Updates in Parathyroid Disease

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Disclosures

- Research grants from Amgen

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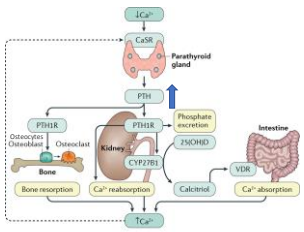
PTH – Principal Regulator of Serum Calcium



PTH ↑
Serum Calcium ↑
Serum Phosphate ↓
Bone resorption ↑

Mannstadt, M. *et al.* (2017) Hypoparathyroidism. *Nature Reviews Disease Primers* 3:17055

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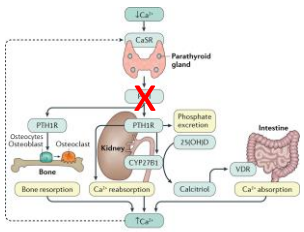
PTH – Principal Regulator of Serum Calcium



PTH ↓
Serum Calcium ↓
Serum Phosphate ↑
Bone turnover↓

Mannstadt, M. *et al.* (2017) Hypoparathyroidism. *Nature Reviews Disease Primers* 3:17055

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New Clinical Guidelines for Hyperparathyroidism and Hypoparathyroidism

- International Workshop on Parathyroid Disease
  - 5th Workshop on Primary Hyperparathyroidism
  - 2nd Workshop on Hypoparathyroidism
- Summary of guidelines presented at ASBMR 2021 conference
  - Hyperparathyroidism guidelines presented by Dr. John Bilezikian
  - Hypoparathyroidism guidelines presented by Dr. Aliya Khan
- 17 articles in JBMR to be published in 2022

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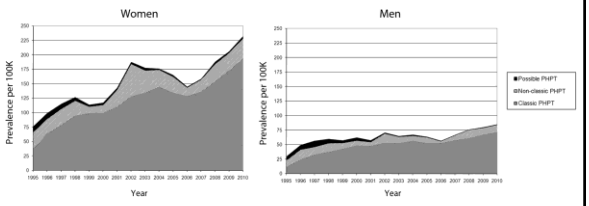
Primary hyperparathyroidism: prevalence



Yeh et al JCEM 2013

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Primary Hyperparathyroidism: Diagnosis

- Elevated serum calcium adjusted for albumin in the presence of an elevated or inappropriately normal intact PTH
  - PTH should be assessed with either a 2nd or 3rd generation assay, in absence of biotin supplements
  - Lab pattern should be observed on 2 occasions at least 2 weeks apart
  - In absence of end-stage kidney disease
- Albumin-correction for serum calcium for albumin < 4 g/dL
  - Corrected calcium = serum calcium + 0.8 * (4 – serum albumin)
  - Less clear whether similar correction should be applied for high albumin levels

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Normocalcemic Primary Hyperparathyroidism: Diagnosis

- Normal adjusted calcium and normal ionized calcium in the presence of an elevated intact PTH
  - Lab pattern should be observed on 2 occasions over 3-6 months
  - All alternative causes of secondary hyperparathyroidism should have been ruled out
    - Stage 3-5 CKD (eGFR <60)
    - Calcium malabsorption
    - Vitamin D deficiency
    - Primary hypercalciuria
    - Bisphosphonate or denosumab use
- Some (but not all) studies show progression to hypercalcemic primary hyperparathyroidism over time
- Some studies also show high prevalence of renal/bone disease, although may reflect referral bias

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Differential Diagnosis

85% of primary HPTH is due to single benign parathyroid adenoma

- Thiazide diuretics (induce hypocalciuria)
- Lithium (induce parathyroid adenomas and hyperplasia)
- Ectopic PTH secretion (rare)
- Parathyroid carcinoma (rare)
- Genetic disorders
  - Familial Hypocalciuric Hypercalcemia (FHH)
  - Hyperparathyroidism jaw tumor syndrome
  - MEN1 or MEN 2

Consider if age <30 yrs, multigland disease, or family history

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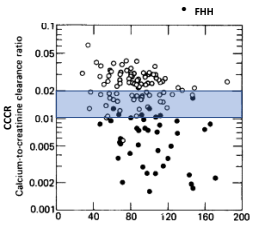
Familial hypocalciuric hypercalcemia (FHH)

- Usually defect in CaSR, autosomal dominant
  - Calcium elevated from birth
- Urinary Calcium / Creatinine Clearance Ratio (CCCR)
  - CCCR = [24-hour Urine Ca x serum Cr] / [Serum Ca x 24-hour Urine Cr]
- Typically asymptomatic, no treatment required
- Gene sequencing of CaSR can confirm, but 2 other genes can also cause



Marx, SJ. Calcium Disorders 1988

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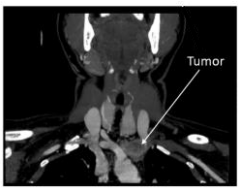
Hyperparathyroidism jaw tumor syndrome

- Defect in HPRT2 gene, which encodes parafibromin
- Tumor predisposition
  - Parathyroid adenomas and carcinomas
  - Fibrous tumors of jaw
  - Nephroblastomas
- Requires early parathyroidectomy and bilateral exploration due to carcinoma risk



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Primary hyperparathyroidism: clinical phenotypes

Symptomatic*

- Marked hypercalcemia
- Osteitis fibrosa cystica, fractures
- Chronic kidney disease, nephrolithiasis, nephrocalcinosis
- Proximal myopathy

*Due to lack of sufficient data, neurocognitive symptoms and cardiovascular manifestations should not be considered when classifying as symptomatic

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Primary hyperparathyroidism: clinical phenotypes

Symptomatic*	Asymptomatic
• Marked hypercalcemia • Osteitis fibrosa cystica, fractures • Chronic kidney disease, nephrolithiasis, nephrocalcinosis • Proximal myopathy	• No overt symptoms • With target organ damage (diagnosed after evaluation), or • Without target organ damage

*Due to lack of sufficient data, neurocognitive symptoms and cardiovascular manifestations should not be considered when classifying as symptomatic to guide parathyroid surgery

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Primary hyperparathyroidism: clinical phenotypes

Symptomatic*	Asymptomatic	Normocalcemic
• Marked hypercalcemia • Osteitis fibrosa cystica, fractures • Chronic kidney disease, nephrolithiasis, nephrocalcinosis • Proximal myopathy	• No overt symptoms • With target organ damage (diagnosed after evaluation), or • Without target organ damage	• No symptoms • May or may not have target organ damage

*Due to lack of sufficient data, neurocognitive symptoms and cardiovascular manifestations should not be considered when classifying as symptomatic to guide parathyroid surgery

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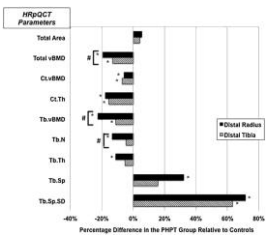
Skeletal outcomes in primary hyperparathyroidism

- Classically thought to predominantly affect cortical bone
- More recent data demonstrate defects in cortical *and* trabecular compartments
  - HR-pQCT bone microarchitecture
  - Lower TBS



Stein et al JCEM 2012

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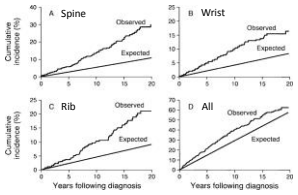
Skeletal outcomes in primary hyperparathyroidism

- Classically thought to predominantly affect cortical bone
- More recent data demonstrate defects in cortical *and* trabecular compartments
  - HR-pQCT bone microarchitectures
  - Lower TBS
- Increased fracture risk at vertebral and non-vertebral sites



Khosla et al JBMR 1999

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Renal outcomes in primary hyperparathyroidism

- Among patients with eGFR < 60 ml/min
  - Without surgery, persistent declines in eGFR are seen
  - Low eGFR associated with greater declines in bone density and increased fracture risk
- Stones and renal calcifications are common complications
  - Hypercalciuria is a risk factor
  - Other risk factors (hyperuricosuria, hypomagnesuria, hyperoxaluria, hypocitraturia, cystinuria) may play a role

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Primary hyperparathyroidism: Evaluation

Labs	Bone	Kidney
• Simultaneous calcium, albumin, PTH on 2 occasions separated by 2 weeks • 25-hydroxyvitamin D • Creatinine • Phosphorus (optional)	• 3-site DXA (lumbar spine, hip, distal 1/3 radius) • Vertebral imaging (VFA, x-rays) • TBS (optional)	• Creatinine clearance or eGFR • 24 hr urine calcium and other stone risk factors • Imaging for nephrolithiasis or nephrocalcinosis (CT, U/S, x-rays)

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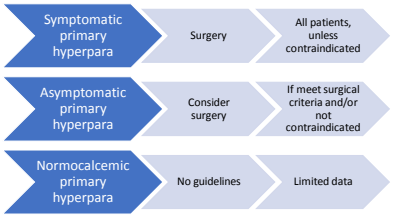
When to consider parathyroidectomy?



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Symptomatic patients: surgery recommended (unless contraindicated)

- Symptomatic primary hyperparathyroidism
  - Marked hypercalcemia
  - Osteitis fibrosa cystica, fractures
  - Chronic kidney disease, nephrolithiasis, nephrocalcinosis
  - Proximal myopathy
- Due to lack of sufficient data, neurocognitive symptoms and cardiovascular manifestations should not be considered when deciding on parathyroid surgery

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Neuropsychiatric symptoms after parathyroidectomy (PTX)

- RCT of n=192 adults with primary hyperparathyroidism
  - Randomized to PTX or observation
  - Followed for 10 years, 33% dropout
- PTX achieved biochemical cure vs no change in Ca/PTH in controls
- Overall, no meaningful change in quality of life for either group

Pretorius et al JBMR 2021

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Asymptomatic patients: Surgical indications*

Parameters	Criteria
Age	<50 years
Serum calcium	>1 mg/dL above upper limit of normal
Bone involvement	T-score < -2.5 at PA spine, total hip, fem neck, 1/3 radius Radiographic vertebral fractures
Kidney involvement	Creatinine clearance or eGFR <60 ml/min Nephrolithiasis or nephrocalcinosis Hypercalciuria (>4.4 mg/kg/day in men, >3.8 in women)

*Any patient without contraindications can choose surgery

Bilezikian et al JCEM 2014

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Normocalcemic primary hyperparathyroidism

- No definitive guidelines for surgery due to limited data
- Management typically involves annual lab/imaging monitoring
  - If progression to hypercalcemia then follow guidelines
  - If significant renal/bone disease then some experts recommend to consider surgery

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Parathyroid imaging

- Parathyroid imaging is not recommended for diagnostic purposes
- Preoperative imaging is recommended for those who are going to have parathyroid surgery
  - Ultrasound
  - Contrast-enhanced 4D-CT
  - Technitium-99m-sestamibi

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Surgical considerations

- Surgical outcomes are improved (and complications are lowered) with experienced parathyroid surgeon
  - 98% with biochemical cure
- Minimally invasive "selective" surgery (+/- intra-op PTH) can be considered if enlarged gland localized pre-operatively
  - 95-97% success rate with shorter operative time and fewer complications
- Parathyroidectomy significantly increases bone density

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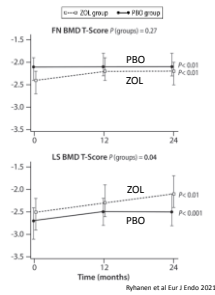
Timing of parathyroidectomy and bisphosphonates

- RCT of 56 adults with primary hyperparathyroidism and osteoporosis, undergoing PTX
  - Received zoledronic acid or placebo 1-3 months post-parathyroidectomy
- Bone turnover markers reduced in both groups, more so in ZOL group
- Bone density increased in both groups, more so in ZOL group



Ryhanen et al Eur J Endo 2021

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Goals of medical management of hyperparathyroidism

- Avoid symptomatic hypercalcemia
  - Maintain normal intake of dietary calcium (follow IOM guidelines)
  - Consider cinacalcet (lowers PTH modestly, no improvement in bone density)
- Avoid kidney stones
  - Low sodium diet, adequate fluid intake
  - Avoid thiazides, which can precipitate hypercalcemia
- Avoid osteoporosis and fractures
  - Bisphosphonates, denosumab*
- Aim for normal 25OH-vitamin D level
  - Vitamin D deficiency associated with higher PTH and bone turnover markers

*denosumab is not FDA-approved for primary hyperparathyroidism

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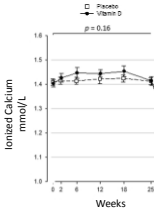
Vitamin D replacement in mild primary hyperparathyroidism

- RCT of 46 adults with primary hyperparathyroidism
  - Placebo or Vitamin D3 2800 IU/day for 6 months
  - Excluded ionized calcium >1.6 mmol/L
- Uncontrolled studies suggest safety of vitamin D repletion in mild primary hyperparathyroidism
  - 2000 IU/day to 50,000 IU/week
  - PTH levels decline
  - Typically excluded moderate hypercalcemia Ca >12 mg/dL at baseline



In Vitamin D group:
- ←→ Serum Calcium
- ←→ Urinary Calcium
- ↓ PTH
- ↓ CTX
- ↑ Spine BMD

Rolighed et al JCEM 2013

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Primary hyperparathyroidism: monitoring

Type of Monitoring	Frequency (US)
Serum Ca (ionized or albumin-corrected), PTH, 25OHD, eGFR or creatinine clearance	Annually
DXA bone density at spine, hip, and 1/3 radius	Every 1-2 years
24-hour urinary calcium and renal imaging (x-ray, CT, or U/S)	If clinically indicated
Vertebral imaging (x-ray, VFA, or TBS)	If clinically indicated

Bilezikian et al JCEM 2014
Bilezikian, *J. Clinical Hypoparathyroidism Guidelines (oral presentation)*. ASBMR 2021

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Indications to transition from monitoring to parathyroid surgery

- If serum calcium consistently >1 mg/dL above upper limit of normal
- Low-trauma fracture
- Kidney stone
- Significant bone loss (exceeding least significant change) and T-score less than -2.5 at any site
- Significant reduction in creatinine clearance

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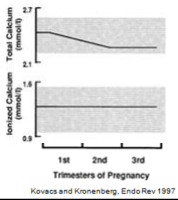
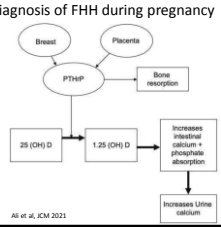
Pregnancy & Primary hyperparathyroidism: Diagnosis

→ Due to physiologic low albumin, follow ionized calcium levels during pregnancy



Kovacs and Kronenberg, Endo Rev 1997

→ Physiologic hypercalciuria complicates diagnosis of FHH during pregnancy



Ali et al, JCM 2021

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Pregnancy & Primary hyperparathyroidism: Management

- For mild cases, manage with hydration and lab monitoring
- If serum calcium >11.0 mg/dL, then consider parathyroidectomy during second trimester
- Preoperative imaging limited to ultrasound
- Pharmacologic considerations:
  - Calcitonin: can use short-term, doesn't cross placenta
  - Bisphosphonates and denosumab: avoid due to potential fetal toxicities
  - Cinacalcet: limited data, crosses placenta
- If surgery deferred, then monitor neonate closely for hypocalcemia and plan PTX after delivery and before next pregnancy

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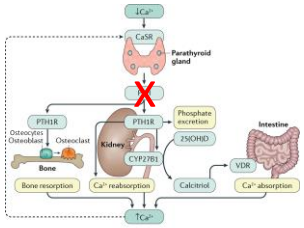
Hypoparathyroidism



PTH ↓
Serum Calcium ↓
Serum Phosphate ↑
Bone turnover↓

2nd International Workshop on Hypoparathyroidism

Mannstadt, M. *et al.* (2017) Hypoparathyroidism. *Nature Reviews Disease Primers* 3:17055

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Hypoparathyroidism: Diagnosis

- Low albumin-corrected calcium or ionized calcium with concurrent low or inappropriately normal PTH
  - PTH should be assessed with either a 2nd or 3rd generation assay, in absence of biotin supplements
  - Lab pattern should be observed on 2 occasions at least 2 weeks apart
- Postsurgical hypoparathyroidism is considered permanent if persists >12 months

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Hypoparathyroidism: Etiology

- Post-surgical (~75% of all hypoparathyroidism cases)
- Autoimmune (isolated or APCED)
- Genetic variants
- Functional (magnesium deficiency or excess)
- Other
  - Infiltrative (granulomatous)
  - Mineral deposition (copper, iron)
  - Metastatic
  - Radiation
  - Transient (severe burns or acute illness)
  - Maternal hyperparathyroidism
- Idiopathic

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Predicting permanent hypoparathyroidism following total thyroidectomy

- Recommend measuring PTH 12-24 hours after total thyroidectomy
  - If PTH >10 pg/mL (1.05 pmol/L), then unlikely to develop permanent hypoparathyroidism
  - If PTH <10 pg/mL (1.05 pmol/L), then possibility of developing permanent hypoparathyroidism, but still less than 50%
- Recommendation based on systematic review and meta-analysis
- To minimize risk of permanent surgical hypoparathyroidism, parathyroid autotransplantation should not be used routinely during neck surgery

Khan A. *Clinical Hypoparathyroidism Guidelines (oral presentation)*. ASBMR 2021

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Genetic etiology of hypoparathyroidism

- First exclude postsurgical, magnesium, or infiltrative disorders
- Then undertake genetic testing if the following:
  - Family history of hypoparathyroidism
  - Syndromic features (e.g. concurrent endocrinopathies, congenital anomalies)
  - Younger than 40 years

Khan A. *Clinical Hypoparathyroidism Guidelines (oral presentation).* ASBMR 2021

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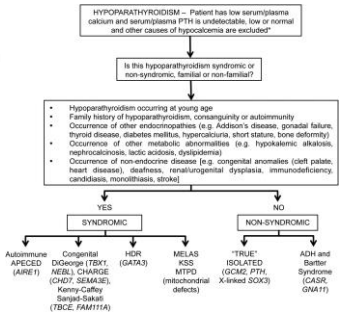
Genetic etiology of hypoparathyroidism



Clarke B, et al. JCEM 2016

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Symptoms and complications of hypoparathyroidism

- Most common symptoms (median prevalence)
  - 24% Cataracts
  - 18% Infection
  - 15% Nephrocalcinosis/Nephrolithiasis
  - 12% Seizures
  - 11% Depression
  - 9% Ischemic heart disease
  - 7% Arrhythmias

Khan A. *Clinical Hypoparathyroidism Guidelines (oral presentation).* ASBMR 2021

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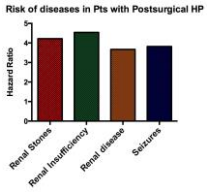
688 Danish Postsurgical Patients and Controls



Cases (n=688) and controls (n=2,064)

Renal stones: 1.9%/0.4%
Renal insufficiency: 5.1%/1.0%
Renal disease: 7.8%/1.8%
Seizures: 3.8%/1.0%

Underbjerg L et al. *J Bone Miner Res.* 2013; 28:2277-2285.

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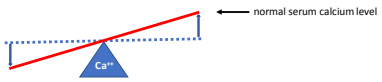
The Central Challenge in Management of Hypoparathyroidism: Serum vs. Urinary Calcium



Hypocalcemia	Calcium too high
Symptoms: Paresthesia Muscle cramps Tetany	Hypercalciuria Nephrocalcinosis Chronic Kidney Disease Basal Ganglia Calcifications

Slide provided by courtesy of Michael Mannstadt

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Goals of hypoparathyroidism therapy

- Maintain calcium in lower half of (or just below) normal reference range
- Alleviate symptomatic hypocalcemia
- Avoid hypercalciuria (<250/300 mg /24hr for women/men)
  - Low sodium diet + adequate fluid intake
  - Consider thiazide diuretic
- Avoid hyperphosphatemia
  - Low phosphate diet
  - Calcium supplements with meals to serve as phosphate binders
  - Judicious use of active vitamin D analogue
- Aim for normal levels of magnesium and 25OH-vitamin D

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Monitoring for hypoparathyroidism

Type of Monitoring	Frequency (US)
Serum Ca (ionized or alb-corr), Phos, Mg, Creatinine, 25(OH)D	Yearly, or more frequently if indicated
24-hour urinary calcium	Yearly, or more frequently if indicated
Renal imaging	**At baseline**, and as clinically indicated
Monitor serum calcium following changes in therapy	**Within days** of a change in medical treatment

Bollerslev J, et al. *European J of Endocrinology*. 2015;173:2,G1
Brandi ML, et al. *J Clin Endocrinol Metab*, June 2016, 101(6):2273–2283
Khan A. *Clinical Hypoparathyroidism Guidelines (oral presentation)*. ASBMR 2021

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Conventional therapy for hypoparathyroidism

Medication	Dose	Comments
Calcium carbonate or citrate	Range from 500-3,000 mg TID, preferably with meals to enhance phosphate-binding effects	Calcium citrate preferred if concurrent PPI use
Vitamin D2 or D3	1000-100,000 weekly or daily based on 25OHD levels	Half-life 4-6 hrs
Calcitriol	0.25-3 mcg total daily dose, administered in divided doses	Half-life 5-8 hrs
Thiazide diuretics	25-100mg	Half-life 6-12 hrs

Steady state reached in 5-6 half-lives

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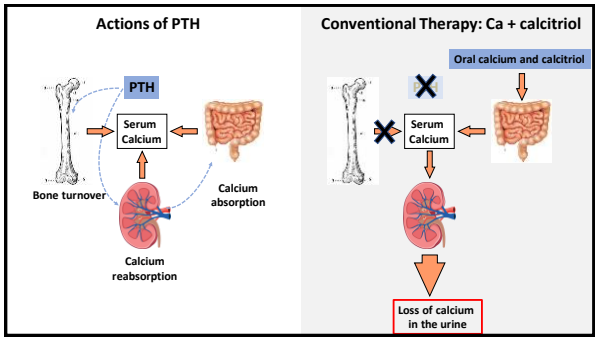

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PTH vs conventional therapy

- Meta-analysis of 6 RCTs of PTH therapy
  - 2 RCTs of PTH 1-84
  - 3 RCTs of PTH 1-34 (not FDA-approved for treatment of hypoparathyroidism)
  - 1 RCT of Transcon PTH (not FDA-approved)
- In comparison to conventional therapy, PTH treatment:
  - Maintains eucalcemia
  - Lowers hyperphosphatemia
  - No effect of hypercalciuria
  - Increase in hypercalcemia

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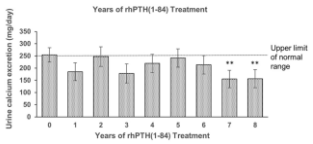
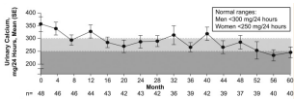
PTH may reduce hypercalciuria in long-term open-label studies

Columbia study (n=24)



RACE study (n=40)



Tay et al *JCEM* 104: 5601-5610, 2019
Mannstadt et al *JCEM* 104: 5136-5147, 2019

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PTH vs conventional therapy

Outcomes with PTH treatment	Quality of evidence
Allows reductions in active vitamin D and calcium by >=50%	High
Small improvement in quality of life: physical health	Moderate
Little to no impact on quality of life: mental health	Low
Possible small increase in serious adverse events (e.g. hypercalcemia)	Low

In patients with chronic hypoparathyroidism, conventional therapy is first-line
When conventional therapy is deemed unsatisfactory, consider PTH

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Candidates for PTH therapy

- Difficult to manage / fluctuating serum calcium
- Hyperphosphatemia
- Renal insufficiency, hypercalciuria, nephrolithiasis
- High doses of conventional therapy
- Poor adherence, GI side effects, and/or malabsorption of calcium supplements

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Current Recall of PTH(1-84)

Sept 5, 2019: Recall due to the potential for rubber particulate
Fixing the problem takes time

Options:
1. Apply for "Special Use Program" (life-threatening condition)
2. Prescribe off-label teriparatide (need multiple injections)
3. Switch to calcium/calcitriol (watch for "hungry-bone" effect)

Slide provided by courtesy of Michael Mannstadt

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Hypoparathyroidism treatment during pregnancy

- Calcium requirements increase due to fetal demand
  - Either maternal hypocalcemia or hypercalcemia can result in fetal parathyroid hypo/hyperactivity and fetal skeletal defects
- Physiologic increases in PTHrP and 1,25D tend to lower requirements for calcium supplements and active vitamin D
- Monitor albumin-adjusted or ionized calcium every 3-4 weeks during pregnancy and lactation
- Avoid thiazides (Class B) and PTH analogs (Class C) during pregnancy

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Emerging therapies (not FDA-approved)

Proposed therapy	Pharmacology / Mechanism	Investigational Stage
Frequent PTH dosing	BID or continuous pump	In small trials, more consistent eucalcemia, minimizing hypercalciuria
Long-acting PTH analog	PTH/PTHrP hybrid analog for prolonged intracellular signaling	In phase 1 trials
Calcilytics	CaSR antagonists (for Autosomal Dominant Hypocalcemia)	In phase 2 trials
Oral PTH (1-34)	QID tablet	Recent phase 2 results
TransCon PTH (1-34)	Sustained release via cleavage of TransCon linker at physiologic pH and temperature	Recent phase 2 results

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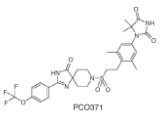
Oral PTH (not FDA-approved)

- oral PTH(1-34)
- QID tablet
- 15 patients treated for 16 weeks



PCO371

ORIGINAL ARTICLE JBMR

Safety and Efficacy of Oral Human Parathyroid Hormone (1-34) in Hypoparathyroidism: An Open-Label Study

Sofia Ish-Shalom,[1] Yoseph Caraco,[2] Nariman Saba Khazen,[1] Michal Gershinsky,[1] Auryan Sealat,[2] Phillip Schwartz,[2] Ehud Arbit,[3] Hillel Gallitzer,[3] Jonathan CY Tang,[4] Gregory Burshtein,[2] Ariel Rothner,[1] Arthur Raskin,[1] Miriam Blum,[1] and William D Fraser[4,5]

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- Maintained eucalcemia and lower phosphate with 42% reduction in calcium/calcitriol dose
- Possible 26% reduction in urinary calcium (p=0.07)

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Transcon PTH (not FDA-approved)

PaTH Forward Study
Phase 2 RCT 4 weeks + 22 weeks open-label extension
N=59 (placebo, 15, 18, 21 mcg/d)

91% independence from SoC (Ca<500 mg)
Mean 24-hour calcium 415 → 178 mg/24 hours
Ca, P, CaxP normal
QoL: improved scores

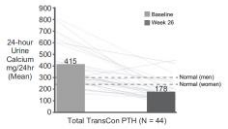

Figure 4. Mean 24-hour urine calcium at baseline and week 26. Gray lines represent individual patient data from baseline to week 26.

Khan AA, et al. *J Clin Endocrinol Metab.* 2022;107:e372-e385.

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Summary

- New clinical guidelines for primary hyperparathyroidism
  - Diagnosis / Classification
  - Indications for surgery
  - Medical management
  - Pregnancy
- New clinical guidelines for hypoparathyroidism
  - Diagnosis
  - Conventional treatment
  - PTH treatment
  - Pregnancy
  - Emerging therapies

Official guidelines to be released later this year

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