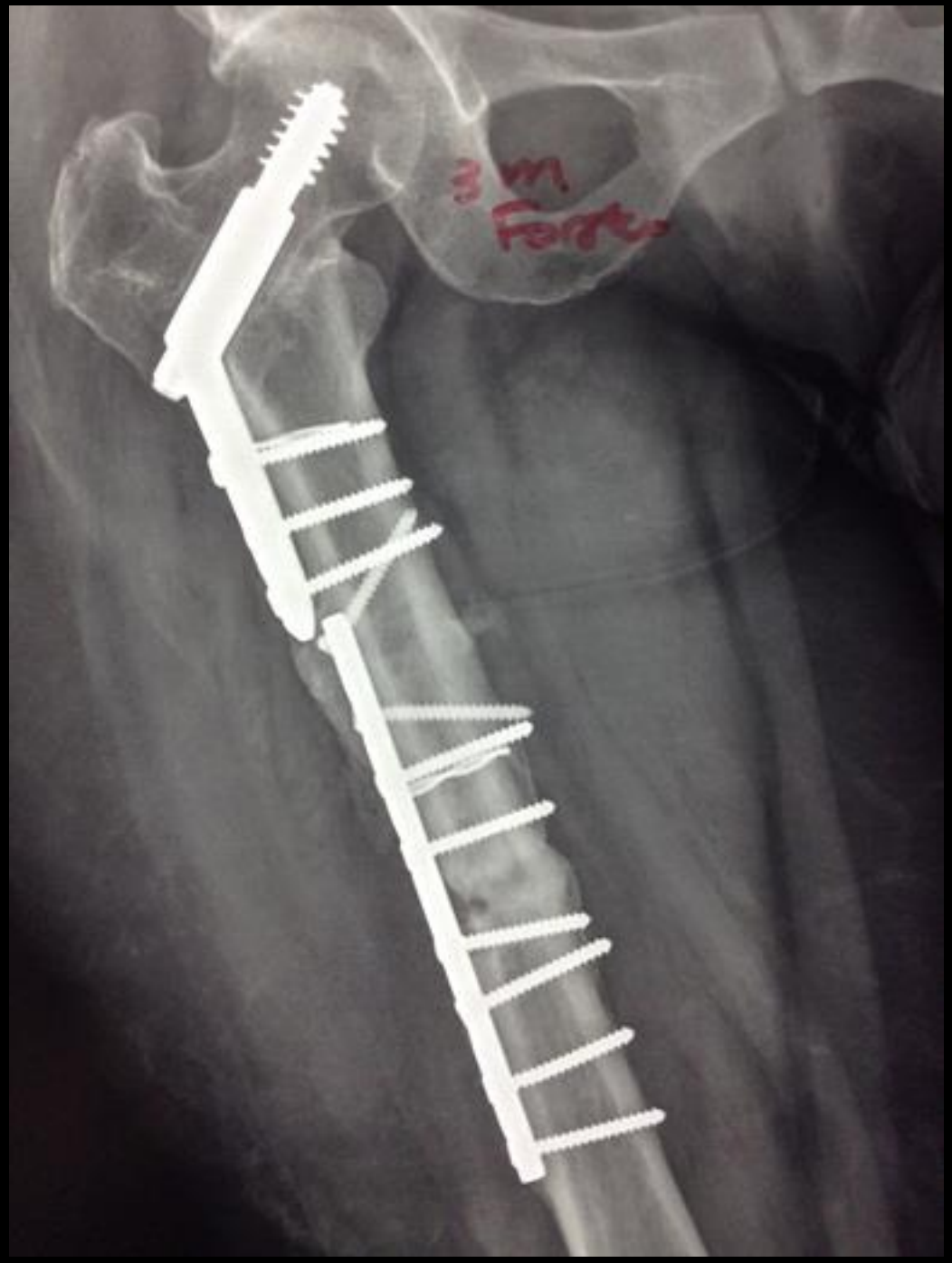
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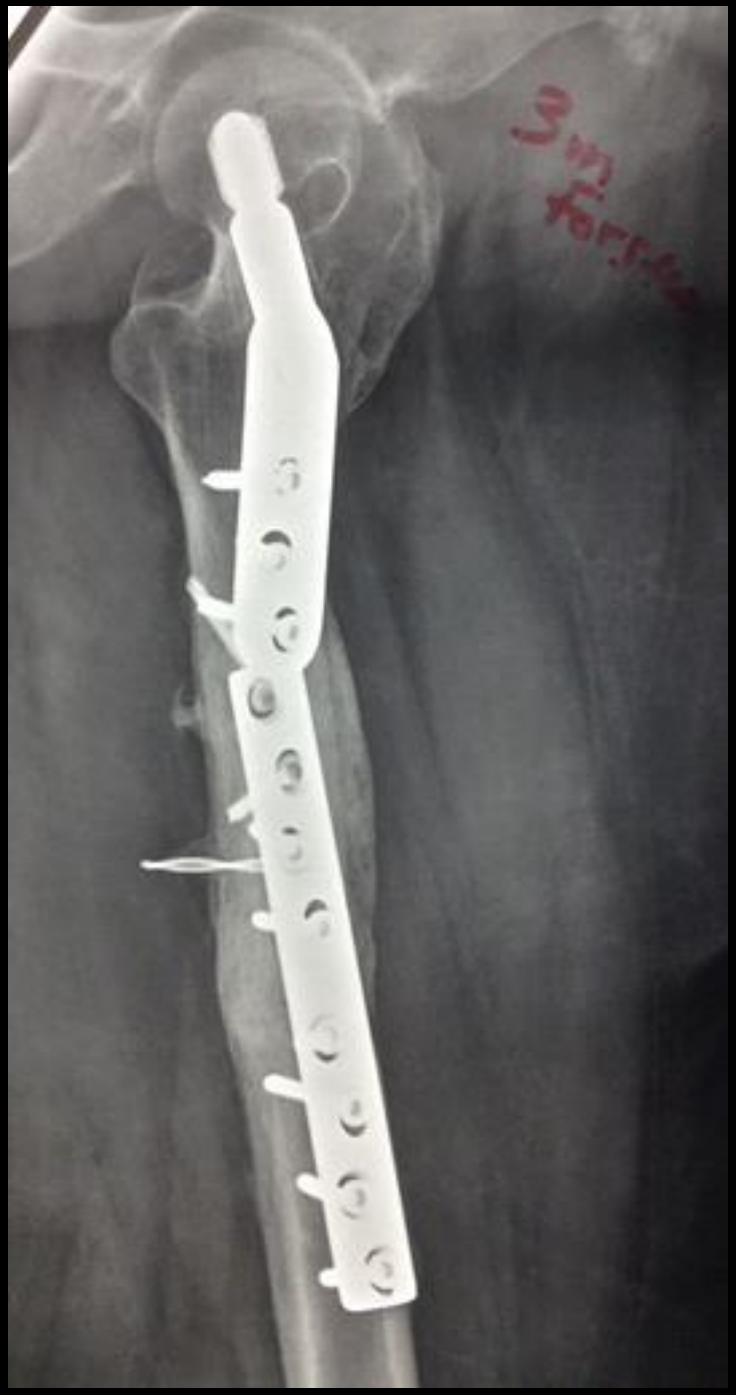

3m

Atypical fractures

Table 1 ASBMR criteria for the diagnosis of atypical femoral fractures.[3]

Principal features

1. Located in any part of the femur, from the distal portion of the minor trochanter to the proximal portion of the supracondylar prominence.
2. Associated to minimal trauma, such as a fall whilst standing or at less height, or without previous trauma
3. Short oblique or transversal configuration
4. Without comminution
5. Complete fractures extend through both corticals and may be associated to a medial spicula; incomplete fractures only affect the lateral cortical

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.

Rev Esp Cir Ortop Traumatol. 2013;57(2):95–105

ELSEVIER DOYMA

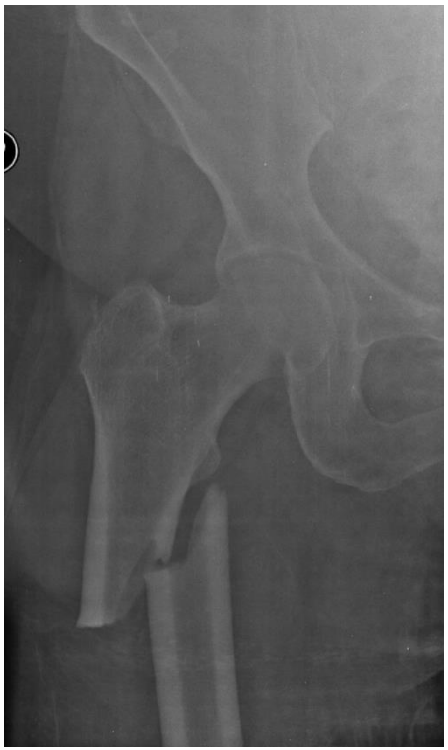
Revista Española de Cirugía Ortopédica y Traumatología

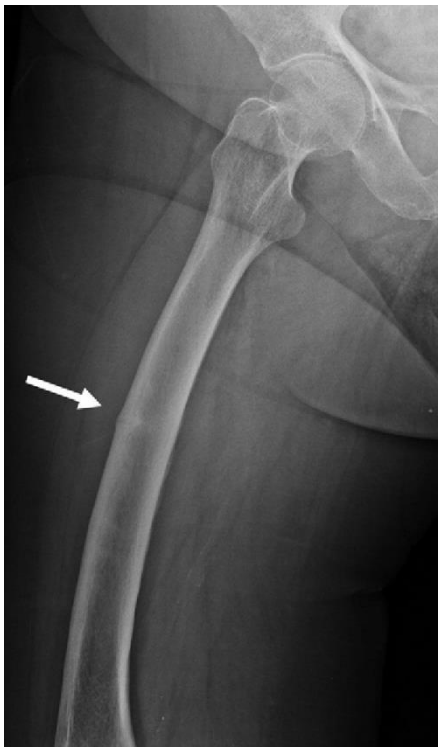
www.elsevier.es/rot

ORIGINAL ARTICLE

What do we know about atypical fractures in patients on bisphosphonates treatment? A literature review using a case series☆

A. Méndez-Gil*, S. Prat-Fabregat, A. Domingo-Trepat, M. Navarro-López, P. Camacho-Carrasco, A. Carreño-Delgado, J.A. Zumbado-Dijeres, R. García-Elvira, M. Ríos-Martín, R. García-Tarriño, O. Ares-Rodríguez, J.R. Ballesteros-Betancourt, S. Suso-Vergara





Original Full Length Article

Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy

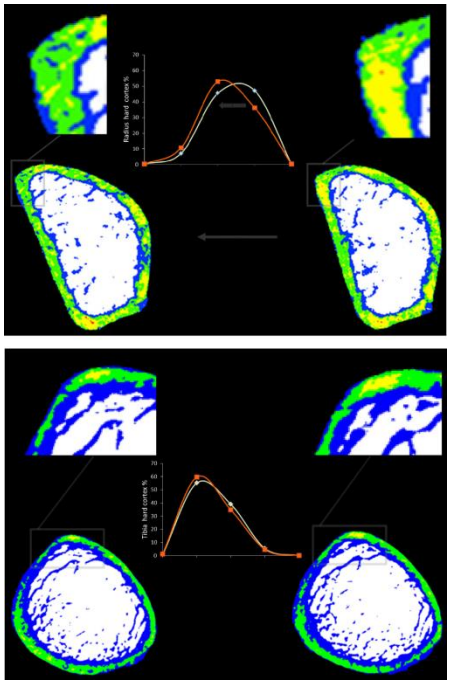
Cherie Ying Chiang [a,b,*], Roger M.D. Zebaze [a,b], Ali Ghasem-Zadeh [a,b], Sandra Iuliano-Burns [a,b], Andrew Hardidge [c], Ego Seeman [a,b]

Bone 52 (2013) 360–365

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teriparatide and Osseous Regeneration in the Oral Cavity

Jill D. Bashutski, D.D.S., Robert M. Eber, D.D.S., Janet S. Kinney, M.S., Erika Benavides, D.D.S., Ph.D., Samopriyo Maitra, M.S., Thomas M. Braun, Ph.D., William V. Giannobile, D.D.S., D.Med.Sc., and Laurie K. McCauley, D.D.S., Ph.D.

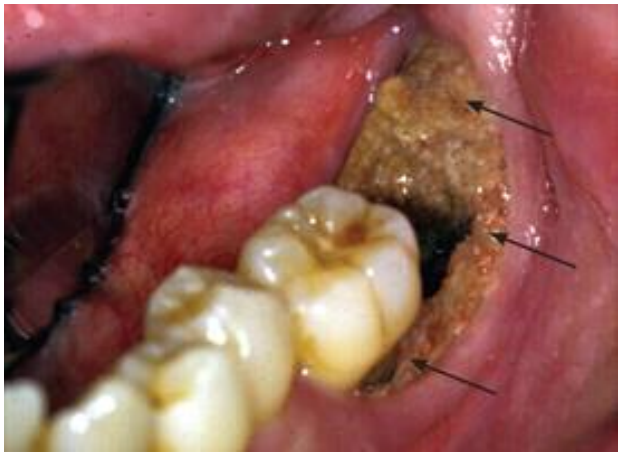
40 patients with chronic periodontitis had periodontal surgery and daily injections of teriparatide (20 µg) or placebo (follow-up 1 year)

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

Bisphosphonate-associated osteonecrosis of the jaw, with healing after teriparatide: a review of the literature and a case report

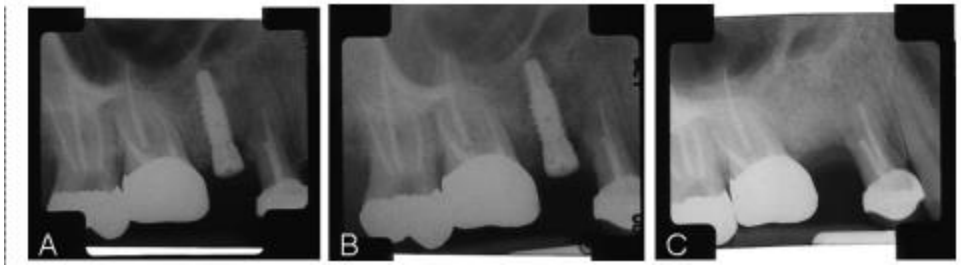
Spec Care Dentist 30(2): 77-82, 2010

Pongthorn Narongroeknawin, MD;[1] Maria I. Danila, MD, MSc;[1] Lewis G. Humphreys Jr., DMD;[2] Andrei Barasch, DMD, MDSc;[3] Jeffrey R. Curtis, MD, MPH[1]*



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



Sci Transl Med. 2011 September 21; 3(101): 101ra93. doi:10.1126/scitranslmed.3002214.

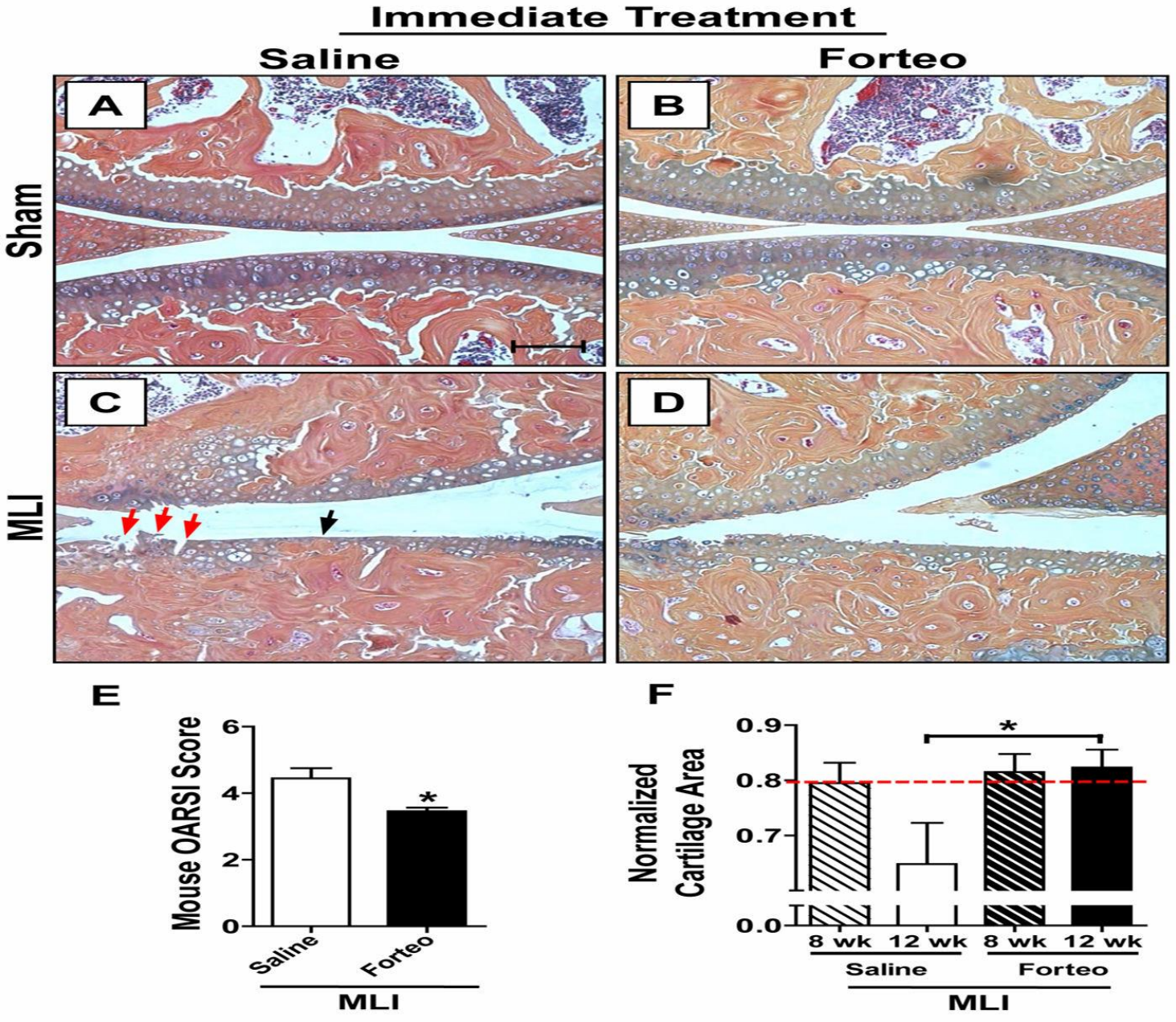
Teriparatide, a Chondro-Regenerative Therapy for Injury-Induced Osteoarthritis

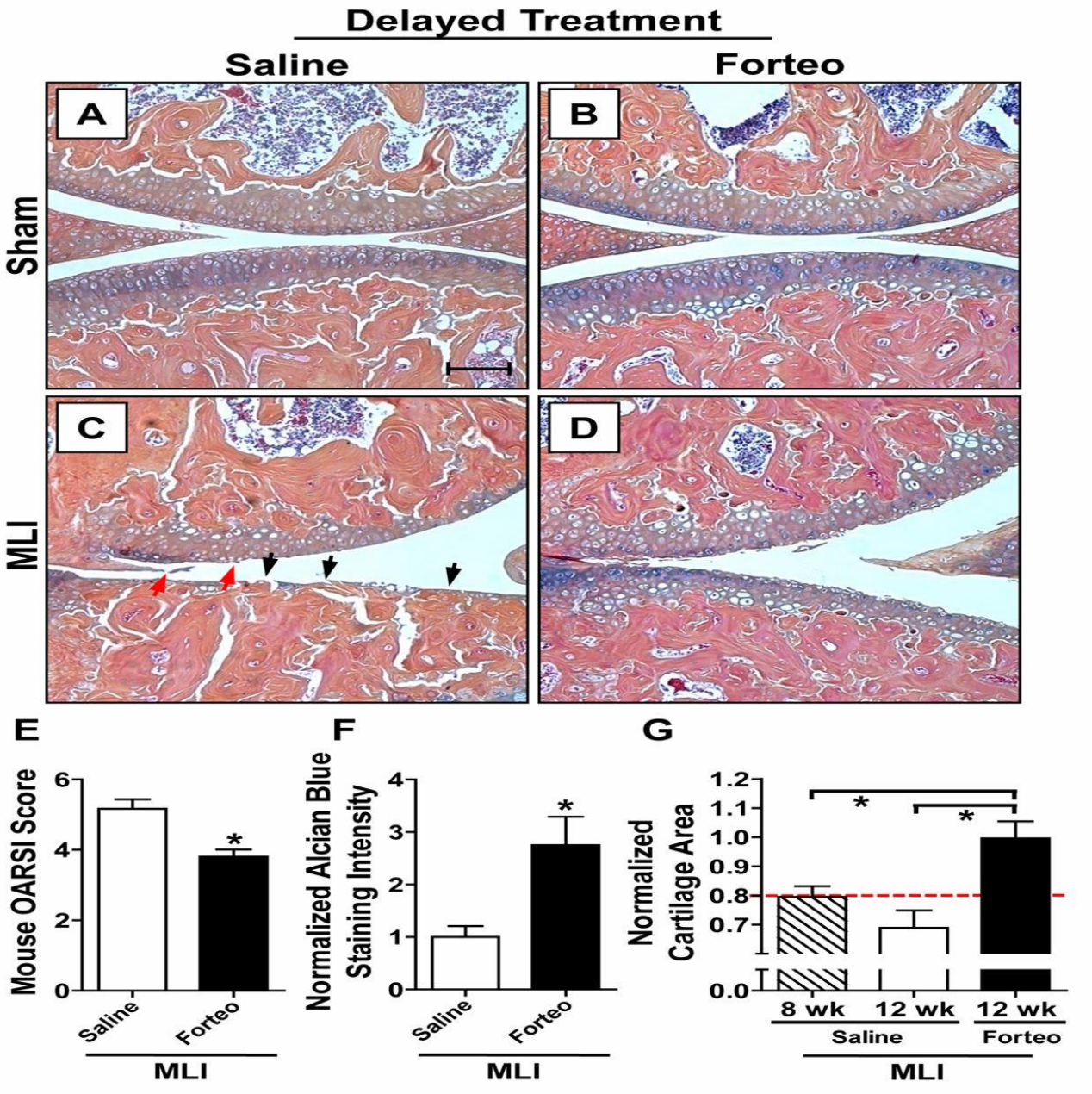
Erik R. Sampson[1], Matthew J. Hilton[1], Ye Tian[1], Di Chen[1], Edward M. Schwarz[1], Robert A. Mooney[2], Susan V. Bukata[1], Regis J. O'Keefe[1], Hani Awad[3], J. Edward Puzas[1], Randy N. Rosier[1,†], and Michael J. Zuscik[1,†]

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 etalloproteinase-13 and the c-terminal aggrecan cleavage product NITEGE.


Immediate Treatment
Saline
Forteo
Sham
MLI
A
B
C
D
E
Mouse OARSI Score
6
4
2
0
*
Saline
Forteo
MLI
F
Normalized Cartilage Area
0.9
0.8
0.7
0.0
*
8 wk
12 wk
8 wk
12 wk
Saline
Forteo
MLI


Delayed Treatment
Saline
Forteo
A
B
C
D
Sham
MLI
E
Mouse OARSI Score
6
4
2
0
*
Saline
Forteo
MLI
F
Normalized Alcian Blue Staining Intensity
4
3
2
1
0
*
Saline
Forteo
MLI
G
Normalized Cartilage Area
1.2
1.1
1.0
0.9
0.8
0.7
0.0
*
*
8 wk
12 wk
12 wk
Saline
Forteo
MLI

Teriparatide therapy enhances devitalized femoral allograft osseointegration and biomechanics in a murine model

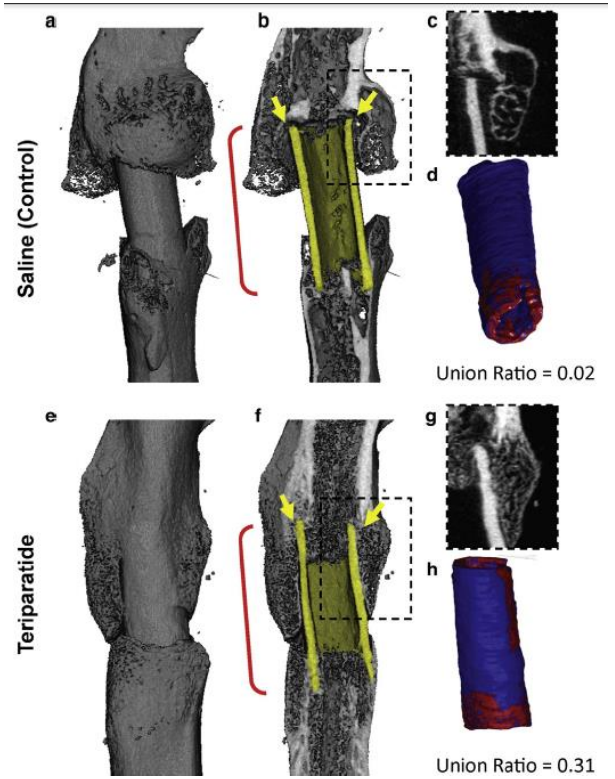
David G. Reynolds [a,b], Masahiko Takahata [b], Amy L. Lerner [a,b], Regis J. O'Keefe [b,c], Edward M. Schwarz [a,b,c], Hani A. Awad [a,b,c,*]

Bone 48 (2011) 562–570

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



Medical Hypotheses 77 (2011) 701–704

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

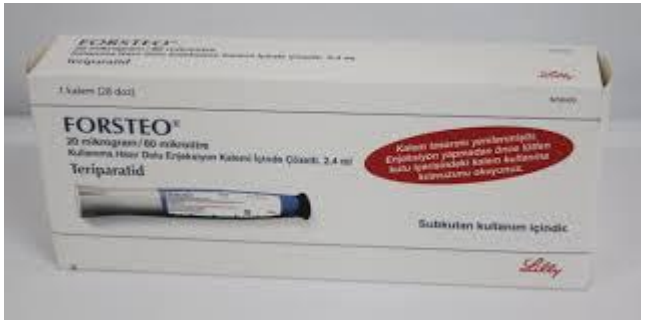
A potential therapeutic approach to overload-induced bone loss around implant: Parathyroid hormone (PTH)

Xiaohua Zeng [a,b], Hao He [a,b], Liang Zhang [a,b], Yingying Wu [a,b], Yanying Wang [a,b], Ping Gong [a,b,*]

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

Cautions & side effects



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.

Materials **2011**, *4*, 1117-1131; doi:10.3390/ma4061117

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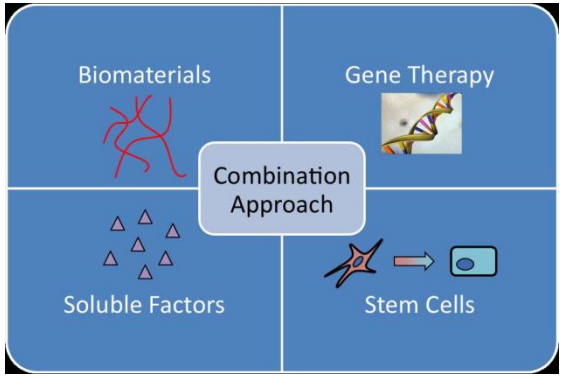
Article

Teriparatide Therapy as an Adjuvant for Tissue Engineering and Integration of Biomaterials

Robinder S. Dhillon [1,2] and Edward M. Schwarz [1,2,*]



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.