Emerging Therapies for Treatment of Hypoparathyroidism

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• Off-Label Usage: None
Objectives

- Describe the pathogenesis and complications of hypoparathyroidism
- Discuss the symptoms of hypoparathyroidism
- Summarize currently available and new management options for hypoparathyroidism

Mechanism of Hypocalcemia in Hypoparathyroidism
Biochemical Diagnosis of Hypoparathyroidism

- **Biochemical Parameters:**
  - Low-normal to decreased serum calcium
  - High-normal to increased serum phosphate
  - Inappropriately low-normal or decreased intact parathyroid hormone
  - Low-normal to decreased total alkaline phosphatase
  - Low-normal to decreased markers of bone turnover
    - Serum bone specific alkaline phosphatase
    - Serum beta-CTx-telopeptide
  - Low-normal to decreased urinary calcium and calcium to creatinine clearance ratio (<0.01)
  - Low-normal to decreased serum 1,25-dihydroxyvitamin D
  - Decreased serum chloride and bicarbonate
  - Normal serum magnesium

Differential Diagnosis of Hypoparathyroidism

- Post-surgical hypoparathyroidism
- Autoimmune hypoparathyroidism
- Iron overload due to thalassemia or hemochromatosis
- Copper overload due to Wilson’s Disease
- Metastatic disease to parathyroid glands
- Radioactive iodine therapy
- Magnesium deficiency or excess
- Genetic causes
• Anterior neck surgery is most common acquired cause of acute or chronic hypoparathyroidism
  – Post-surgical hypoparathyroidism usually due to inadvertent removal of, or damage to, parathyroid glands or their blood supply
  – May occur with surgery on thyroid or parathyroid glands, or during neck dissection surgery
  – Permanent hypoparathyroidism present for longer than 6 months after surgery

• Post-surgical hypoparathyroidism:
  – Estimates of post-thyroid surgical permanent hypoparathyroidism range from 0.5-6.6%, with centers doing endocrine surgery reporting 0.9-1.6%
  – Estimates of post-thyroid surgical transient hypoparathyroidism range from 6.9-46%
  – Higher risk of hypoparathyroidism if reoperation, more extensive thyroid resection, substernal goiter, cancer, or Graves' disease
Postoperative Day 2 PTH and Calcium Levels Predict Hypoparathyroidism


Reoperative Parathyroidectomy in 228 Patients Before and After Intraoperative PTH Monitoring

### Non-Surgical Causes of Acquired Hypoparathyroidism

**Acquired Disorders:**
- Autoimmune hypoparathyroidism
  - Autoimmune polyglandular syndrome type I
  - Isolated
- Accumulation of iron (thalassemia or hemochromatosis): 19% of 44 cases of hemochromatosis
- Accumulation of copper (Wilson’s disease): 1:50,000 to 1:100,000
- Very rarely may occur after I-131 therapy for thyroid disease
- Rarely occurs with metastatic infiltration of glands
- Magnesium deficiency (e.g., PPI therapy) or excess (e.g., tocolytic therapy during pregnancy)

### Genetic Causes of Hypoparathyroidism

**Genetic Disorders: Isolated hypoparathyroidism**
- Autosomal dominant familial hypocalcemia: activating mutations in CaSR on 3q13 may be among most common causes of isolated hypoparathyroidism
- DiGeorge (velocardiofacial) syndrome: 1:2,000-3,000 live births, with TBX1 and other mutations on 22q11.2
- Familial isolated hypoparathyroidism due to autosomal recessive or dominant mutation in pre-proPTH on 11p15, or parathyroid gland dysgenesis due to mutations in transcription factors and other regulators of parathyroid gland development such as GCMB (glial cells missing B) or GCM2 (glial cells missing 2)
Genetic Causes of Hypoparathyroidism

- Genetic Disorders: Syndromic hypoparathyroidism
  - Autosomal dominant hypoparathyroidism with deafness and renal anomalies due to mutations in GATA3 on 10p14-10-pter or SOX3 (Sry-box 3)
  - Autosomal recessive hypoparathyroidism, growth and mental retardation, and dysmorphism due to mutations in TBCE on 1q42-q43
  - Hypoparathyroidism with metabolic disturbances and congenital anomalies associated with maternal mitochondrial gene defects
  - Hypoparathyroidism associated with X-linked recessive mutations on Xq26-27

Clinical Manifestations of Hypoparathyroidism

Large spectrum of symptoms: mild – debilitating

- Most symptoms and signs due to hypocalcemia
- Large inter-individual difference in threshold of calcium
- Highly variable descriptions of symptoms

Neuromuscular irritability:
- Tingling of fingers and toes, perioral numbness
- Muscle cramps, laryngospasm, seizure

Neurocognitive and neuropsychiatric manifestations:
- “Brain fog” (mental lethargy)
- Inability to focus/concentrate
- Increased anxiety
Chvostek’s Sign

Tapping facial nerve in front of ear results in ipsilateral twitching of upper lip

Trousseau’s Sign
Cardiac Manifestations: Long QT

Calcium 7.3 mg/dL
QT 518 msec
QTc 543 msec

Calcium 9.2 mg/dL
QT 466 msec
QTc 457 msec

Abnormal Microarchitecture in Hypoparathyroidism

Hypoparathyroid  Control
Bone Turnover Decreased  
BMD Increased

Bone Turnover Markers

Bone Density (DXA)


Other Manifestations of Hypoparathyroidism

Dental enamel hypoplasia  
Short, blunted roots (premolars)  
Delay/absence of eruption  
Hypoplastic → prone to caries

Cataract

A cataract is an opacity (clouding) of the normally clear lens, which may develop as a result of aging, metabolic disorders, trauma or heredity.

Basal ganglia calcifications

Normal, clear lens  
Lens clouded by cataract
Prevalence, Incidence, and Mortality of Hypoparathyroidism
Clarke BL et al. J Clin Endocrinol Metab 2016; Mar 4 [Epub ahead of print].

<table>
<thead>
<tr>
<th></th>
<th>Hypoparathyroidism</th>
<th>Postsurgical Hypoparathyroidism</th>
<th>Nonsurgical Hypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>37/100,000 person-years</td>
<td>29/100,000 person-years</td>
<td>8/100,000 person-years</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>0.8/100,000 person-years</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>-</td>
<td>HR 0.98; 95% CI, 0.76-1.26</td>
<td>HR 1.25; 95% CI, 0.90-1.73</td>
</tr>
</tbody>
</table>

Prevalence of Hypoparathyroidism

Data from a large health plan claims database: 77 million unique patients, combining 75 health plans from across the U.S.

1. Estimated number of diagnoses of hypoparathyroidism over 12 months and projected to the U.S. population
2. Proportion of neck surgeries resulting in hypoparathyroidism: entered into an epidemiologic model to derive an estimate of prevalence
3. ~60,000 patients in the US: 75% postsurgical, 75% female, and 75% 45 years or older
## Risk of Complications of Hypoparathyroidism

Clarke BL et al. J Clin Endocrinol Metab 2016; Mar 4 [Epub ahead of print].

<table>
<thead>
<tr>
<th>Risk of hospitalization for Complications</th>
<th>Postsurgical Hypoparathyroidism</th>
<th>Nonsurgical Hypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Insufficiency</td>
<td>HR 3.10; 95% CI, 1.73-5.55</td>
<td>HR 6.01; 95% CI, 2.45-14.75</td>
</tr>
<tr>
<td>Renal stones</td>
<td>HR 4.02; 95% CI, 1.64-9.90</td>
<td>-</td>
</tr>
<tr>
<td>Ischemic CV disease</td>
<td>HR 1.09; 95% CI, 0.83-1.45</td>
<td>HR 2.01; 95% CI, 1.31-3.09</td>
</tr>
<tr>
<td>Neuropsychiatric Disease</td>
<td>HR 1.26; 95% CI, 1.01-1.56</td>
<td>HR 2.45; 95% CI, 1.78-3.35</td>
</tr>
<tr>
<td>Seizures</td>
<td>HR 3.82; 95% CI, 2.15-6.79</td>
<td>HR 10.05; 95% CI, 5.39-18.72</td>
</tr>
<tr>
<td>Cataracts</td>
<td>HR 1.17; 95% CI, 0.66-2.09</td>
<td>HR 4.21; 95% CI, 2.13-8.34</td>
</tr>
<tr>
<td>Upper Extremity Fractures</td>
<td>HR 0.69; 95% CI, 0.49-0.97</td>
<td>HR 1.93; 95% CI, 1.31-2.85</td>
</tr>
<tr>
<td>Intracranial Calcifications</td>
<td>56%</td>
<td>69-74%</td>
</tr>
</tbody>
</table>

## Medical Costs Associated with Prevalent Hypoparathyroidism: A Population-Based Study

Higher Anxiety Scores in Patients with Postsurgical Hypoparathyroidism

- 25 women with postsurgical hypoparathyroidism
- 25 age- and sex-matched controls status-post thyroidectomy but with intact parathyroid glands
- Most scales worse in patients with postsurgical hypoparathyroidism

Quality of Life is Reduced by SF-36 Assessment

- Cusano et al (Columbia) (n=54)
  - Significantly worse in all 8 domains compared to normative data

- Cho et al (Harvard) (n=340) and controls (n=200)
  - Scores lower in all 8 domains

- Sikjaer et al (Denmark) (n=62)
  - QOL significantly reduced

Treatment of Acute Symptomatic Hypoparathyroidism

- Dilute 10 mL of 10% calcium gluconate solution in 100 mL D5W and infuse over 5-10 minutes to give 90 mg elemental calcium immediately
- Longer infusion of 10 ampules of calcium gluconate (900 mg) diluted in 1 L D5W at 50 mL/hour to give 15 mg elemental calcium/kg
- Infusion will raise serum calcium by 2 mg/dL over 8 hours
- Avoid calcium chloride due to venous irritation
- Magnesium supplementation if deficient
- Begin oral calcium and vitamin D supplementation as appropriate

Diagnosis of Chronic Hypoparathyroidism
Brandi ML et al. J Clin Endocrinol Metab 2016; Mar 4 [Epub ahead of print].

- Low-normal to decreased albumin-adjusted serum calcium on at least 2 occasions, separated by at least 2 weeks
- Inappropriately low-normal or decreased parathyroid hormone by 2nd or 3rd generation assay in presence of hypocalcemia on at least 2 occasions
- High-normal to increased serum phosphate
- Chronic hypoparathyroidism after neck surgery is diagnosed only if present for more than 6 months
Conventional Management of Chronic Hypoparathyroidism
Brandi ML et al. J Clin Endocrinol Metab 2016; Mar 4 [Epub ahead of print].

- Guidelines published by:
  - European Society of Endocrinology
  - First International Conference on the Management of Hypoparathyroidism
  - AACE/ACE Disease State Clinical Review on Postoperative Hypoparathyroidism

- Treatment targets:
  - Low-normal serum calcium
  - High-normal serum phosphorus
  - 24-hr urine calcium <7.5 mmol
  - Calcium-phosphate product <55 mg²/dL²

- Calcium citrate or carbonate, 1-9 g/day in divided doses
- Calcitriol 0.25-2.00 mcg/day, often in divided doses
- Vitamin D2 or D3 800-2,000 IU/day
- Thiazide diuretics and low-salt diet when necessary to manage hypercalciuria
- Phosphate binders and low phosphate diet if necessary to control hyperphosphatemia
European Society of Endocrinology
Guidelines for Management of Chronic Hypoparathyroidism

- Serum calcium in lower half of reference range without hypocalcemia
- Serum phosphate within reference range
- Calcium x phosphate product within reference range
- Serum magnesium within reference range
- Urinary calcium within reference range for gender
- Adequate vitamin D
- Focus on long-term well-being and QOL

Indications for Considering Use of rhPTH(1-84) in Hypoparathyroidism
Brandi ML et al. J Clin Endocrinol Metab 2016; Mar 4 [Epub ahead of print].

- Inadequate control of serum calcium
- Oral calcium/vitamin D medications required to control serum calcium or symptoms that exceed 2.5 g calcium or >1.5 μg active vitamin D
- Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (< 60 ml/min)
- Hyperphosphatemia and/or calcium x phosphate product that exceeds 55 mg2dl2 (4.4 mmol2L2)
- GI tract disorder associated with malabsorption
- Reduced Quality of Life
Monitoring Guidelines on Conventional Therapy of Hypoparathyroidism

Brandi ML et al. J Clin Endocrinol Metab 2016; Mar 4 [Epub ahead of print].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monitoring Interval</th>
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<tbody>
<tr>
<td>Serum calcium</td>
<td>During initial treatment phase or with change in therapy: weekly to monthly After treatment stabilization: Twice yearly to yearly</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td></td>
</tr>
<tr>
<td>Serum magnesium</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine/BUN</td>
<td></td>
</tr>
<tr>
<td>Serum eGFR</td>
<td></td>
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<tr>
<td>24-Hour urinary calcium/creatinine</td>
<td>Yearly or as clinically indicated</td>
</tr>
<tr>
<td>Renal imaging for nephrolithiasis and nephrocalcinosis</td>
<td></td>
</tr>
<tr>
<td>Ophthalmology exam for cataracts</td>
<td></td>
</tr>
<tr>
<td>CNS imaging for basal ganglia and other intracerebral calcification</td>
<td></td>
</tr>
<tr>
<td>Bone Mineral Density</td>
<td>As clinically indicated</td>
</tr>
</tbody>
</table>

Treatment of Hypoparathyroidism

- Possible adjunctive options for treatment of chronic hypoparathyroidism:
  - PTH 1-34 (Teriparatide)
  - PTH 1-84 (Natpara)
  - Other PTH analogues
  - PTH by pump therapy
  - PTH by implantable microchip
  - Stem cell therapy
  - Parathyroid gland transplantation
Treatment of Hypoparathyroidism in Adults

- Randomized 30 subjects aged 18-70 years with hypoparathyroidism to open-label treatment with synthetic hPTH 1-84 100 mcg q OD with calcium 1,000 mg QID vs. calcitriol BID + calcium 1000 mg BID for 24 months
- Mean calcium supplement dose fell from 3030 ± 2325 to 1661 ± 1267 mg/day, and number of subjects on calcium supplementation >1500 mg/day decreased from 22 (73%) to 12 (40%) by end of study
- Mean calcitriol supplement dose fell from 0.68 ± 0.5 mcg/day to 0.40 ± 0.5 mcg/day, and number of subjects on calcitriol supplementation >0.25 mcg/day fell from 25 (83%) to 15 (50%) by end of study
- Concluded that PTH 1-84 SQ q OD allows significant reduction in calcium and calcitriol supplementation while maintaining normal serum and urine calcium levels

Treatment of Hypoparathyroidism in Adults
Sikjaer T et al. JBMR 2011;26:2358-2370.

- Randomized 62 subjects with hypoparathyroidism to double-blind treatment with rhPTH 1-84 100 mcg/d vs. placebo for 24 weeks, as add-on therapy to calcium and active vitamin D supplementation
- Subjects treated with PTH 1-84 reduced their daily calcium and active vitamin D doses by 75% and 73%, respectively, compared to placebo, without developing hypocalcemia
- Hypercalcemia occurred frequently during down-titration of calcium and active vitamin D supplements
- Plasma phosphate, and renal calcium and phosphate excretion, did not change
Treatment of Hypoparathyroidism in Adults
Sikjaer T et al. JBMR 2011;26:2358-2370.

- PTH 1-84 treatment increased serum BSAP by 226 ± 36%, osteocalcin by 807 ± 186%, P1NP by 1315 ± 330%, and CTx-telopeptide by 1209 ± 459%, and 24-hour urinary NTx-telopeptide by 830 ± 165%
- PTH 1-84 treatment decreased BMD at the total hip by 1.59 ± 0.57%, lumbar spine by 1.76 ± 1.03%, and total body by 1.26 ± 0.49%, but not the forearm
- Concluded that treatment markedly reduces need for calcium and active vitamin D supplementation, maintains serum calcium and phosphate levels in the physiological range, and decreases BMD due to increased bone turnover, causing a more physiologic bone metabolism

Pump vs. Injection rhPTH 1-34
for Treatment of Hypoparathyroidism

<table>
<thead>
<tr>
<th>TABLE 1. Baseline subject characteristics</th>
</tr>
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<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
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<tr>
<td>E</td>
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<tr>
<td>F</td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>H</td>
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<tr>
<td>Mean ± sd</td>
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</table>

* Normal range in parentheses.
Pump vs. Injection rhPTH 1-34 for Treatment of Hypoparathyroidism

rhPTH 1-84 Reduces Need for Calcium and Vitamin D Supplementation

- Double-blind, placebo-controlled, randomized phase 3 trial in 134 patients with hypoparathyroidism
- 90 received SQ PTH 1-84 and 44 SQ placebo for 6 months
- Primary outcome was % patients at week 24 achieving ≥50% reduction in calcium and active vitamin D while maintaining serum calcium at or above baseline and below ULN
- 53% of patients on PTH 1-84 achieved primary outcome, vs. 2% of patients on placebo
- AEs similar between groups, with hypocalcemia, muscle spasms, paresthesias, headache, and nausea most common
- Concluded that PTH 1-84 is efficacious and well-tolerated
rhPTH 1-84 Reduces Need for Calcium and Vitamin D Supplementation
rhPTH 1-84 Reduces Need for Calcium and Vitamin D Supplementation

<table>
<thead>
<tr>
<th>rhPTH(1-84)</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Key AE</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Yes</td>
<td>84 (83%)</td>
</tr>
<tr>
<td>All events</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>25 (25%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>44 (48%)</td>
</tr>
<tr>
<td>Severe</td>
<td>55 (58%)</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are number of patients; n of patients and number of events. If a patient had more than one AE in a category, the patient was counted only once in that category, and each event is counted. AE adverse event; rhPTH(1-84) recombinant human parathyroid hormone 1-84; *Patients with severe adverse events were classified according to their event with the highest severity. Includes hypocalcemia (n=3), hypercalcemia (n=2), pancreatitis (n=1), cerebrovascular accident (n=1), and dementia (n=1). All cases were defined as either the case of cerebrovascular accident, cerebrovascular accident, or uterine artery aneurysm. One patient reported a single chronic obstructive pulmonary disease that was not study drug related or not the case of cerebrovascular accident.

Table 2: Summary of adverse events
Approval of PTH 1-84 (Natpara)

- FDA Advisory Board approved PTH 1-84 on September 12, 2014
- FDA announced delay in final decision on October 24, 2014 to allow time for an amendment to the New Drug Application to be processed
- Final FDA approval as adjunct to calcium and active vitamin D supplementation on January 23, 2015

Safety Concerns with Parathyroid Hormone Therapy

- Hypercalcemia
  - No hypercalcemia in PTH(1-34)-treated adults and children for 3 years
  - PTH(1-84) for 4 years: 11 episodes of hypercalcemia in 8 subjects over 4 years
- Osteosarcoma: FDA black box warning
  - No osteosarcoma since teriparatide approved in 2002, and no signals from the use of PTH(1-84)
  - Worldwide human exposure: >1.5 million patients
Summary and Conclusions

• Hypoparathyroidism is a rare disorder with multiple symptoms and comorbidities
• Caused by surgery in 75% of cases, but other acquired causes are due to autoimmunity, iron or copper overload, metastatic disease, radioactive iodine therapy, magnesium deficiency or excess, or genetic causes
• Treatment includes calcium and calcitriol supplementation, magnesium and thiazide-type diuretic as needed, and PTH treatment when appropriate