NOVEL USES OF PARATHYROID HORMONE AND NONSURGICAL MANAGEMENT OF HYPERPARATHYROIDISM

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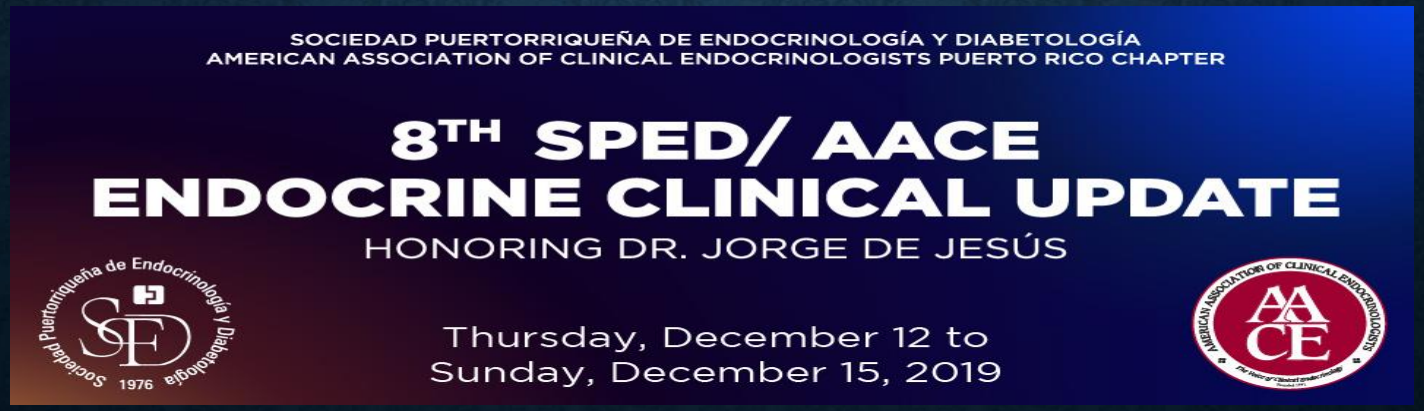


DISCLOSURES

- No conflict of interest
- Will discuss non-FDA approved uses of parathyroid hormone analogs

OBJECTIVES

- Discuss the available PTH analogs and their FDA approved uses
- Discuss novel uses of PTH analogs
- Discuss the nonsurgical management of hyperparathyroidism

PARATHYROID HORMONE ANALOGS

- Teriparatide
  - PTH (1-34)
  - Forteo; Bonsity
  - FDA approved on 2002 for osteoporosis

- Parathyroid hormone (1-84)
  - Europe: Preotact (2006) for osteoporosis
  - Natpara
    - FDA approved on 2015 for hypoparathyroidism…

INDICATIONS FOR CONSIDERING USE OF RH-PTH (1-84) IN HYPOPARATHYROIDISM

- Labile serum calcium
- High requirements for calcium (>2.5 g/day), or calcitriol (> 1.5 mcg/day)
- Hypercalciuria, renal stones, nephrocalcinosis, eGFR < 60 mL/min
- Hyperphosphatemia or Ca-P product > 55
- Gastrointestinal malabsorption disorder
- Reduced quality of life (neuro-cognitive alterations)

JCEM 2016;101(6):2273-83

PARATHYROID HORMONE ANALOGS

- Abaloparatide
  - Synthetic PTHrp
  - Tymlos
  - FDA approved on 2017 for osteoporosis

PTH ANALOGS FDA-MANDATED BLACK BOX WARNING

- All active PTH molecules, to date, when tested in high doses for 18 to 24 months in rats, will cause osteosarcoma.

- For this reason, all analogs approved for human use carry the FDA-mandated black box warning.

- Up to 10 years of safety data has been reported of rhPTH(1-84) use
  - No safety findings identified

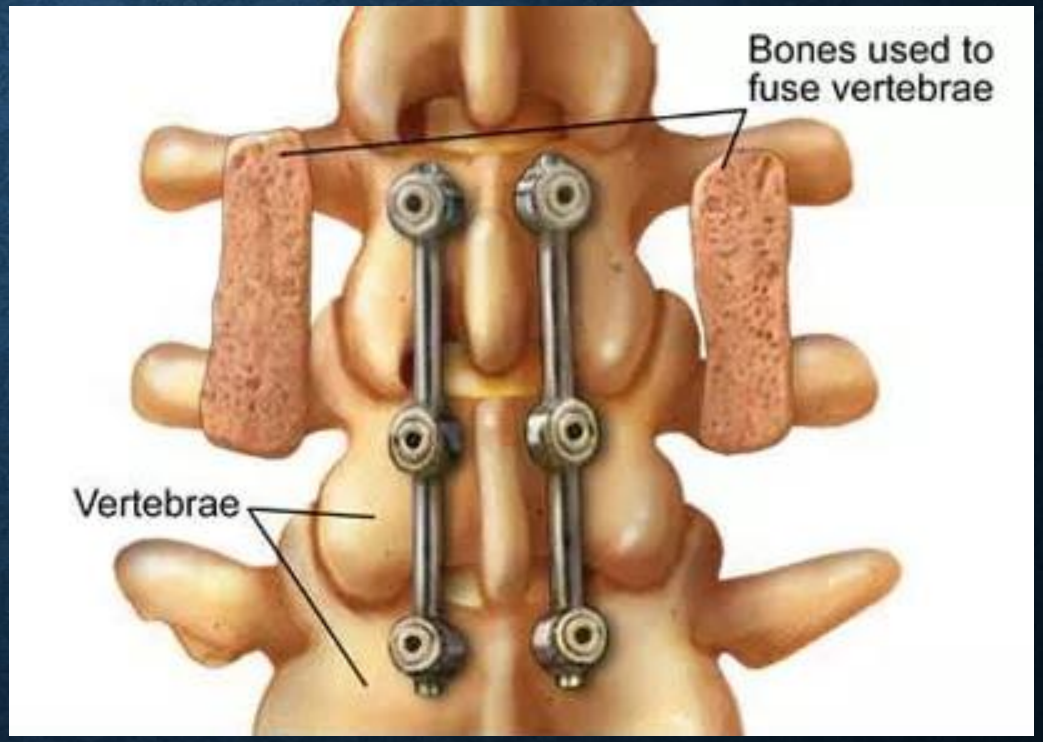
NOVEL USES OF PARATHYROID HORMONE ANALOGS

DISCLOSURES

- Will discuss non-FDA approved uses of parathyroid hormone analogs.
- Available information is mostly of teriparatide (PTH 1-34).
- Lack of published controlled studies
  - Case reports
  - Small case series
- No generally accepted treatment course

SPINAL FUSION

- Low bone mass/poor bone quality may increase the risk of hardware loosening, lack of appropriate fusion, and the need for revision surgery.



SPINAL FUSION

- The effectiveness of intermittent PTH has been demonstrated in multiple rodent and rabbit models.

- Limitations:
  - Rodents: noninstrumented fusion, due to small boney architecture
  - Rabbits: instrumented fusion BUT nonosteoporotic

Clin Spine Surg(32)5;June 2019

SPINAL FUSION

- Humans:
  - Fusion rate are higher at 6 months
  - No difference at 12 and 24 months

- NIH supported randomized study (NCT-01292252)
  - Study ended on December 2017
  - No final results still reported

Osteoporosis Int (2018)29:1009-1022

•Mayo Clinic

- "it seems to improve the chances of a successful fusion based on the available evidence."

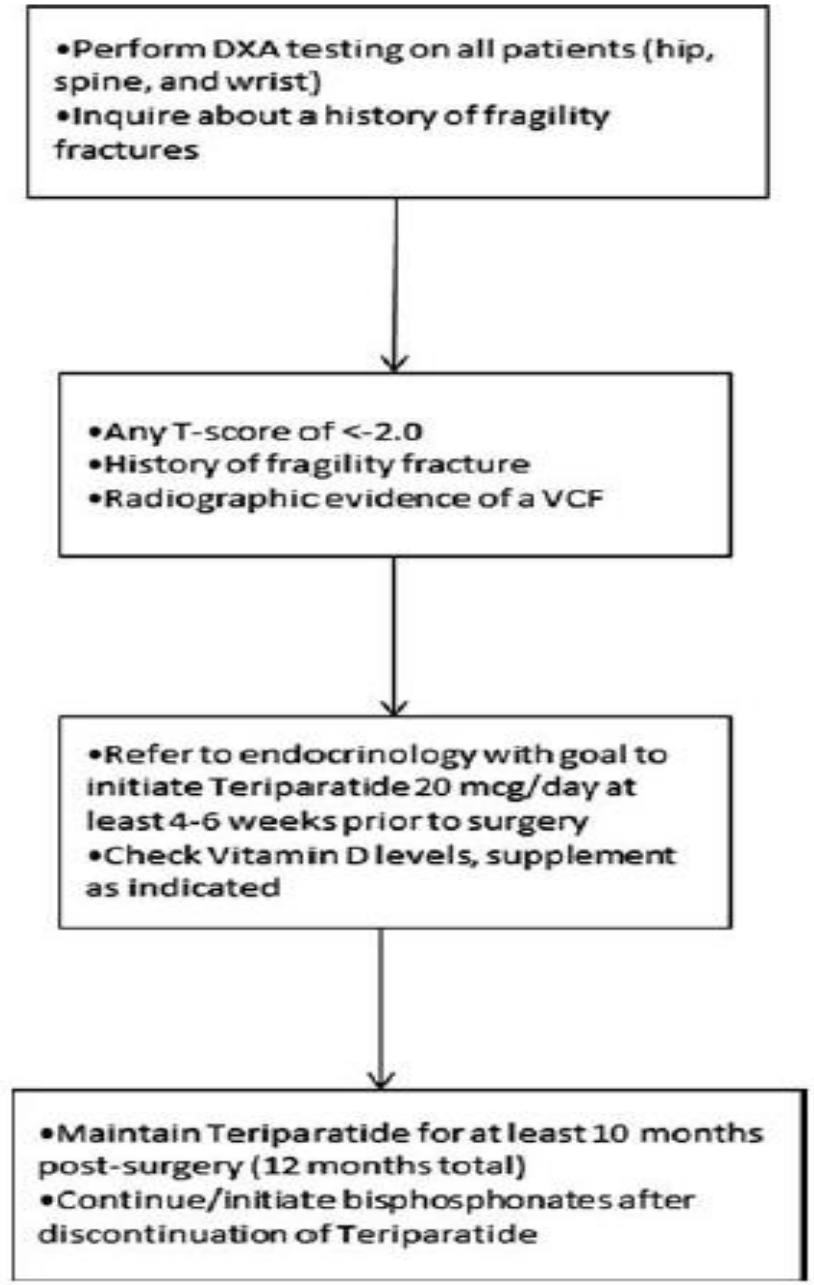


FIGURE 1. Algorithm for use of teriparatide in spine fusion patients.

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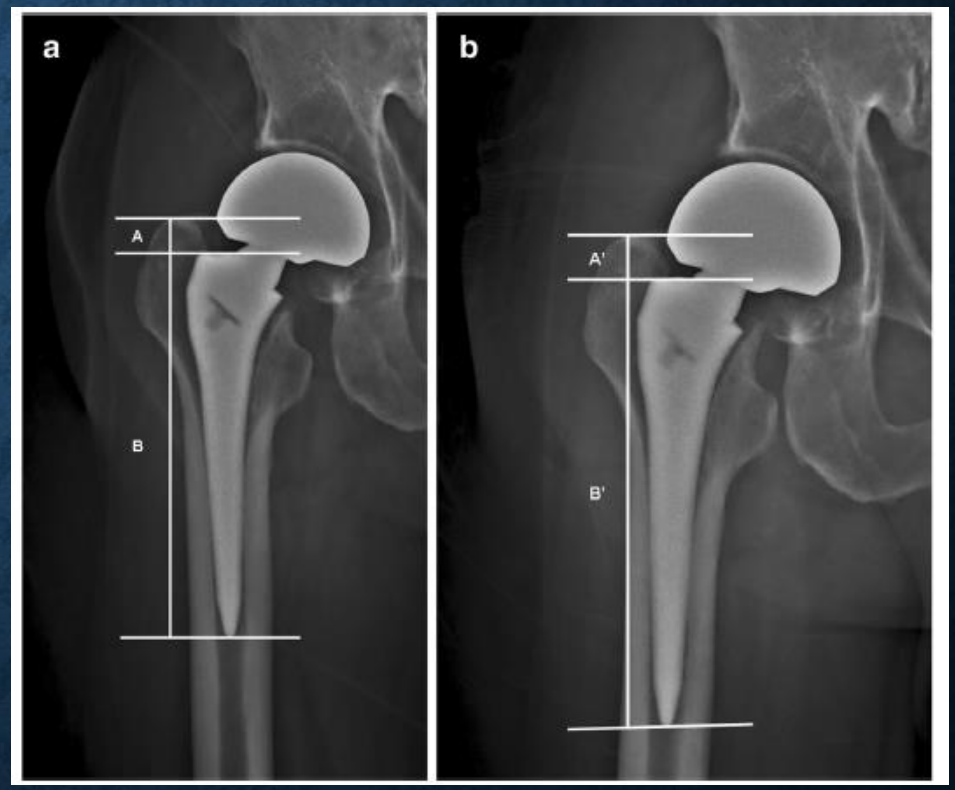
HIP FRACTURE

- Teriparatide:
  - Reduction in femoral stem subsidence

- A prospective, randomized clinical trial (NCT-022972424) is now been conducted



BMC Musculoskeletal Disorders (2016)17:300

OTHER NOVEL USES OF PTH ANALOGS

- Osteonecrosis of the jaw
- Atypical femoral fractures
- Stress fractures
- Sternal fractures
- Periodontitis
- Orthodontic prosthesis
- Kummell's disease
  - Avascular necrosis of a vertebral body
- Odontoid fracture (axis of C2 vertebra)
- Osteogenesis imperfecta
- Psoriasis
  - Topical PTH(1-34)
- Osteoarthritis
  - Stimulation of chondrocytes lineages
- Adult hypophasphatasia
  - Longstanding non-healing fractures

NONSURGICAL MANAGEMENT OF PRIMARY HYPERPARATHYROIDISM

PRIMARY HYPERPARATHYROIDISM

- Parathyroidectomy is the only curative treatment of primary hyperparathyroidism (PHPT).

- Parathyroidectomy decreases the risk of kidney stone, improves BMD, and may decrease fracture risk, and modestly improve some quality of life measurements.

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PRIMARY HYPERPARATHYROIDISM

- A pharmaceutical agent that would be able to normalize biochemical, skeletal, renal and other abnormalities associated with the disease is NOT available.

- Therefore, nonsurgical management should NOT be offered as an (elective) alternative to parathyroidectomy.

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PRIMARY HYPERPARATHYROIDISM

- A nonsurgical approach could be considered in patients who:
  - Have failed surgery
  - Have contraindications to surgery
  - Are unwilling to undergo surgery

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TABLE 4

2013 Guidelines for Parathyroid Surgery in Asymptomatic Patients with PHPT

Measurement	Indication*
Serum calcium (> upper limit of normal)	> 1 mg/dL
Skeletal	BMD by DEXA: T-score < –2.5 at lumbar spine, total hip, femoral neck, or distal one-third of radius Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	Creatinine clearance < 60 mL/min 24-h urine for calcium > 400 mg/dL and increased risk for stones by stone risk analysis Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Age (yr)	< 50

Abbreviations: BMD, bone mineral density; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging; PHPT, primary hyperparathyroidism; VFA, vertebral fracture assessment.
*Patients need to meet only one criteria for parathyroid surgery to be recommended.
Source: Bilezikian et al. *J Clin Endocrinol Metab.* 2014.[19]

The table below summarizes what some test results may indicate:

Test	Result Indicating Increased Kidney Stone Risk	Stone Formation / Comments
Creatinine	N/A	Blood and urine creatinine levels reflect kidney function; they may be used for comparing to other substances as the level of creatinine in blood is normally stable and, in urine, it reflects how dilute or concentrated the urine is.
Urine calcium	High	Possibility for calcium oxalate or calcium phosphate stones
Urine oxalate	High	Possibility for calcium oxalate stones
Urine uric acid	High	Uric acid stones may form; many who have increased uric acid also have gout
Urine citric acid	Low	Citric acid helps inhibit stone formation.

https://labtestsonline.org/tests/kidney-stone-risk-panel

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Table 2. Guidelines for Monitoring Patients with Asymptomatic PHPT Who Do Not Undergo Parathyroid Surgery: A Comparison of Current Recommendations With Previous Ones[a]

Measurement	1990	2002	2008	2013
Serum calcium	Biannually	Biannually	Annually	Annually
Skeletal	DXA, annually (forearm)	DXA, annually (3 sites)	DXA, every 1–2y (3 sites)[a]	Every 1–2 y (3 sites),[a] x-ray or VFA of spine if clinically indicated (eg, height loss, back pain)
Renal	eGFR, annually; serum creatinine, annually	eGFR, not recommended; serum creatinine, annually	eGFR, not recommended; serum creatinine, annually	eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by x-ray, ultrasound, or CT

Abbreviation: eGFR, estimated glomerular filtration rate.

[a] This recommendation acknowledges country-specific advisories as well as the need for more frequent monitoring if the clinical situation is appropriate.

J Clin Endocrinol Metab, October 2014, 99(10):3561–3569

Table 4. Indications for Parathyroid Surgery During Monitoring

Measurement	2013
Serum calcium (>upper limit of normal)	>1 mg/dL (>0.25 mmol/L)
Skeletal	A. T-score <−2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius; or a significant reduction in BMD[a] B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	A. CrCl < 60 cc/min B. Clinical development of a kidney stone or by imaging (x-ray, ultrasound, or CT)

Abbreviations: MRI, magnetic resonance imaging; CrCl, creatinine clearance.

[a] A significant change is defined by a reduction that is greater than the least significant change as defined by the International Society for Clinical Densitometry (11).

J Clin Endocrinol Metab, October 2014, 99(10):3561–3569

HYDRATION

- Adequate hydration is always recommended.

- Dehydration should be avoided because it will be associated with worsening hypercalcemia.

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CALCIUM INTAKE

- Avoid calcium restriction
  - Exacerbate parathyroid hypersecretion

- Keep adequate calcium intake, as suggested by national guidelines.

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VITAMIN D SUPPLEMENTATION

- The latest International guidelines suggest that PHPT patients with vitamin D deficiency should be replete with 800-1000 IU cholecalciferol daily to attain a serum 25OHD level greater than 20 ng/ml or even higher (>30 ng/ml according to some opinion leaders).

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PHYSICAL ACTIVITY

- Minimize bone resorption

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AVOID FACTORS THAT CAN AGGRAVATE HYPERCALCEMIA, IF POSSIBLE

- Thiazide diuretics
  - *Low doses have been studied for the treatment of hypercalciuria
  - *Close monitoring of serum calcium is required
- Lithium carbonate
- Prolonged bed rest

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ANTIRESORPTIVE THERAPY

- Rational:
  - Bone turnover is increased
    - Responsible of bone loss

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ANTIRESORPTIVE THERAPY: ALENDRONATE

- Has been the more extensively investigated bisphosphonate
- Transient decline in serum calcium
- Bone turnover markers declined
- BMD increases, particularly at sites rich of cancellous bone (spine and hip)
- No data available on fractures

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ANTIRESORPTIVE THERAPY: DENOSUMAB

- One retrospective study
  - 24-month therapy
  - N = 25 elderly women with PHPT-related osteoporosis
- Significant decline in alkaline phosphatase
- Significant increase in hip BMD
- No data available on fractures

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ANTIRESORPTIVE THERAPY SUMMARY

- Should be considered in patients with:
  - Fragility fractures (*regardless of decision for parathyroidectomy*)
  - T-score < -2.5 at any site

- **T-score < -2.5 at any site + Parathyroidectomy**
  - *Start antiresorptive therapy 1-2 years **after** successful surgery*

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CALCIMIMETICS: CINACALCET

- FDA-approved for "the reduction of hypercalcemia in patients with parathyroid carcinoma and for treatment of severe hypercalcemia in patients with PHPT who are unable to undergo parathyroidectomy".

- Safety has not been established in pediatric patients.

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CALCIMIMETICS: CINACALCET

- Serum calcium concentration should be checked in 1 week after beginning of treatment or dose adjustment.

- Patients should be monitored for side effects (nausea; headaches), and the occurrence of hypocalcemia.

- Treatment has NO impact on BMD at any site.

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CINACALCET THERAPY: SUMMARY

- Decreases and often normalizes serum calcium
- Increases serum phosphorus
- The effect on plasma PTH levels is less pronounced
- The effect of BMD is neutral
- Could become cost-effective at an annual cost much lower that the current one

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CINACALCET + BISPHOSPHONATES

- Therapy could be an option in patients with low BMD and serum calcium levels in the range that is appropriate for cinacalcet use.

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FUTURE THERAPIES: DRUGS IN THE HORIZON

- Calcitriol analogues that inhibit PTH secretion but do not stimulate GI calcium absorption

- Drugs that block the PTH receptor

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SUMMARY

NOVEL USES OF PTH ANALOGUES

- Information available limited to pre-clinical studies (animals), case reports and small case series

- Most studied novel use has been on spinal fusion
  - Pending report of NCT-01292252

- Active prospective, RCT (NCT-02972424)
  - -Teriparatide effect in osteoporotic patients with pelvic fracture

NONSURGICAL MANAGEMENT OF PRIMARY HYPERPARATHYROIDISM

- Nonsurgical management should NOT be offered as an (elective) alternative to parathyroidectomy
- Adequate hydration
- No need to restrict calcium
- Correct vitamin D insufficiency/deficiency
- Antiresorptive therapy
- Cinacalcet
- Future therapies: calcitriol analogues; PTH receptor blockers

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS PUERTO RICO CHAPTER

8TH SPED/ AACE ENDOCRINE CLINICAL UPDATE

HONORING DR. JORGE DE JESÚS

Thursday, December 12 to
Sunday, December 15, 2019