Update on Hypoparathyroidism: New Therapeutic Options and Management Guidelines

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Disclosures

• Investigator on NPS (Shire)-sponsored clinical trial REPLACE on use of PTH (1-84) in adults with hypoparathyroidism

• Consultant: Shire, Ascendis Pharmaceuticals
OUTLINE

• Disorder

• Epidemiology, risk factors

• Long-term consequences

• New treatment approaches

• Guidelines – European Society of Endocrinology (2015) and First International Conference (2016)
CASE

40 year old man referred by endocrinologist with question - *should I change my treatment for hypoparathyroidism?*

History:
- 6 mos old: left cervical neuroblastoma resected, foll by radiation
- 15 yrs old: papillary thyroid cancer ➔ total thyroidectomy; 2 RAI-131 treatments (last in 1997); TG, anti-TG Ab – undetectable
- Acute foll by chronic hypoparathyroidism with low Ca++ and undetectable PTH
- Symptomatic hypocalcemia X 1 year; asymptomatic X 24 years
- Regimen: 1000 mg elemental Ca BID, vitamin D₃ 3,000 IU QD, calcitriol 0.5 mcg BID, Mg SR 84 mg – 3 BID, multivitamin QD

Exam – unremarkable, healed scar
CASE

His 2 most recent lab tests showed

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* First 24 hour urine he ever collected
Causes of Hypoparathyroidism - 1

- **Post-surgical** (thyroid, parathyroid, laryngeal)  
- Functional: Mg depletion (gastrointestinal or renal losses), hyper Mg  
- Constitutive activation of CaSR signaling  
  - Heterozygous gain of function mutations in genes - - *CASR* and in *GNA11*  
  - Activating CaSR antibodies (acquired)  
- Autoimmune

*Schafer and Shoback, Primer of Metabolic Bone Diseases, 2013; Shoback, NEJM, 2008*
Causes of Hypoparathyroidism - 2

- Other genetic causes
  - GCM2 mutations
  - PTH mutations

- Syndromes
  - DiGeorge sequence/CATCH22
  - Hypopara, renal anomalies, deafness (HDR) – GATA3 mutations
  - Kenny-Caffey
  - Sanjad-Sakati
  - Kearns-Sayre and mitochondrial DNA mutations

- Destructive: hemochromatosis/thalassemia (transfusional iron overload), Wilson’s disease, metastatic tumor, $^{131}$I therapy

Postsurgical Hypoparathyroidism - Rates

7.6% of neck surgeries result in hypoparathyroidism

- 75% transient hypoparathyroidism
  < 6 months

- 25% chronic hypoparathyroidism
  > 6 months

- < 2%

38% total thyroidectomy
21% parathyroidectomy
9% partial thyroidectomy
5% others

→ Rates vary substantially, know rate for your surgeon and procedure

Powers J et al. JBMR 2013; 28: 2570
Surgical Experience – Thyroid Operations

High-volume surgeons (on average) → better outcomes (HIGH > 99 cases/yr; low <10, intermediate 10-99)

- Total thyroidectomy - higher risk for ALL complications vs lobectomy (incl hypopara)

Hauch A. Ann Surg Oncol 2014. 21: 3844
Intraoperative PTH Monitoring

Surgical outcomes after re-operation for PHPT in era before (1989 to 1997) and after (1998 to 2005) widespread use of routine IO-PTH monitoring

Use of io-PTH: UCSF

- **Parathyroidectomy**: obtain 2 baseline values: Pre-incision ("Pre-1", before skin incision) or Pre-excision ("Pre-2", before interrupting blood supply to adenoma), then the "Post-1” (5 minutes after excision) and "Post-2” (10 minutes post excision) should drop from baseline by more than 50%. If not, there is risk for additional adenoma, and further exploration is indicated.

- **Thyroid cases**: use “end-of-case” PTH levels to estimate the likelihood of significant post-op hypoparathyroidism
  - If PTH is < 10 pg/ml (1 pmol/L), then patient is at risk; start patient on calcitriol in addition to oral calcium.
  - If PTH > 10, patient given 1 Gm Ca twice daily; stop if no symptoms after 3 or 4 days.
  - If PTH > 10 and symptoms later, give additional oral Ca, check at post-op visit

* Do only for “at risk” cases (not routine or lobectomy cases)

Dr. Quan Duh; Lang et al, World J Surg, 2012
Etiologies of Hypoparathyroidism

75% Post-surgical

25% Medical

- Autoimmune
- Genetic
  - Mg excess or deficiency
  - Infiltration of PT glands (copper, iron, tumor)
  - Radiation (destruction)
Autoimmune Hypoparathyroidism

• Isolated or part of APS-1 (autoimmune polyendocrinopathy syndrome)
  • 68 patients with APS-1 (NEJM, 1990)
    - 100% candidiasis
    - 79% hypoparathyroidism
    - 72% adrenal insufficiency
    - 60% gonadal failure (women, 14% men)
  • 2/3 make diagnosis

• Loss of function mutations in AIRE (autoimmune regulator of endocrine function) → central tolerance/self Ag

• Auto-antibodies are markers
  - CaSR (50-60% of pts)
  - PTC signaling molecule, NALP5 (~50% of pts)
  - Neutralizing Ab’s to IFN alpha* & omega*, IL-17* and IL-22* (*pathogenic*; ~100% of APS-1 pts)
Genetic Forms of Hypoparathyroidism

1. Ca sensing pathway: constitutive suppression of PTH secretion through CaSR
   **Autosomal dominant hypocalcemia** – Gain of function mutations in Casr (type 1) and G alpha 11 (type 2)

2. Parathyroid dysgenesis/agenesis - Loss of function mutations in transcription factors

3. Mutations in PTH
   Inactive or not secreted from cell
Conventional Management

- **Ca supplements** (3-4 times/day)
  - 0.5 – 1.0 G elemental Ca (with meals - if Ca carbonate)
  - Ca citrate – if achlorhydria or patient on PPI
- **Calcitriol** - 0.25 mcg twice daily
- Replace **Mg** if low
- Give **vitamin D3** - correct low 25 OH vitamin D levels
- **Thiazide diuretics*** – to lower U-Ca
  - Hydrochlorothiazide or chlorthalidone (longer duration) (25-100 mg/d) + K supplement or K-sparing diuretic; combine with **low salt diet**
  - Consider **low phosphate diet*** (phosphate binders*) – if vascular/soft tissue calcifications present (high Ca X P product >55)

*almost to no data*
How well does conventional management work? What are outcomes of long-term treatment?
53 patients (44%) had at least one 24-hr urine Ca

- 14 (26%) had urine Ca >300 mg (most recent)
- 20 (38%) had ≥1 urine Ca >300 mg (over time)

Impaired Renal Function:
% with CKD stage 3 or higher

- 0%
- 10%
- 20%
- 30%
- 40%
- 50%
- 60%
- 70%
- 80%
- 90%
- 20-39
- 40-59
- 60-69
- >69

54 with any renal imaging (45% of cohort)

17 with renal calcification (31% of those imaged)

2/120 patients required renal transplantation

Hypopara
NHANES

54 with any renal imaging (45% of cohort)

17 with renal calcification (31% of those imaged)

2/120 patients required renal transplantation

Ectopic Calcifications: Current Therapy

31 with head CT (26% of cohort)

16 with basal ganglia calcification (52% of those imaged)

Over time, 22% had at least one >55

Mitchell et al JCEM 2012
688 Danish Postsurgical Patients and Controls: Population-Based Study

Replacing the Missing Hormone

Intact PTH (1-84)

Teriparatide

- COOH

H_{2}N \begin{array}{cccccccccc}
1 & Ser & Val & Ser & Glu & Ile & Gln & Leu & Met & His & Leu & Asn \\
20 & Glu & Val & Arg & Glu & Met & Ser & Asn & Leu & His & Lys & Gly
\end{array}

Leu

Trp

Leu

Arg

Lys

Lys

Leu

Gln

Asp

Val

His

Asn

Phe

- COOH
Studies in Adults with Hypoparathyroidism: PTH (1-34) *

- PTH(1-34) given once daily reduced U-Ca compared to calcitriol + Ca ¹

- Twice-daily PTH(1-34) SC injections better controlled serum [Ca] and urine Ca than calcitriol + Ca ²

- Cross-over study (8 adults) treated (3 months) with continuous subcutaneous PTH by pump compared to twice-daily injections showed greater than 50% reduction in U-Ca and restored it to normal range (pump) ³

* Not FDA approved for this

¹Winer et al, JAMA, 1996; ²Winer et al, JCEM, 2003; ³Winer et al, JCEM, 2012
Open-Label PTH(1-84) - 6 Years (N=33; no pbo)

- Maintained serum Ca
- Lowered U-Ca
- Lowered S-phosphate

Patients took less supplements, quality of life (SF-36) improved

Rubin et al, JCEM, 2016
Bone in Hypoparathyroidism – low turnover state

Turnover markers increased – marked initially, persisted for 6 years above baseline

Rubin et al, JCEM, 2016
**BMD: Baseline DXA T and Z scores**

- **Spine**: +1.34 +/- 0.35  
  +1.95 +/- 0.35

- **TH**: +0.82 +/- 0.24  
  +1.21 +/- 0.24

- **FN**: +0.72 +/- 0.29  
  +1.34 +/- 0.30

- **Radius**: +0.2 +/- 0.15  
  +0.86 +/- 0.17

*With PTH (1-84) treatment → BMD increased at spine, stable (+) at hip, decreased at radius*

*Rubin et al, JCEM, 2016*
ADVERSE EVENTS – 6 Years
(Rubin et al, JCEM, 2016)

- **Hypercalcemia**: 12 episodes (9 patients), generally in first 6 months, resolving with supplement adjustment
- Musculoskeletal complaints (especially in year 1); gastrointestinal, nausea, headaches, fatigue
- **Hypocalcemia** – 5 episodes in 3 patients
- 8 fractures (6 patients): 3 wrist, 3 toe, 1 elbow, 1 leg
- 3 stones (3 patients)
- Open-label, no placebo control
REPLACE Study
(Mannstadt M et al, Lancet Diab Endo, 2013)

Randomized, double-blind, PBO-controlled trial of 24 weeks duration – 134 adults with hypoparathyroidism

• **Design:**
  – First optimized on Ca + calcitriol/alfacalcidol $\rightarrow$ S-Ca low normal range (8-9 mg/dL)
  – Randomized (PBO or 50 mcg PTH1-84 daily)
  – Calcitriol supplements were reduced 50% (later Ca) as PTH or PBO was up-titrated every 2 weeks (to 75 then 100 mcg) - if supplements could be further reduced *(OUTPATIENT)*
REPLACE Study

1° endpoint: % of subjects whose supplemental Ca and D analogue intake fell by ≥ 50% while maintaining serum [Ca]

53% PTH(1-84) vs 2% PBO (p<0.0001*)

Replace Study: 2° endpoint – No Active Vitamin D and Ca Dose ≤500 mg/day

43% rhPTH(1-84) vs 5% PBO (P<0.001)

Biochemical Outcomes

- Placebo injections – A
- PTH(1-84) injections – B
- Open symbols - serum
- Closed symbols - urine
- Shaded: optimal ranges

With active dose-reductions in supplements, S-Ca **fell** in PBO-treated pts (as did U-Ca); S-Ca **rose** in the PTH-treated pts with stable U-Ca
Serum phosphate declined

Ca x phosphate product improved

Clarke B et al, Endocrine, 2016
Adverse Events – 24 Weeks

93% of PTH-treated, 100% of placebo-treated

- Hypocalcemia, muscle spasms, headaches, nausea – most common
  - Hypocalcemia – seen throughout study – 26% pts on PTH, 21% pts on placebo

- **Serious AE’s:** 11% in PTH-treated, 9% in placebo-treated; 1 admission for hypercalcemia in PTH-treated (considered related); no deaths

- No changes in cardiovascular (BP, QTc) or renal parameters

- Stopped due to AE’s: 3% pts on PTH, none on placebo
Principles - rhPTH (1-84) Therapy - Adults

- GOAL: Serum [Ca] in **lower half of normal range**
- Maintain “sufficient” 25 OH vit D (50 nM, 20 ng/ml)
- Serum [Ca] 7.5 mg/dL or > before starting
- Initial dose: 50 mcg/d (injected into thigh) – given in office with training
- Decrease dose of active vitamin D analogue by 50% if serum [Ca] is > 7.5 mg/dL (titrate every 2 weeks or wait longer)
- Monitor serum [Ca] every 3 to 7 days when starting or adjusting PTH

* NATPARA, Prescribing Information (FDA)
Principles - rhPTH (1-84) Therapy in Adults

“Recommended only for patients who cannot be well-controlled on Ca supplements and active forms of vitamin D alone”

* NATPARA, Prescribing Information
Guidelines for Management and Monitoring
European Society Endocrinology Guideline (Bollerslev et al, *EJE*, 2015)

- **Management goals for chronic hypoparathyroidism in adults** – (‘suggest’)
  - Target treatment to achieve serum [Ca] in lower part or slightly below normal range - keeping patients free of symptoms or signs of hypocalcemia
  - Maintain 24-hr U Ca within sex-specific reference ranges
    - <250 mg (<6.25 mmoles) – women; <300 mg (<7.5 mmoles) - men
  - Serum [phosphate] and [Mg] in normal range
  - Ca x Phos product <4.4 mmol²/L² or 55 mg²/dL²
  - Aim for “adequate vitamin D status”
  - **Recommend** - personalized treatment focusing on quality of life and well-being
Treatment Recommendations – 1.
(Bollerslev et al, EJE, 2015)

- **Recommend** treatment of patients with symptoms and/or serum Ca <2.0 mM (<8.0 mg/dL) (+)

- **Recommend** offering treatment to asymptomatic patients with serum [Ca] of 2.0 mM (8.0 mg/dL) up to the lower limit of normal range (+)

- **Recommend** use of activated vitamin D analogues plus Ca supplements (divided doses) (+) (or use cholecalciferol)

- **Recommend** titrating treatment to achieve control of symptoms and serum [Ca] in target range (+)

- **Recommend** vit D: 400-800 IU per day (+)

(+) very low evidence base
Treatment Recommendations – 2.
(Bollerslev et al, *EJE*, 2015)

- Hypercalciuria – *suggest* reducing Ca intake, Na-restricted diet and/or thiazide (+)

- Renal stones – *recommend* evaluation for stone risk factors, manage according to international guidelines

- Hyperphos, elevated Ca x phos – *suggest* diet intervention and/or adjustment of Ca and vit D analogues

- Hypomagnesemia – *suggest* treatment

- *Recommend against* - *routine use* of replacement therapy with PTH or PTH analogues
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<th>Parameter - Monitoring</th>
<th>Frequency, When</th>
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<td>Biochemical variables – Ca, P, Mg, creatinine + symptoms</td>
<td>3 to 6 months</td>
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<tr>
<td>* After change in treatment</td>
<td>Weekly or every other week</td>
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<td>24 hr urine Ca</td>
<td>Once yearly or every other year</td>
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<td>* Renal imaging</td>
<td>If stones or if serum creatinine increases</td>
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<td>Clinical monitoring – signs, symptoms, or co-morbidities</td>
<td>Regular intervals - yearly</td>
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<td>Bone mineral density</td>
<td>Advise against routine monitoring</td>
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* recommend
First International Conference on Management of Hypoparathyroidism: Summary Statement and Guidelines
(Brandi ML et al, *JCEM*, 2016)

- **Guideline**
  - Table 1: Diagnosis
  - Table 2: Evaluation
  - Table 3: Conventional Management (reviewed)
  - Table 4: Monitoring on Conventional Therapy
  - Table 5: Indications for PTH
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| Calcium, phosphate, magnesium, BUN/creatinine and eGFR: yearly or more frequently if the clinical situation is appropriate |
| 24-hour urine for calcium and creatinine (annually or less frequently) |
| As clinically indicated |

- Renal imaging (for nephrolithiasis/nephrocalcinosis) *
- Ophthalmological exam (cataracts) (depends on baseline exam)
- Central nervous system imaging (basal ganglia and other sites of calcification) (uncertain, can’t recommend)
- BMD **

* At baseline, then every 5 years if asymptomatic; more frequently if symptomatic
** Not specifically for this condition (use ISCD Guidelines - age, menopause)

Brandi ML et al, JCEM, 2016
**Table 5.** Indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism

1. Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D)
2. Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 μg of active vitamin D or >3.0 μg of the 1-α vitamin D analog
3. Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)
4. Hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg²/dL² (4.4 mmol²/L²)
5. A gastrointestinal tract disorder that is associated with malabsorption
6. Reduced quality of life

*Not evidence-based; differ from ‘label’*  
*Brandi ML et al, JCEM, 2016*
**CASE**

40 yo man with postsurgical hypoparathyroidism x 24 years - referred to consider change in treatment -

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- Ca suppl lowered, calcitriol lowered, thiazide started → → 50 bid
- U/S: three 5 to 7 mm stones in L kidney, one 5 mm stone in R kidney
- Urine Ca ranged from 343-448 mg/day (maximal tolerated thiazide)
- Anytime calcitriol was lowered → symptoms of tetany recurred
- Initiate PTH(1-84) therapy with restoration of U-Ca to ~300 mg/d
CONCLUSIONS

• Hypoparathyroidism – substantial impact on QoL and end-organs
  – Kidney stones, renal/brain/soft tissue calcifications, progressive CKD

• Conventional therapy (Ca salts, 1,25(OH2 vitamin D, thiazide diuretics) – often does not meet goals

• rhPTH(1-84) now treatment option
  – Optimized dosing strategies to use the hormone
  – Who are patients not at goal on “conventional therapy”
    ▪ “Brittle” – unstable serum Ca control, frequent ER visits
    ▪ Inadequate control of symptoms - ? Wide swings in [Ca]
    ▪ Urine Ca not at target; renal or CNS abnormalities