Hypoparathyroidism: From Diagnosis to New Management Options

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Disclosure

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

- **HYPOPARATHYROIDISM**
- Pseudohypoparathyroidism
- Vitamin D deficiency, resistance, or inadequate 1-hydroxylation
- **Mg depletion or excess**
- Chronic kidney failure
- **Miscellaneous:**
  - pancreatitis, acute hyperphos, tumor lysis, crush injury, rhabdomyolysis, IV bisphosphonate, denosumab therapy (esp in CKD), rapid transfusion of citrated blood, “hungry bone” syndrome, osteoblastic metastases, severe (ICU) illness

PTH is low, inappropriately normal = green

Schafer and Shoback, Primer of Metabolic Bone Diseases, 2013

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Causes of Hypoparathyroidism - 1

- **Post-surgical** (thyroid, parathyroid, laryngeal)
- Functional: Mg depletion (gastrointestinal or renal losses), hyper Mg
- Constitutive activation of CaSR’s
  - Heterozygous gain of function mutations in two genes - - *Csr* and in *GNA11*
  - Acquired (activating) CaSR antibodies
- 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
  - Kenny-Caffey
  - Sanjad-Sakati
  - Kearns-Sayre and mitochondrial DNA mutations

- **Destructive**: hemochromatosis/thalassemia (transfusional iron overload), metastatic tumor, 131I therapy

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Prevalence of Hypoparathyroidism

- **~60,000 patients in the US**
  - 75% postsurgical
  - 75% female
  - 75% 45 years or older

- Data from large claims database (77 million pts, 75 health plans across US)
- Projected to US pop. - # neck surgeries and % → hypoparathyroidism

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Powers J et al. JBMR 2013
Postsurgical Hypoparathyroidism

75% transient hypoparathyroidism
< 6 months

7.6% of neck surgeries result in hypoparathyroidism

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

25% chronic hypoparathyroidism
> 6 months

Powers J et al. JBMR 2013; 28: 2570

Postsurgical Hypoparathyroidism Rates

• After total thyroidectomy without central lymph node dissection
  – S-Ca always falls, but generally recovers completely in days to weeks

• Transient
  • 1.6 – 53.6%

• Permanent
  • 0.2 - 9.3%

Highly variable - know rates of your surgeon for procedure

Selberherr et al. Surgery, 2014
Surgical Experience

• 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 HP)

Intra-operative 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
Using io-PTH in Parathyroidectomy and Thyroidectomy Patients (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 lower than 10 pg/ml (1 pmol/L), then patient is at risk; start patient on calcitriol in addition to oral calcium.
  - If higher than 10, they give 1 Gm Ca twice daily; stop if no symptoms after 3 or 4 days.
  - If PTH > 10 and symptoms later, give additional oral Ca
  - 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 of first 3 substantiates diagnosis (most patients 3-5)

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- Loss of function mutations in Aire (autoimmune regulator of endocrine function) → central tolerance/self Ag
- Auto-antibodies: react to CaSR (~56% of pts), parathyroid signaling molecule - NALP5 (NACHT leucine-rich-repeat protein 5) (~49% of APS-1 pts), or neutralizing Abs’s to IFN alpha* & omega*, IL-17* and IL-22* (~100% of APS-1 pts; disease markers) → *pathogenic ones*
1. **Ca sensing**: impaired control of PTH secretion by Ca++. **Autosomal dominant hypocalcemia** – Gain of function mutations in Casr (type 1) and G alpha subunit 11 (type 2) → constitutive signaling and suppression of PTH

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

3. **Mutations in PTH** - Inactive or not secreted from cell

**Therapeutic Approach**

- **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
  - *Separate from T4 replacement by 60 min*

- **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 (25 to 100 mg/day)
  - Chlorthalidone (longer duration)
  - Combine with low salt diet
  - Consider **low phosphate diet** (phosphate binders) – if vascular/soft tissue calcifications present (high Ca × P product)
Complications – Chronic Therapy

• Chart review of **120 pts** with chronic hypopara of diverse etiologies – kidney, brain

  - **17** with renal calcification (31% of patients imaged)
  - **16** with basal ganglia calcification (52% of patients imaged)

  Mitchell DM et al. *JCEM* 2012;97:4507

Renal Function

• 2/120 patients required renal transplantation

• Rates of **CKD stage 3+ or higher** are 2-17 fold higher than age-appropriate norms (*eGFR 30-59*)

  Mitchell DM et al. *JCEM* 2012;97:4507
688 Danish patients (vs controls)

Renal complications

Renal stones

Renal insufficiency

Hospitalization - seizures

No increased risk for arrhythmia, CVD, death

Unterbjerg et al, JBMR, 2013

Other Complications in this Cohort

- Fractures, spinal stenosis: NO increase
- Cataracts: NO increase
- Cancer: NO increase
- Neuropsych–bipolar affective disorder, depression: 1.99 (CI: 1.14-3.46)

INFECTIONS: 1.42-fold increased risk (CI: 1.2-1.67)

Unterbjerg et al, JBMR, 2014

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Human Parathyroid Hormone

Studies of rhPTH (1-84)* Therapy:
Adults with Hypoparathyroidism

Rubin, Cusano, Bilezikian, and colleagues (Columbia Univ, NY)
  - Sikjaer, Rejnmark, Mosekilde, and colleagues (Denmark)
Mannstadt and colleagues (multinational phase 3 trial)

* FDA approved in Jan, 2015
Studies of rhPTH (1-84) Therapy: Adults with Hypoparathyroidism

- Rubin, Cusano, Bilezikian, and colleagues – Open-label trial (no placebo), patients treated every other day with PTH 1-84 (100 ug/dose); 4-year data in 27 patients, QoL data at 5 years

4 years treatment
- Maintained S-Ca
- Tended to lower U-Ca
- Lowered S-phos

3 biochem desired outcomes

Cusano et al, JCEM, 2013
Statistically significant reductions in calcium and calcitriol supplements that persisted over 4 years

Cusano et al, JCEM, 2013

- Hypopara pts - high normal BMD at baseline
- BMD increased at spine, stable at other sites

Cusano et al, JCEM, 2013
Baseline: statistically significantly lower than reference population in 8 domains (    )

Improved by 2 mos and changes persisted for 5 years (open-label study) (+ 7/8 domains) (    )

- QoL scores: 386 +/- 19  ➔  482 +/- 25 (p<0.0001)

VT (vitality), SF (social function), RE (role limit emotional), MH (mental health), PF (physical functioning), RF (role limit), BP (body pain), GH (gen health)

Adverse Events – 4 Years
(Cusano et al, JCEM, 2013)

- Hypercalcemia: 11 episodes in 8 patients (1.9%), usually in first 6 mos, resolved with supplement adjustment
- Musculoskeletal, GI, GU complaints, infections, headaches – highest frequency
- Two fractures, one episode nephrolithiasis
- Open-label, no placebo control
REPLACE Study
(Mannstadt M et al, Lancet Diab Endo, 2013)

Randomized, double-blind, placebo-controlled trial of 24 weeks duration – 134 adults with hypopara

- **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)

- **1° endpoint:** % patients with dose-reductions of 50% in Ca & calcitriol/alfacalcidol & maintained serum [Ca] at baseline or better

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


Secondary Endpoint
36/84

Patients Who Met the Criteria, %
0 10 20 30 40 50 60 70
1 2 3 4 5 6 8 12 16 20 24 Week

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
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 participation due to AE’s: 3% pts on PTH, none on placebo

How Might One Initiate Therapy?

Who Might Be A Candidate for PTH (1-84) Therapy?

3 CASES
**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

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**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**”

- Recommended dose – **minimum** to prevent hypocalcemia and hypercalciuria
- Dosing: 50 ug (titrate up) or titrate down to 25 ug

* NATPARA, Prescribing Information
CASE 1

50 year old woman consulted for hypocalcemia

• Presented with chronic muscle cramping, paresthesias
• NO history of neck radiation or surgery, autoimmune disorders
• Exam: mildly jittery, tremulous; normal VS, mental status; no dysmorphic features, skin changes +Chvostek’s sign

• **LABS:** Ca++ 7.0 mg/dL (4.2 initially; nl 8.8-10.1) 
  PO4 6.6 mg/dL (nl 2.5-4.5) Mg++ 1.5 mg/dL (1.6-2.5) 
  25 OH D 25 ng/mL intact PTH 13 pg/mL (nl 15-65)

*Her Ca and PTH remained low despite Mg, Ca, calcitriol repletion*

• **Treatment (when consulted):**
  - 1500 mg Ca carbonate and calcitriol 0.5 mcg 3 times daily, Mg supplements twice daily
  - Intermittently on IV Ca drip (to avoid symptoms)
  - After 4 days hospitalization ➔ serum Ca 7.0 mg/dL and not stable or symptom-free

• **Trial:**
  - Teriparatide (PTH 1-34) – 20 mcg sc qd (later twice daily) with symptom resolution (2 days) and reduction in dose and other supplements; hospital discharge

*Genetic testing: heterozygous missense mutation in Casr (codon 151)*
CASE 2

55 yo woman followed for hypoparathyroidism

- Presented after surgery for multinodular goiter (2004) with profound fatigue, feeling awful, peri-oral numbness/tingling, cramping in her hands, toes and legs; profound post-op hypocalcemia

- PMH: HTN, chest pain, LVH, migraine HA’s, hand/shoulder arthralgias with serologies suggestive of rheumatoid arthritis (+ANA, +RF, +CCP, high ESR and CRP)

- Meds: Baclofen 10 mg tid, cymbalta 20 mg bid, T4 0.125 mg, metoprolol 50 mg bid, Mg oxide 750 mg, KCl 20 mEq, 1000-2000 mg Ca/day, vitamin D3 1250 IU, calcitriol 0.25 bid, hydrochlorothiazide 25 mg

- PE: MCP, PIP tenderness with synovitis present; +muscle cramping
3/18/16

### CASE 2: Additional Data

- **25 OH vitamin D** → 43, 50, 60 ng/ml range
- **Serum Mg** – low with up-titration of HCTZ → Mg supplements (750 mg Mg oxide/day)
- **U-Ca** → BP has tolerated up-titration of diuretic
  - Serum K+ - monitored, got low, supplements added
  - eGFR ranged from 55 - 60 ml/min and stable
  - Renal ultrasound (2014): punctate non-obstructing left renal stones without nephrocalcinosis
- **BMD by DXA** – all sites T scores 0 to +1.5
- **No clinically significant cataracts** – annual eye exam

**Considering option → rhPTH(1-84) to address U-CA**
CASE 3

• 49 year old woman with post-surgical hypoparathyroidism for 10 years after thyroidectomy for papillary cancer

• Because of difficulties with medical regimen, poor control of symptoms, wanting to “feel better” if possible (… get my life back), and persistently high U-Ca → she volunteered for rhPTH(1-84) study

49 year old woman with post-surgical hypoparathyroidism for 10 years
CONCLUSIONS

• Hypoparathyroidism – rare disorder
• Over time → substantial impact on QoL, end-organ complications
  – Cataracts, stones, renal and brain calcifications, CKD
• Renal function, urinary Ca – monitored
• PTH “replacement” may become option for patients not meeting goals
  – “Brittle” – unstable serum Ca control, frequent ER visits
  – Inadequate control of symptoms - ? Wide swings in [Ca]
  – Urine Ca not at target
### Key Risk Factors - Postsurgical Hypoparathyroidism

- **Thyroid surgery**
  Reoperation, extent of surgery (cancer), substernal goiter, Graves disease

- **PT surgery for primary HPT**
  Localization Studies
  Neck ultrasound, Mibi with SPECT, 4D-CT

  **Minimally Invasive PTX**
  **Intra-operative PTH Monitoring**

- **Surgical “experience” – all procedures**
rh-PTH 1-84 titrations - - hypothetical

<table>
<thead>
<tr>
<th>Serum Calcium</th>
<th>Adjust First</th>
<th>Adjust Second</th>
<th>Calcium Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Above</strong> the Upper Limit of Normal (10.6 mg/dL)</td>
<td>Decrease or Discontinue*</td>
<td>Decrease</td>
<td></td>
</tr>
<tr>
<td>Greater than 9 mg/dL, and below the Upper Limit of Normal (10.6 mg/dL)</td>
<td>Decrease or Discontinue*</td>
<td>No change or decrease if active vitamin D has been discontinued</td>
<td></td>
</tr>
<tr>
<td>Less than or equal to 9 mg/dL, and above 8 mg/dL</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Lower than 8 mg/dL</td>
<td>Increase</td>
<td>Increase</td>
<td></td>
</tr>
</tbody>
</table>

*Discontinue in patients receiving the lowest available dose

- Can dose-reduce to 25 mcg/day if S-[Ca] is > 9.0 mg/dL and active vitamin D has been discontinued and Ca is at maintenance dose (?) – if injectable treatment is needed

NATPARA, Prescribing Information