Hypoparathyroidism: Diagnosis and Managment

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XXXI CONGRESO DE LA SOCIEDAD CHILENA DE OSTEOLOGÍA Y METABOLISMO MINERAL - SCHOMM
26 y 27 DE ABRIL 2024

Declaración de Conflictos de Interés

Fondos para investigación:

The NIDCR received funding from NPS Pharmaceuticals and Calcilytix for the study of the calcilytic drugs NPSP795 and Encaleret for the treatment of autosomal dominant hypoparathyroidism

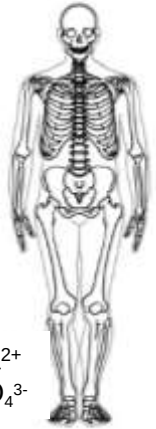
Parathyroid Hormone – It's All About the Calcium!

Tissues

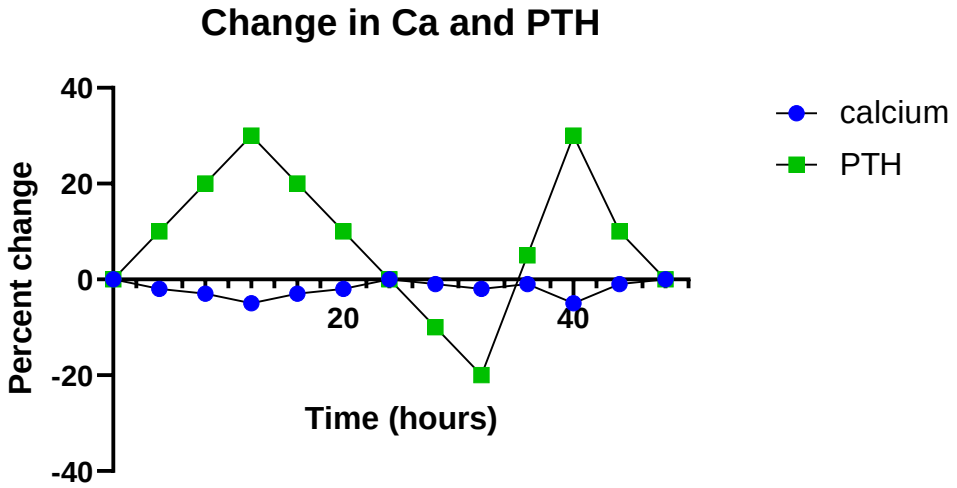
Calcium is critical for:

- Neural function
- Muscle function
- Cell signaling
- Cofactor

Skeleton

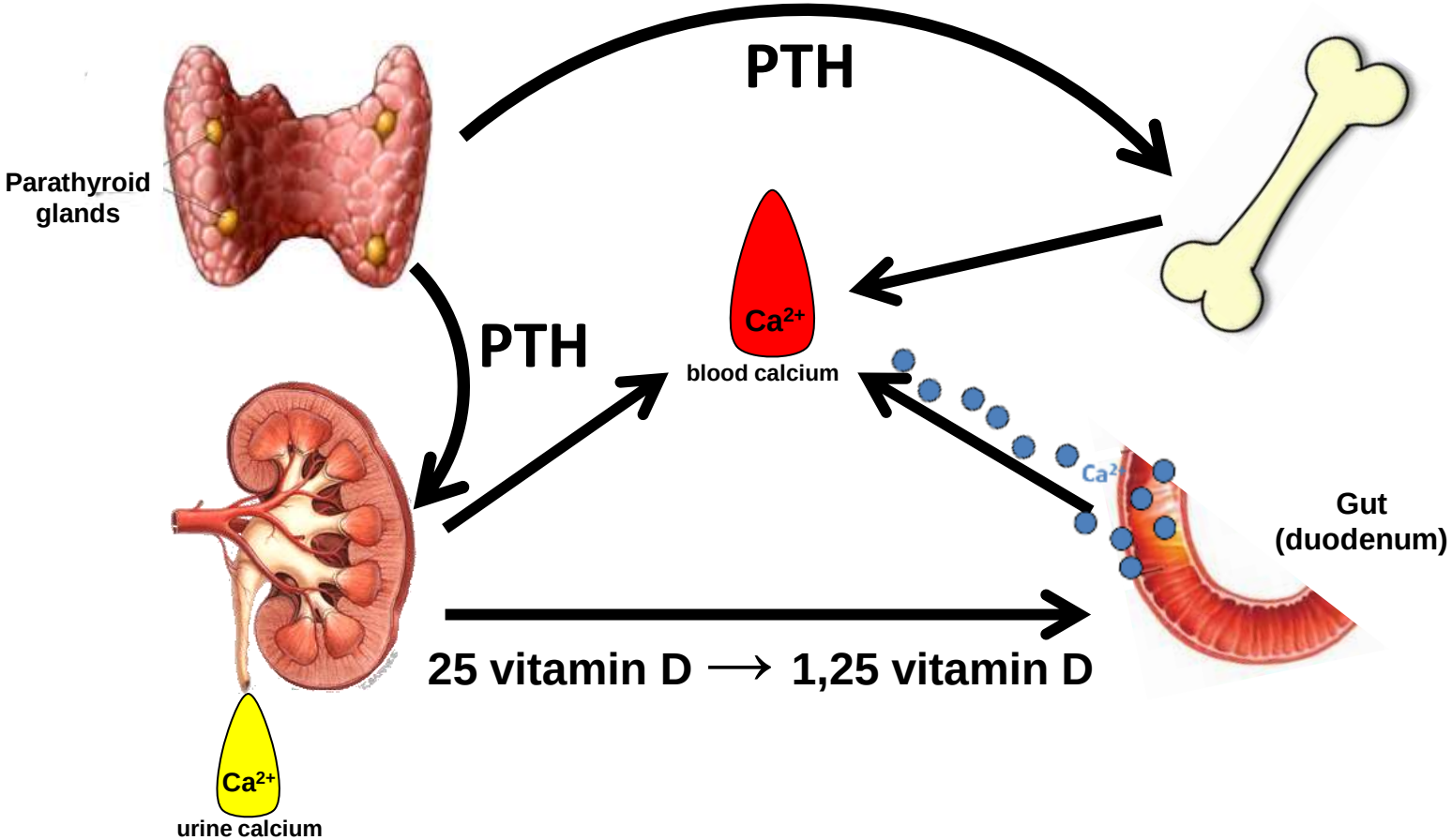


> 1 kg Ca^{2+}
1.6 kg PO_4^{3-}



Blood Calcium is Maintained by Four Organs

Through two pathways: PTH and the calcium-sensing receptor (CaSR)



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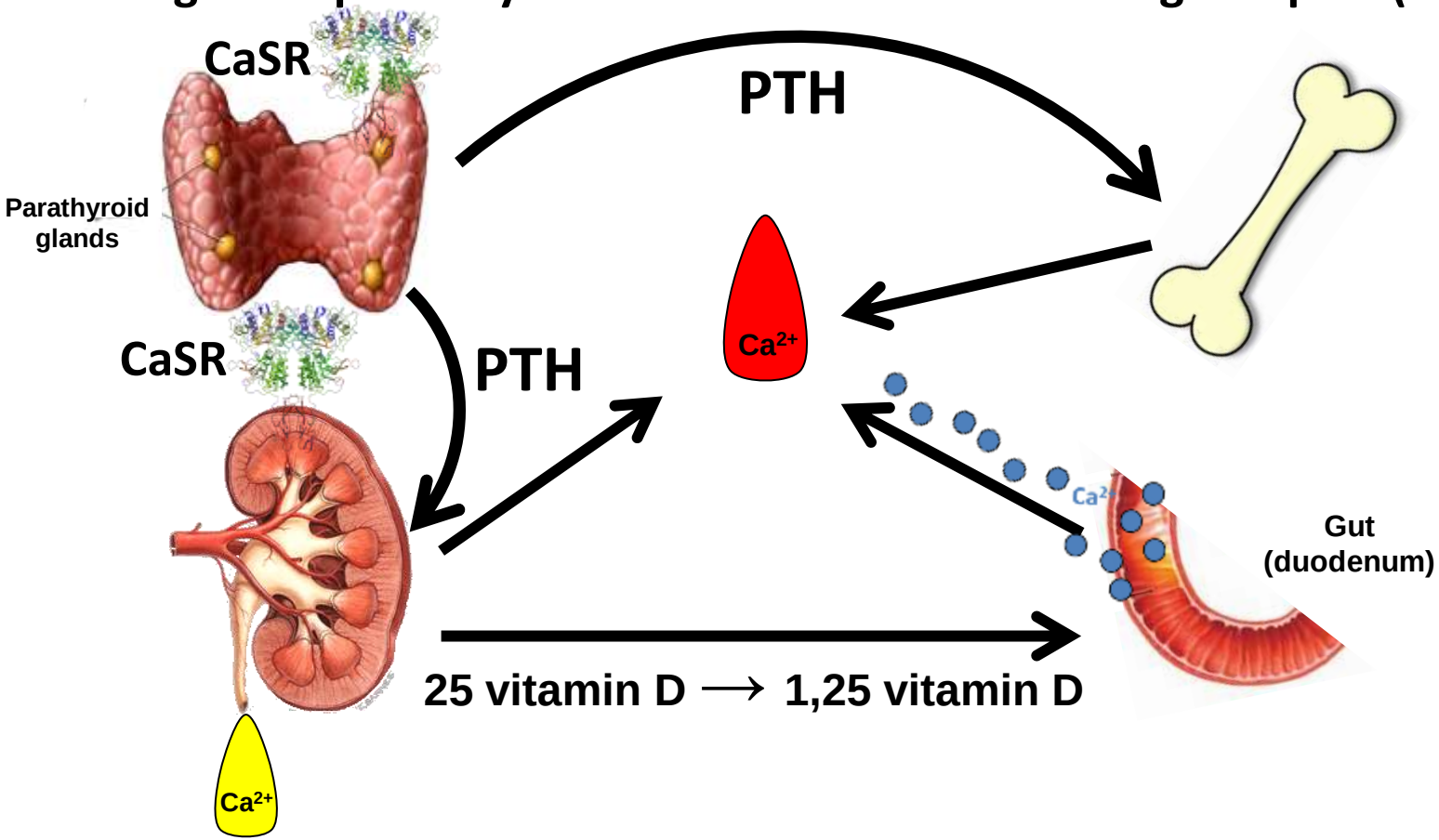

Causes of Hypoparathyroidism

Parathyroid Gland Damage/Destruction

- **Surgery (70% of all cases)**
  - permanent: persists >12 months post surgery
  - PTH 12-24 hr post surgery: <10pg/ml, permanent more likely
- Autoimmune (polyglandular failure, *AIRE,* others)
- Infiltrative (iron, copper)

Disorder of Parathyroid Gland Secretion

- Genetic: PTH, Autosomal dominant (*CaSR, GNA11),* others
- Maternal hypocalcemia, hypo- or hypermagnesemia

Disorders of Parathyroid Gland Formation

- DiGeorge/Velocardial facial (22q11.2)
- Hypoparathyroid deafness (*GATA3*)
- Others

Kahn, JBMR Dec 2022
Mannstadt, JBMR 2022

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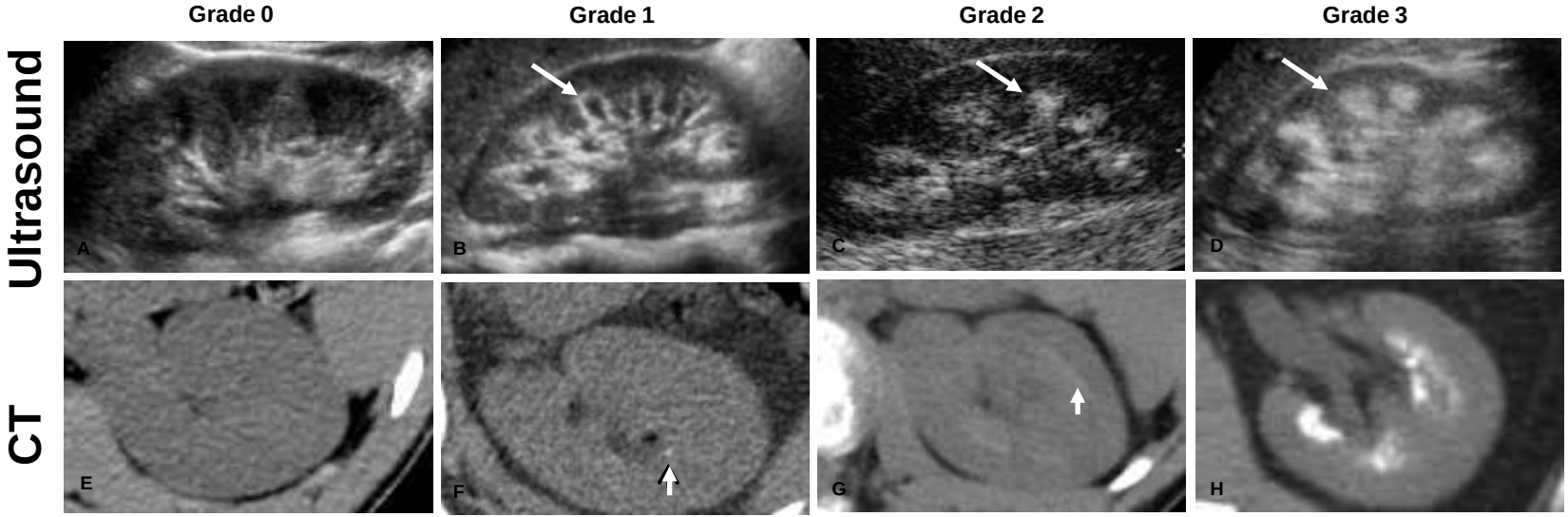
Findings in Hypoparathyroidism

- Low blood calcium with low/inappropriately normal PTH
  - confirmed on 2 occasion at least 2 weeks apart
- Hyperphosphatemia
- Neuromuscular irritability – cramping, tetany, seizures, laryngospasm
- Basal ganglia calcifications
- Decreased quality of life – “brain fog,” fatigue, depression

- Treatment related:
  - Increased urinary calcium
  - Nephrocalcinosis/nephrolithiasis
  - Renal insufficiency

Ultrasound is more sensitive than CT for detecting early nephrocalcinsosis

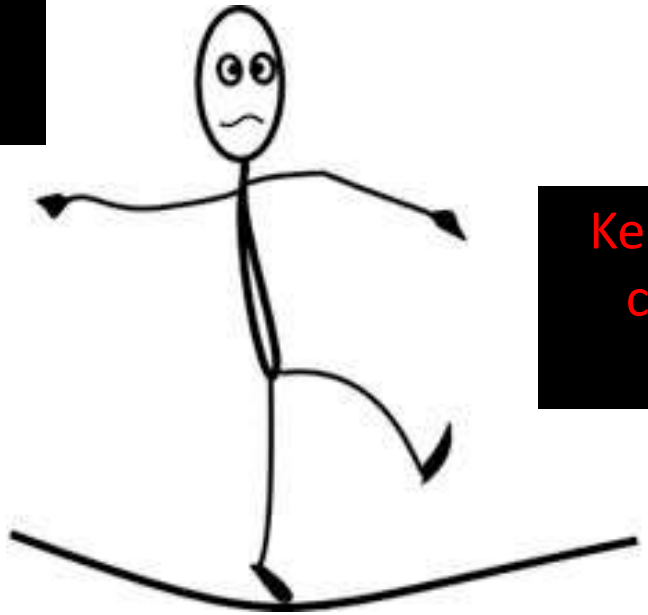


Boyce…Collins, JCEM, 2013

Treating Hypoparathyroidism: Walking the tightrope

easy

Keep blood calcium up



Keep urine calcium down

difficult

Treatment

Conventional Therapy – Consensus* Recommended

- High dose vit D (50,000/day)

or

- Calcium: 500 – 3,000 mg tid (with meals to bind phosphate) +
- Calcitriol (.25-3mcg divided) or Alfacalcidiol (.5-6mcg divided)

- Thiazide diuretics (for hypercalciuria)

Problems

- High pill burden
- Variable responses
- Hypercalciuria – ultrasound annually
  - nephrolithiasis, nephrocalcinosis, renal insufficiency
- “Brain fog” can persist

Gafni and Collins, NEJM 2019
*Khan, et al, JBMR 2022

Goals of Treatment

- Serum total calcium ***low-normal range***
- Serum phosphorus in the high-normal range
- Magnesium low-normal
- ***Avoid hypercalciuria*** (< 4 mg/kg/day; < 0.1 mmol/kg/day)
  - Add thiazide diuretic as needed/tolerated
- Avoid elevated Ca x Phos product <55 (not validated)
- Monitoring
  - Frequent laboratory evaluations – at least every 3-6 mo
  - 24-hour urine collection at least yearly
  - Periodic renal ultrasound

Gafni and Collins, NEJM 2019
Khan, et al, JBMR 2022

Treatment - PTH

Parathyroid Hormone Replacement

Available and/or Approved

- PTH 1-34: **teriparatide* (Forteo/Forsteo™)**
- PTH 1-84: Preotact/Natpara/Natpar™

Use

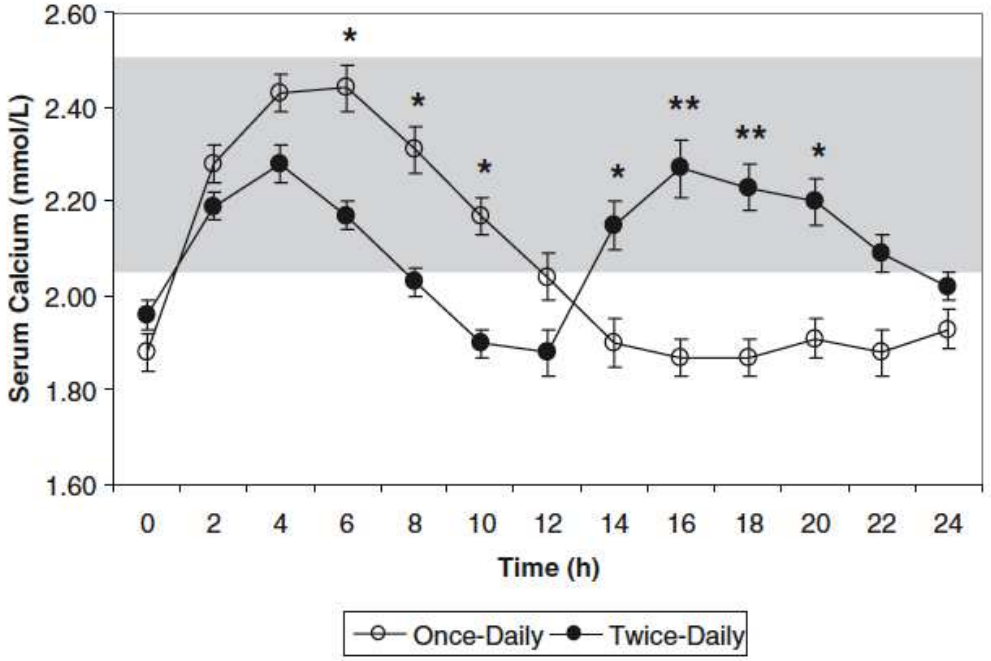
- Divided doses – limited doses available
  - may not improve hypercalciuria
- Continuous pump – reserved for children and severe

Side Effects/Complications

- Nephrocalcinosis/Hypercalciuria
- High bone turnover

*generic approved

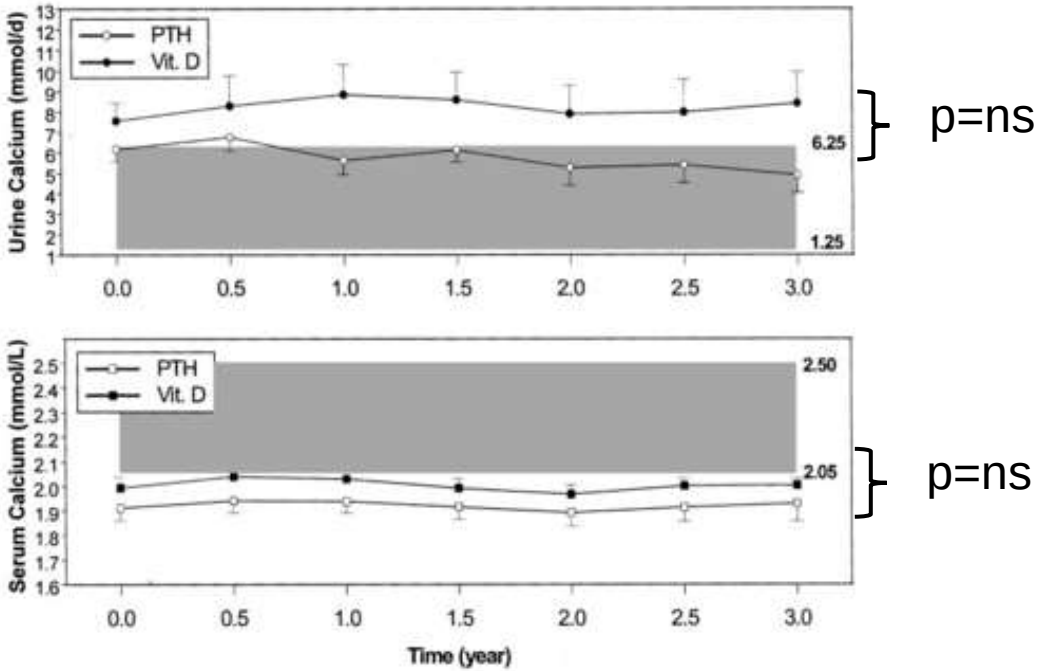
Pharmacodynamics of PTH 1-34 in Hypoparathyroidism: Twice daily is better



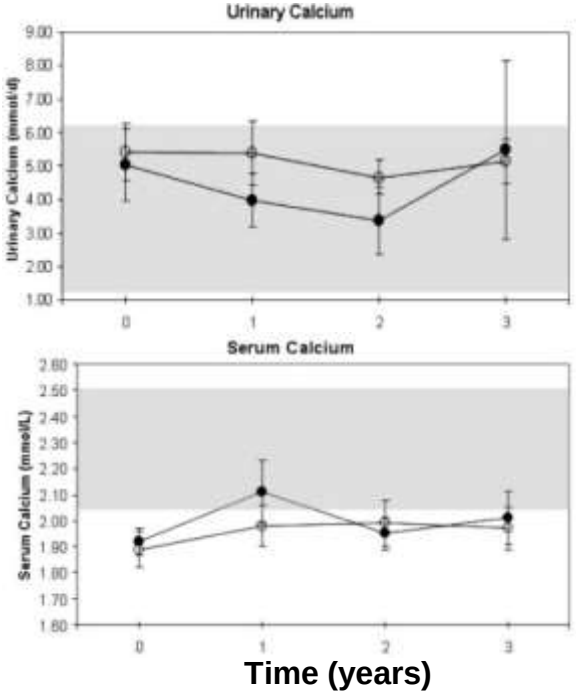
Winer, JCEM, 2008

BID PTH 1-34 vs Calcitriol x 3 yr

Adults



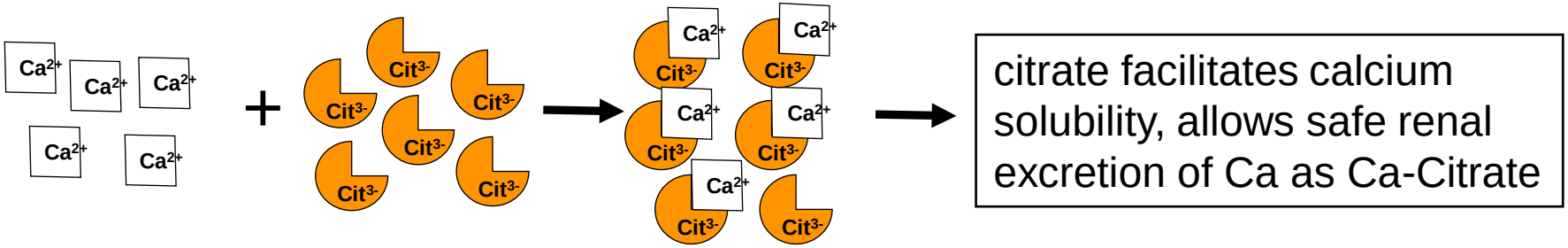
Children



PTH NOT Superior to calcitriol

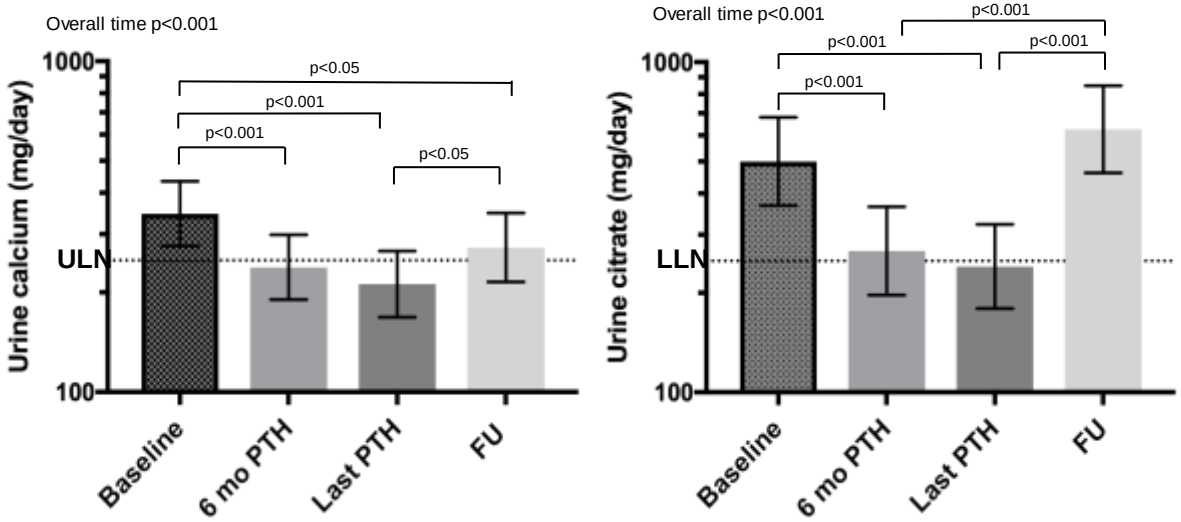
Winer, et al, JCEM 2003, 2010

Urine citrate protects from renal calcification
PTH replacement decreases urine citrate



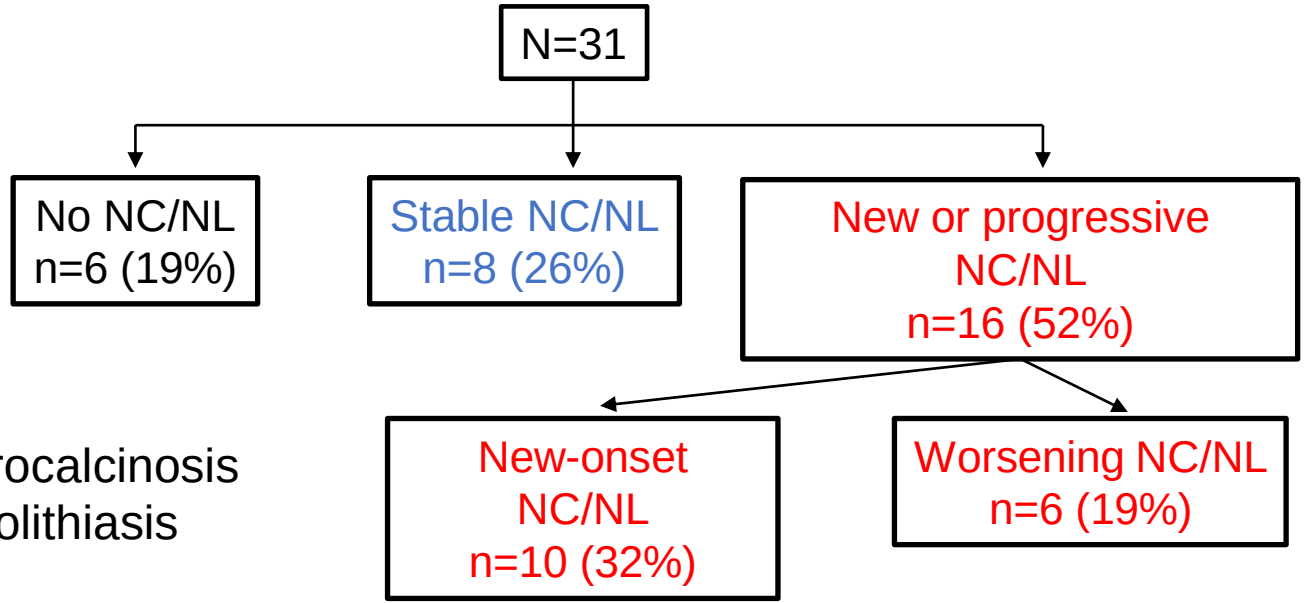
Can PTH replacement increase the risk for renal calcification?

PTH 1-34 bid Decreased Urine Ca and Urine Citrate



Gafni…Collins, JBMR 2018

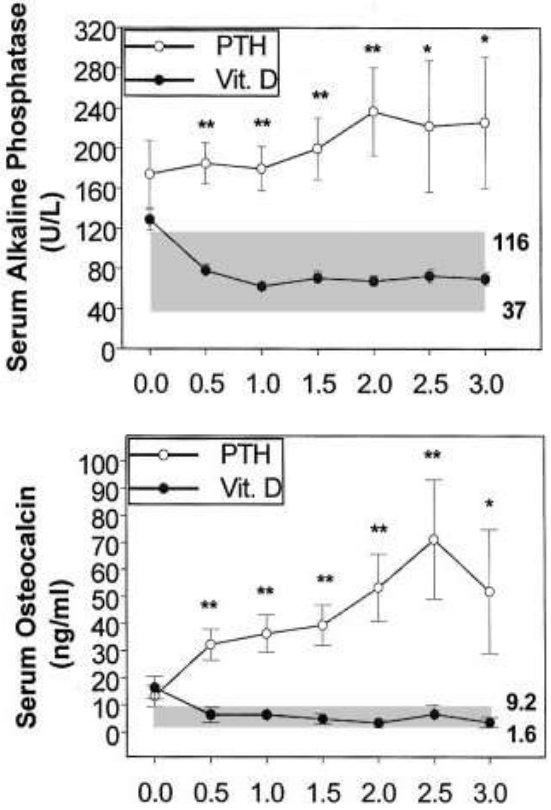
PTH 1-34 bid associated with renal calcification; Even though it lowered urine Ca!!



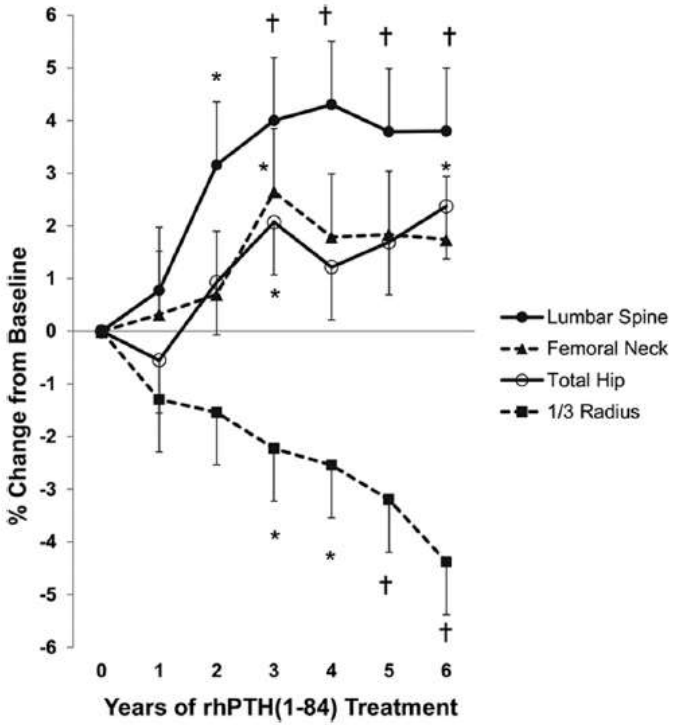
NC = nephrocalcinosis
NL = nephrolithiasis

Gafni…Collins, JBMR 2018

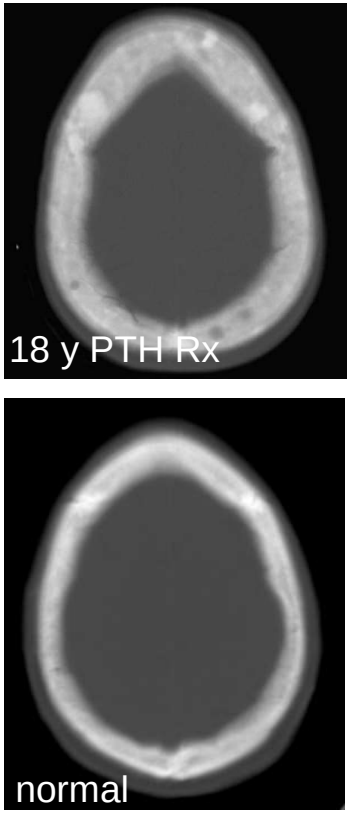
PTH treatment elevates bone turnover, decreases cortical bone mass, changes bone architecture



Winer JCEM, 2003



Rubin JCEM 2016



Theman JBMR, 2009

Treating Hypoparathyroidism: Walking the tightrope

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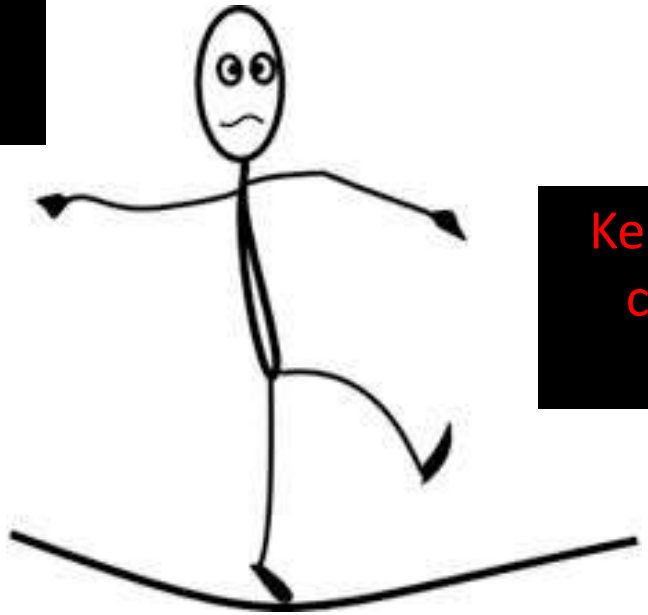
Keep blood calcium up



Keep urine calcium down

difficult

Treating Hypoparathyroidism

easy

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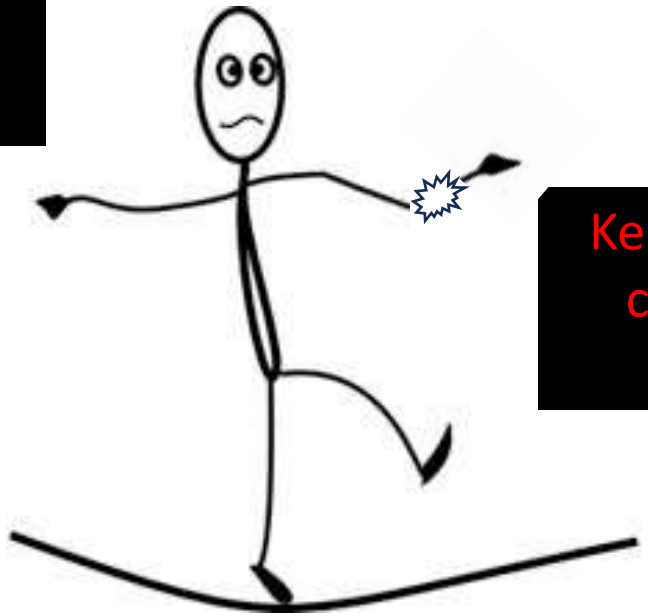


Don’t harm the bones!

the final frontier!

Keep urine calcium down

difficult

Evaluation and Management of Hypoparathyroidism

Summary Statement and Guidelines from the Second International Workshop

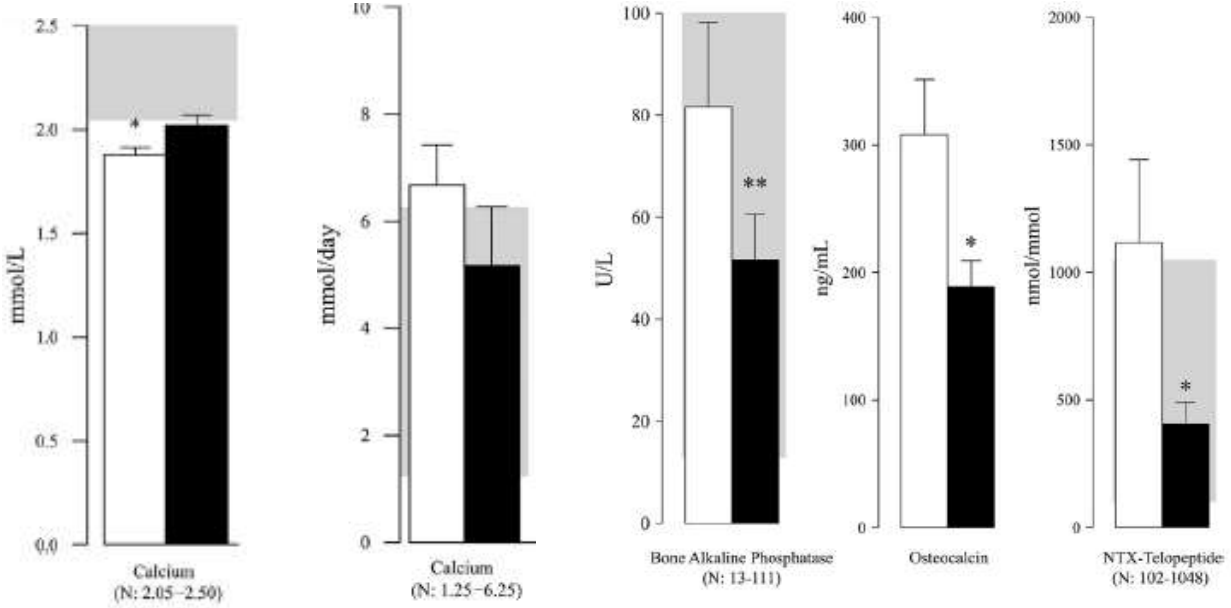
- 50 international experts
- Addresses prevention, diagnosis and management
- Gives expert-based guidance plus **evidence-based recommendations**
- Minimal pediatric information included

8 papers - JBMR, Dec 2022

New Directions

- PTH pump therapy
- Abaloparatide (PTHrP)
- PTH Receptor Modulators (pegylated PTH)
- Long-acting PTH analogues
- Calcilytics – antagonists of the CaSR

Controlled Study PTH Pump vs Injection Therapy: Superior for blood not urine Ca; Decreased bone turnover



Blood Urine Bone Turnover

- Randomized crossover 3 mo per arm
- 12 subjects – mostly teens
- 5 APECED; 7 CaSR

Injection Pump Normal Range

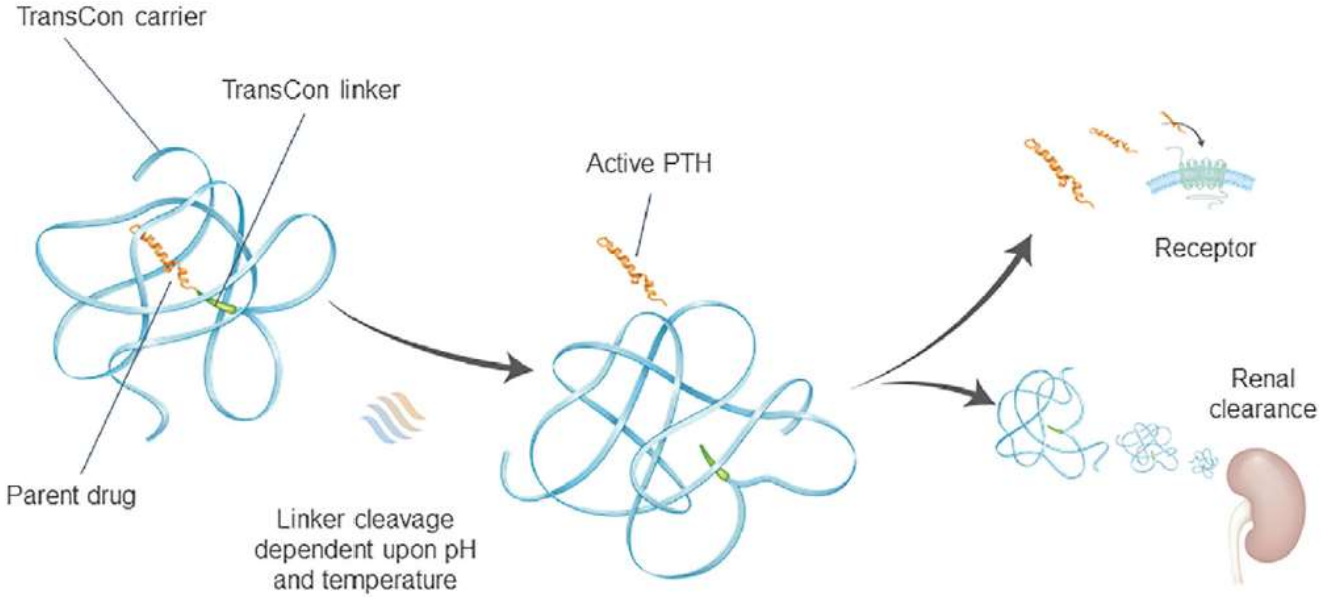
*$P<.05$ **$P<.01$ ***$P<.001$

Winer J Ped, 2014

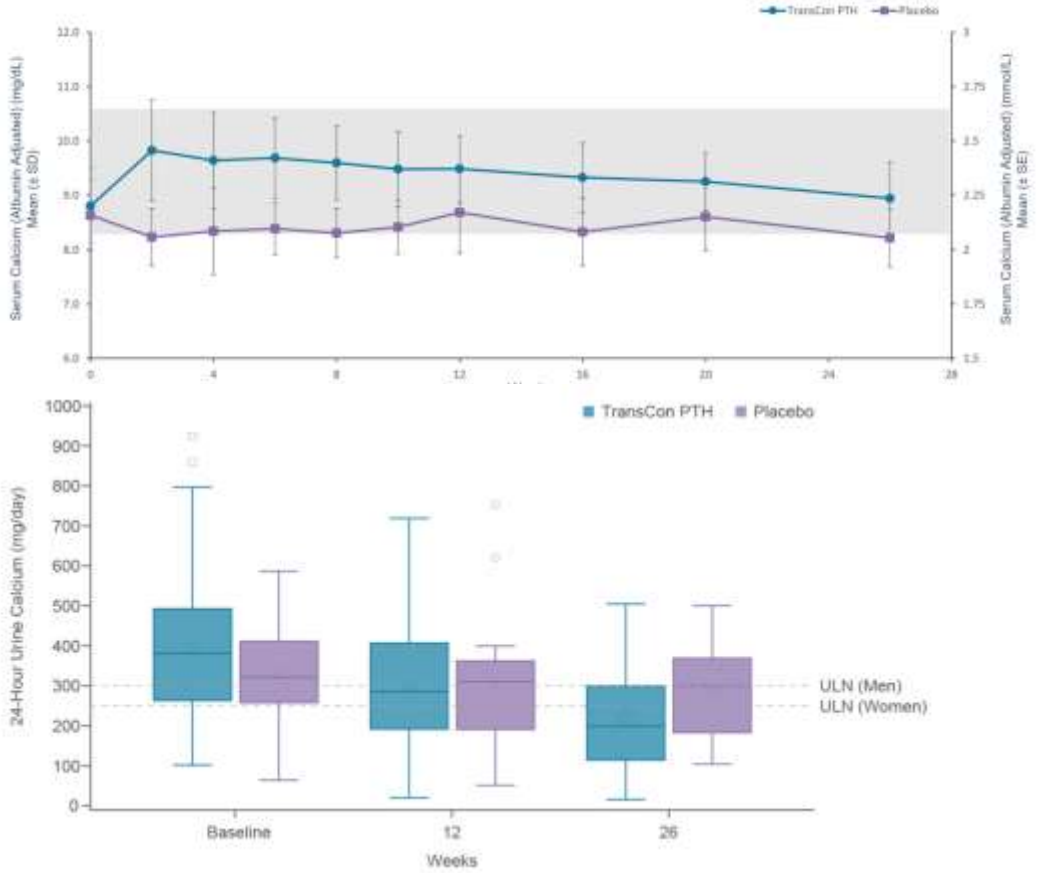
Pediatric Studies Support PTH Pump Therapy

- Linglart JCEM, 2011
  - continuous PTH 1-34 pump x 3 years in 3 children
  - **reduced seizures, hospitalizations, urinary calcium**
- Sastre NEJM, 2021
  - Continuous PTH 1-34 pump 6 children
  - **reduced seizures, hospitalizations and urine calcium/creatinine ratio**
- Several case reports
  - Mittleman, JCEM 2006
  - Sanda, JPEM 2008
  - Cho, JPeds 2011

Pegylated PTH (TransCon PTH, palopegteriparatide)



Palopegteriparatide Normalized Blood and Urine Ca

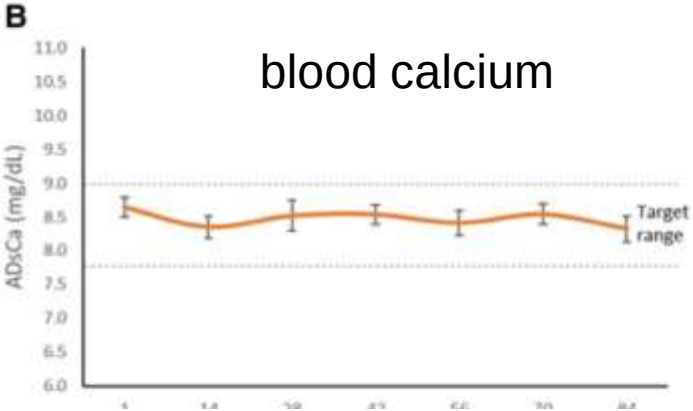


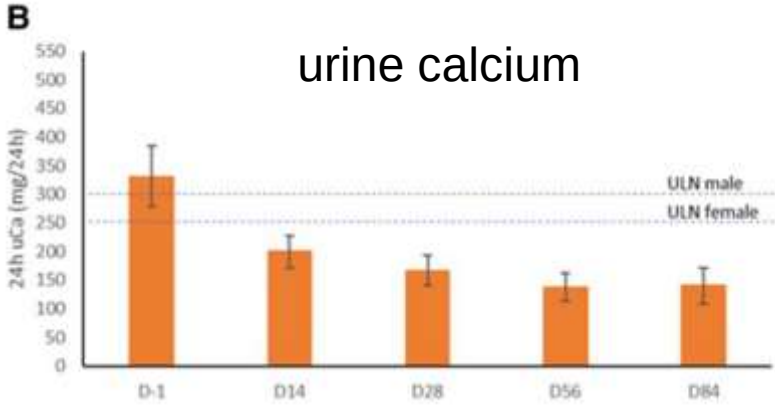
- **Design**
  - 26w Placebo-controlled
  - 82 adults randomized 3:1
  - 85% post-surgical
- **Results**
  - 93% on PTH stopped calcium and calcitriol
  - Urine calcium normalized in 61% on PTH vs 27% on placebo
  - PTH improvement in QOL
  - **Bone turnover?**

EMA approved; FDA rejected initial application - concerns related to the manufacturing control; resubmission under review

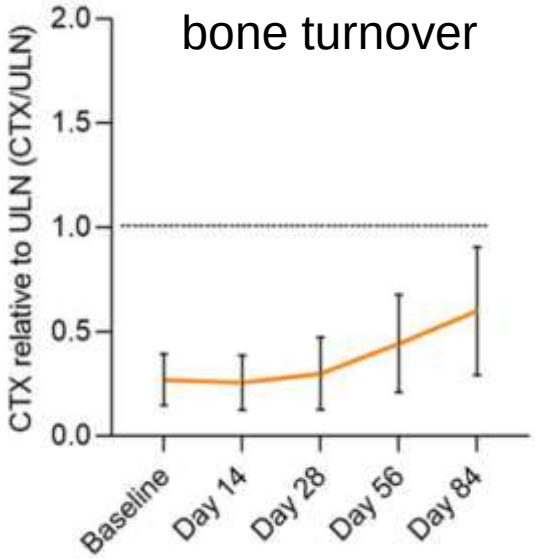
Khan et al, JBMR, Jan 2023

Long-Acting PTH (LA-PTH, Eneboparatide)





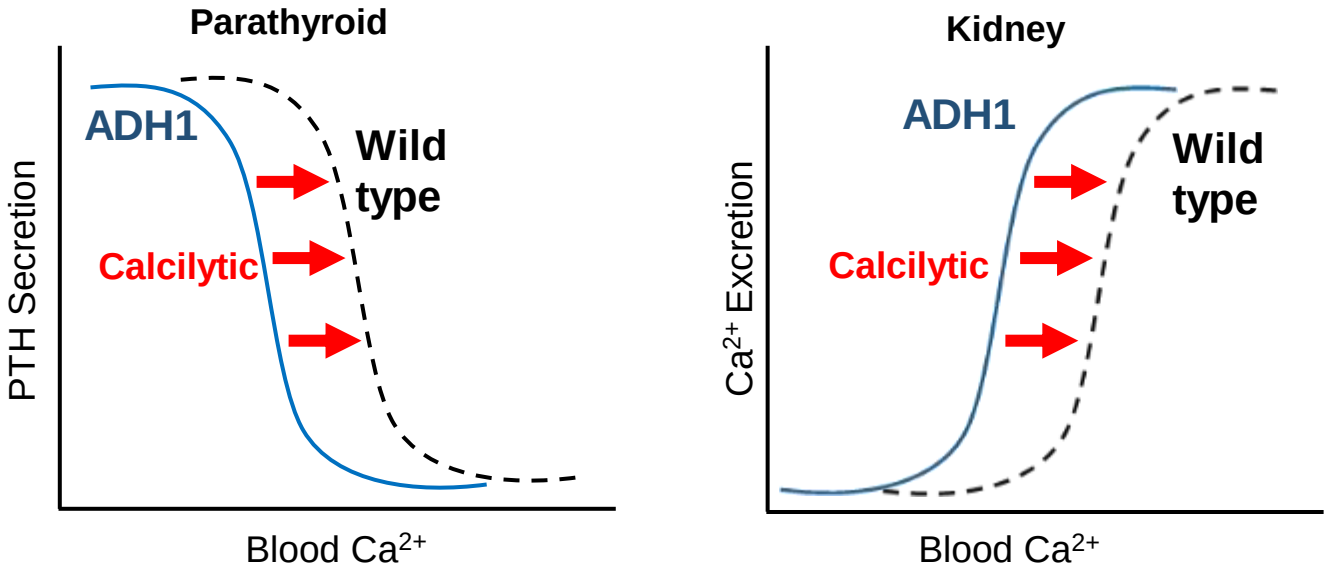
- **Phase 2 study**
- **Normalized blood and urine CA**
- **Did not increase bone turnover above normal at 84 days**



Tackas JCEM, 2024

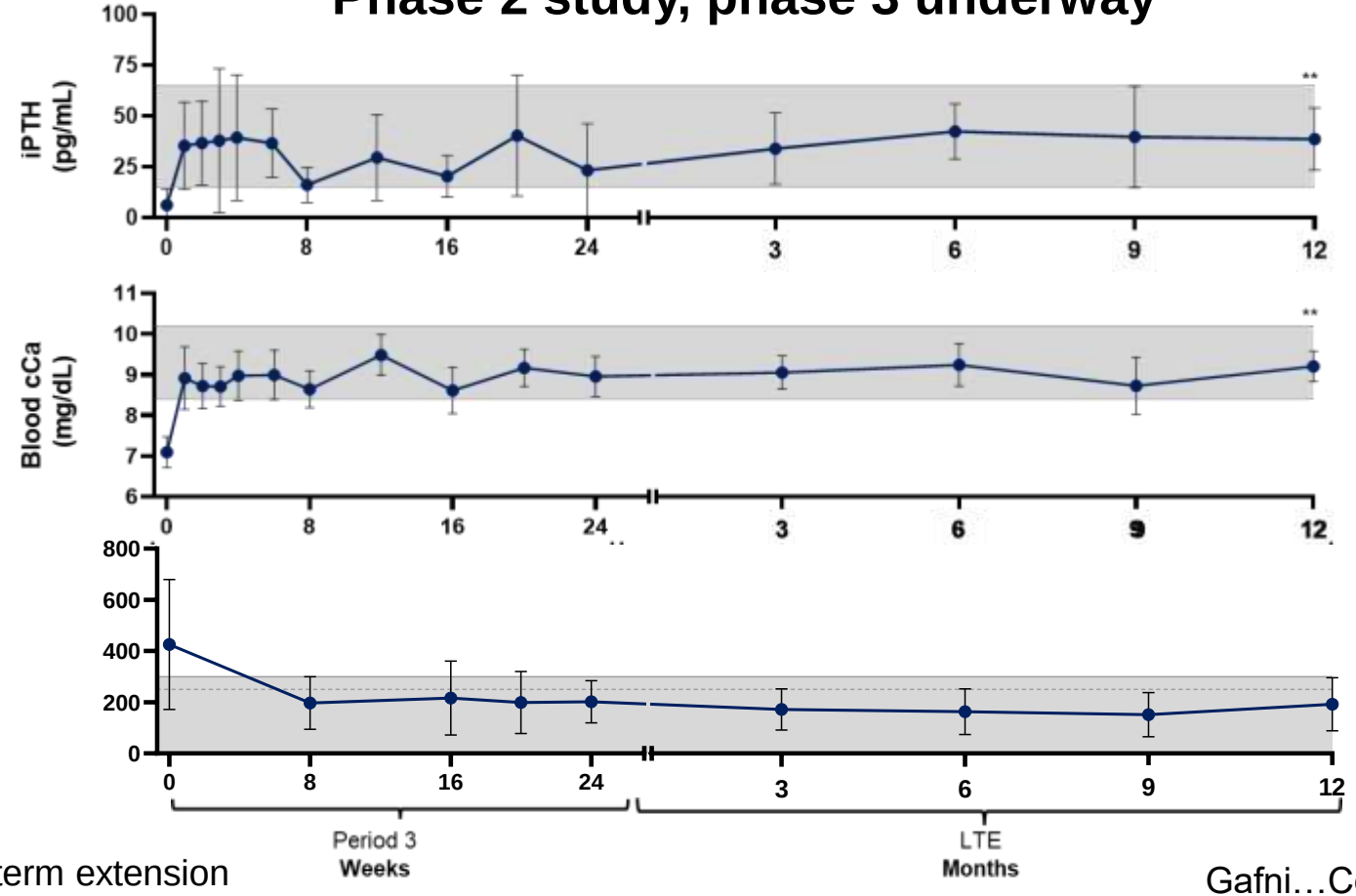
Autosomal Dominant Hypocalcemia Type 1

- Caused by mutations in the calcium-sensing receptor (CaSR)
- Parathyroids and kidneys “sense” hypocalcemia as normal
- Low PTH, high urine calcium – most difficult to treat
- **Calcilytics** are small molecule antagonists of the CaSR



Encaleret normalized PTH and blood and urine Ca

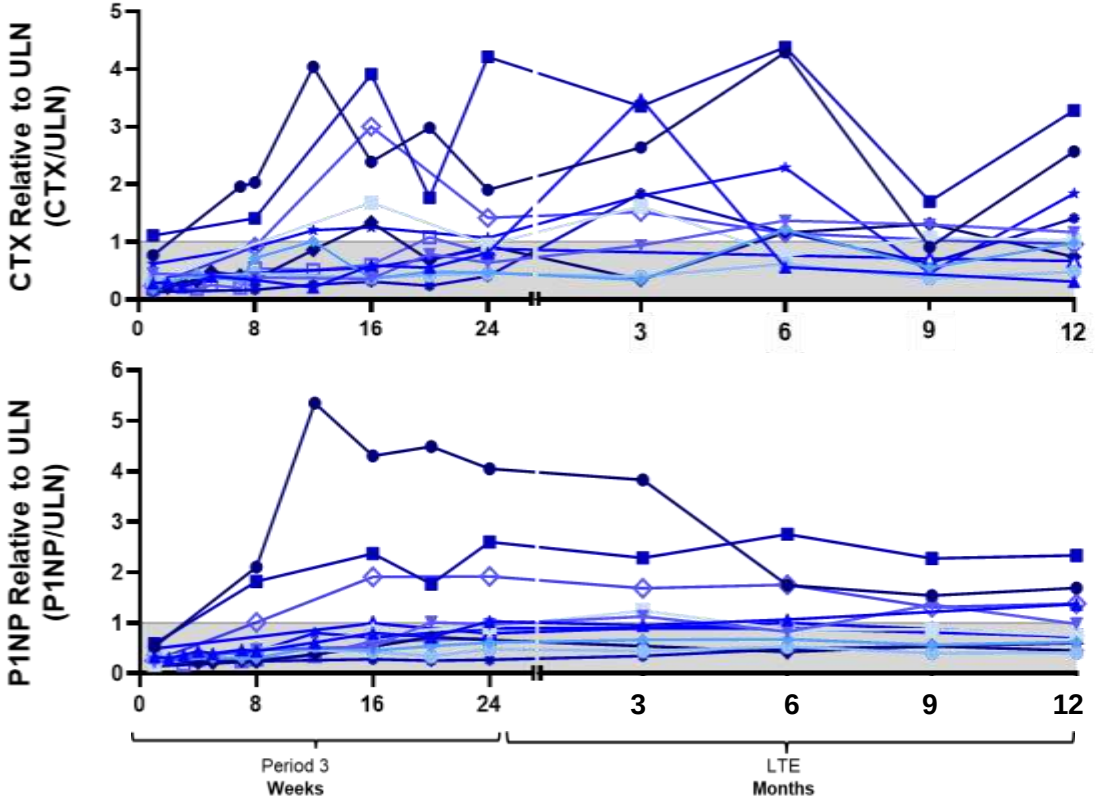
Phase 2 study, phase 3 underway



LTE=long term extension

Gafni…Collins NEJM, 2023

Encaleret increased bone turnover markers

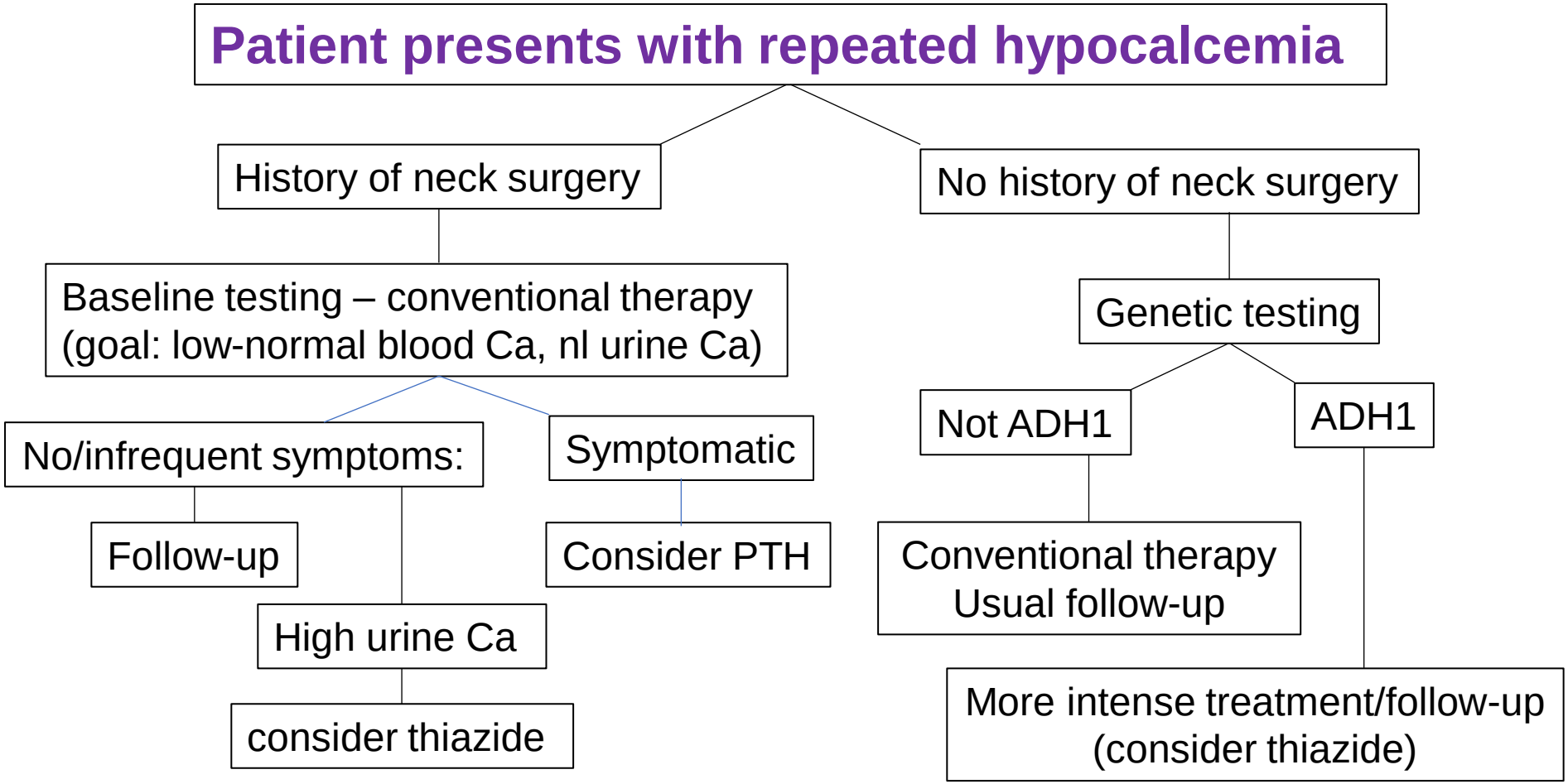


5/12 participants >1 at LTE Month 12

4/12 participants >1 at LTE Month 12

LTE = long term extension

Gafni…Collins NEJM, 2023


Patient presents with repeated hypocalcemia
History of neck surgery
No history of neck surgery
Baseline testing – conventional therapy
(goal: low-normal blood Ca, nl urine Ca)
Genetic testing
No/infrequent symptoms:
Symptomatic
Not ADH1
ADH1
Follow-up
Consider PTH
Conventional therapy
Usual follow-up
High urine Ca
consider thiazide
More intense treatment/follow-up
(consider thiazide)

Skeletal Disorders and Mineral Homeostasis Section

Former Trainees

Mart Scott Roberts, Ultragenyx
Diana Ovejero, Barcelona
Cemre Robinson, Sanofi
Jason Berglund, Tufts
Sri Tella, USC
Tarek Metwally, U MI
Andrea Estrada, CNMC
Diala El-Maouche, Amgen
Andrea Burke, U WA

**a (much) younger Pablo Florenzano

NIH National Institute of Dental and Craniofacial Research

Skeletal Disorders and Mineral Homeostasis Section

Rachel Gafni, MD

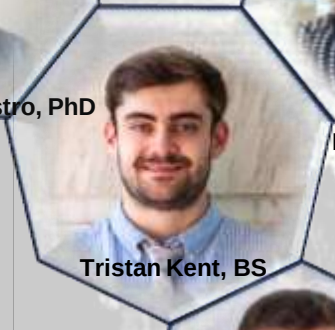
Michael T. Collins, MD

Luis Fernandez De Castro, PhD

Rebeca Galisteo

Fiona Obiezu, BS

Karen Pozo
Research Nurse



Tristan Kent, BS

Kelly Roszko, MD PhD

Will Bryant, BS

Rita Meadows, PhD

Kimberly Ampuero, BS

Iris Hartley, MD

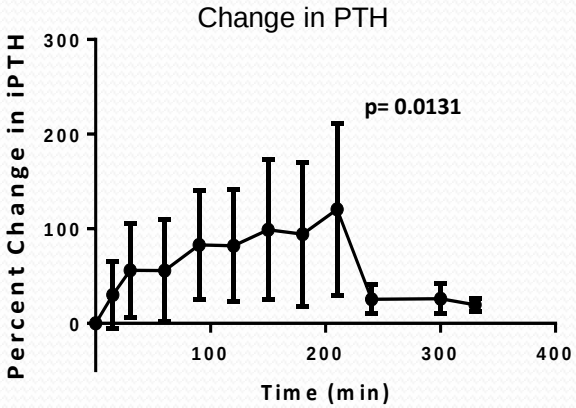

PANDORA

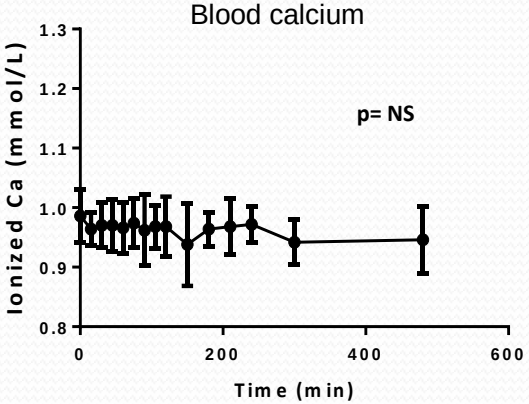
What about giving continuous subcutaneous PTH?

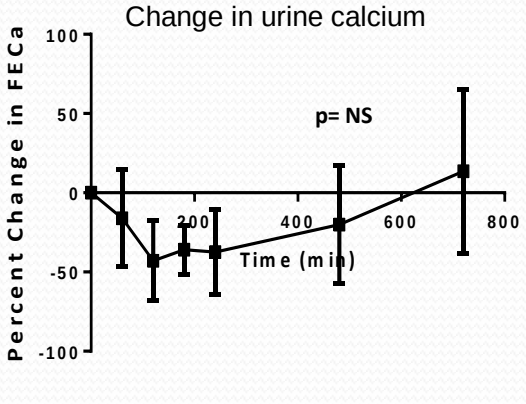
Treatment of Autosomal Dominant Hypoparathyroidism type 1 with SHP635

- Repurposing study
  - class of drugs previously tried in osteoporosis
  - appears safe
- Methods
  - 5 patients with activating CaSR mutations
  - daily 3 ½ hour infusion of SHP635 in increasing doses
  - fasting, on no calcium or calcitriol

Results







Next steps:

- Different doses and/or longer exposure
- Use in other forms of hypoparathyroidism to decrease urine calcium?
- Applications in idiopathic hypercalciuria?

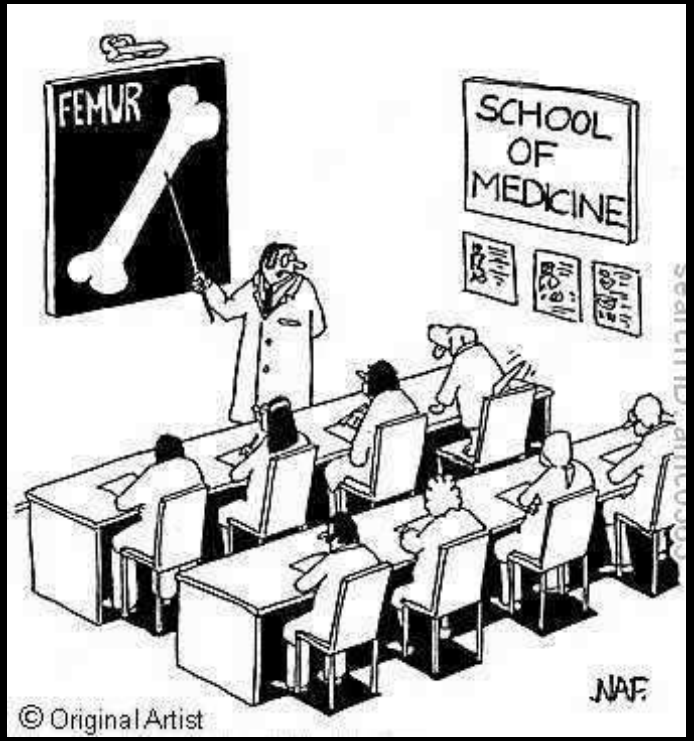
Long-term, rigorous pediatric trials are needed!

NIH
Michael Collins
Marilyn Kelly
Beth Brillante
James Reynolds
Alison Boyce
Lori Guthrie
Jaime Brahim
Andrea Burke
Mary Scott Ramnitz
Cemre Robinson
Tiffany Hu

CNMC
Laura Tosi

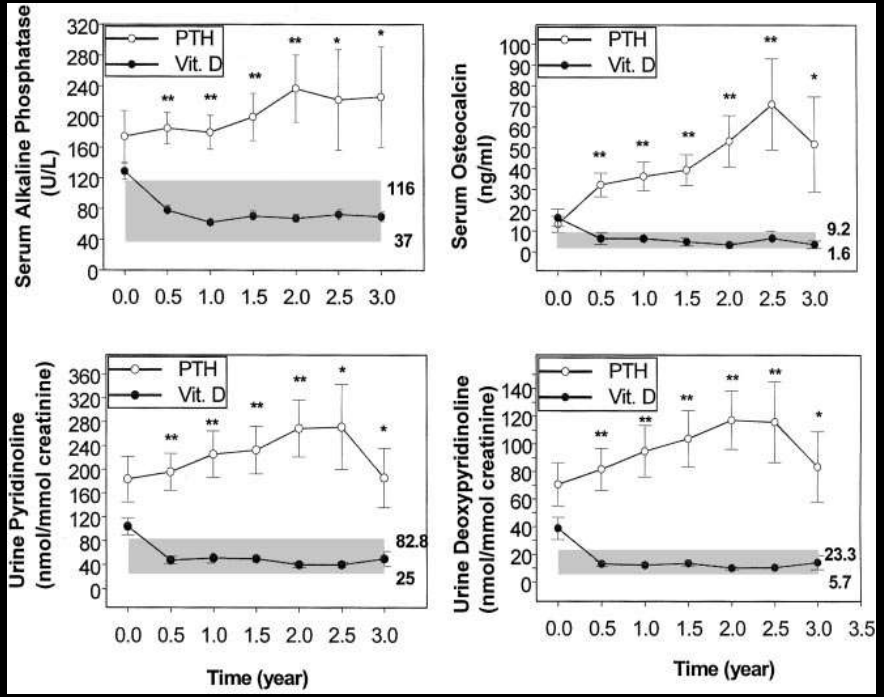
Helen Hayes Hospital
David Dempster
Hua Zhou

Ludwig Botlzmann Inst.
Klaus Klaushofer
Paul Roschger



How does PTH therapy affect the skeleton in hypoparathyroidism?

BID PTH 1-34 vs Calcitriol x 3 yr



No significant differences in BMD between the groups. BMD Z-scores in the femoral neck trended up, distal radius Z-scores trended down in PTH group

Winer, et al, JCEM, 2003

Daily Parathyroid Hormone 1-34 Replacement Therapy for Hypoparathyroidism Induces Marked Changes in Bone Turnover and Structure

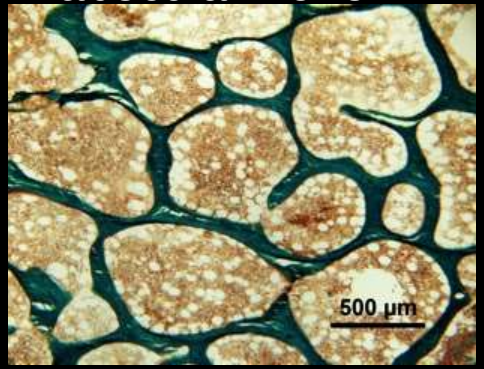
Gafni, et al, JBMR, 2012

- Pilot study – 2 adults, 3 teens treated with BID PTH 1-34 for 18 months

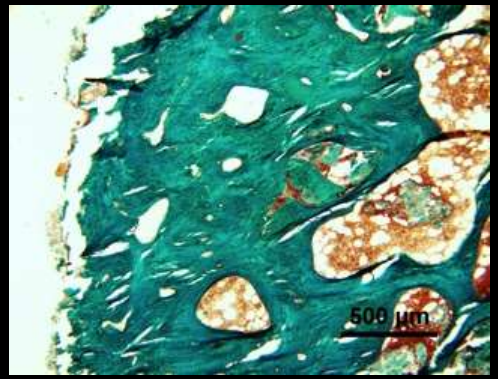
RESULTS:

- Bone markers - increased and stayed markedly elevated
- DXA - increased in total hip, decreased in 1/3 radius
- Bone biopsies – increased bone volume, increased turnover, increased cortical porosity

Trabecular Bone



Cortical Bone



Baseline

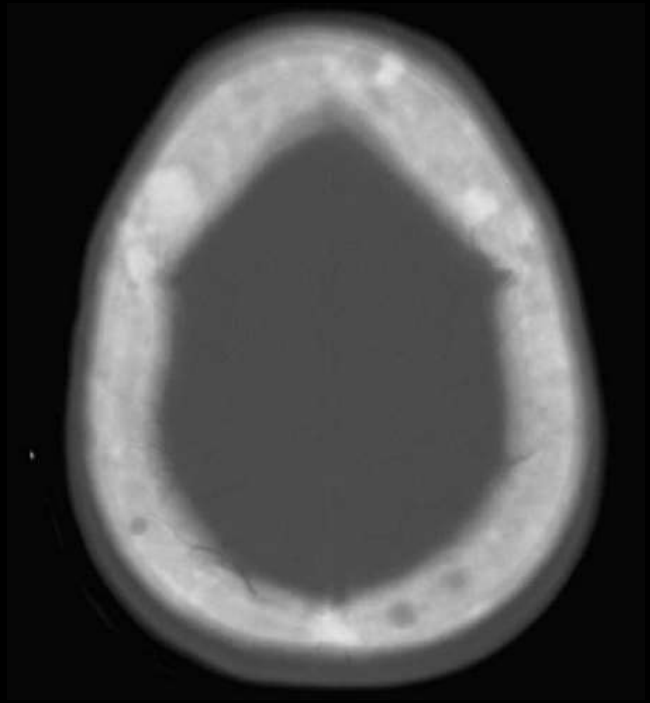
Gafni, et al, JBMR, 2012

PTH(1-34) Replacement Therapy in a Child With Hypoparathyroidism Caused by a Sporadic Calcium Receptor Mutation

Todd A Theman,[1,2] Michael T Collins,[1,2] David W Dempster,[3] Hua Zhou,[3] James C Reynolds,[4] Jaime S Brahim,[5] Paul Roschger,[6] Klaus Klaushofer,[6] and Karen K. Winer[7]

JBMR: 24(5), 2009

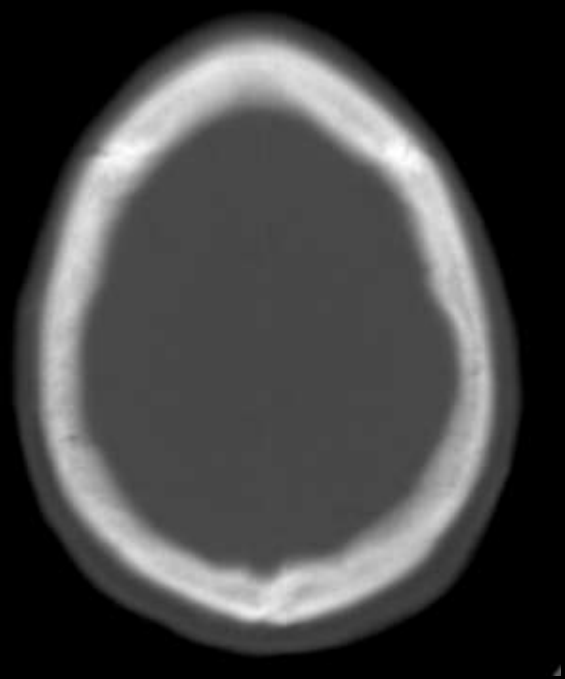
- 20 y/o woman with CaSR mutation
- Treated for 14 years continuously with PTH 1-34
- Urine calcium remained elevated
- No nephrocalcinosis at age 6; extensive nephrocalcinosis by age 19
- Osteocalcin was elevated for age throughout treatment
- BMD increased in the spine and hip AFTER puberty; radius BMD was DECREASED throughout
- Trabecular bone volume +4 SD on iliac crest biopsy



Theman, et al, JBMR 2009

Head CT of patient at 18y:

Diffusely thickened calvarium with patchy sclerotic and lytic lesions

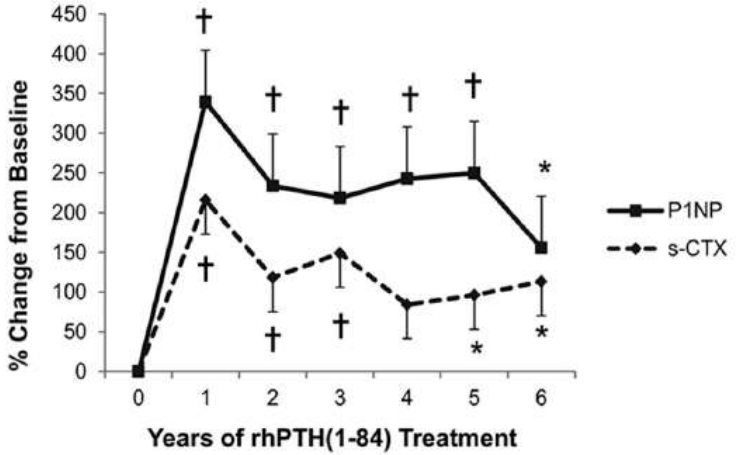


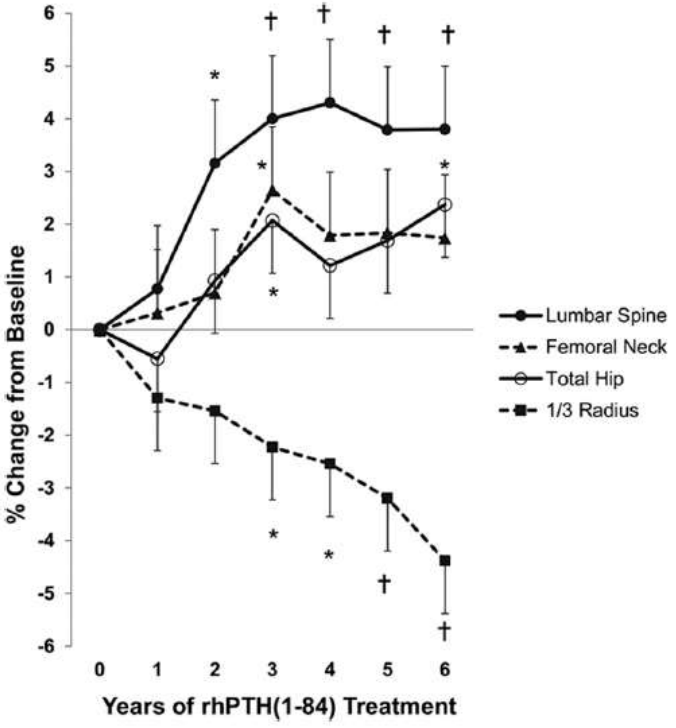
Head CT of adult with CaSR mutation not treated with PTH

PTH 1-84 Effects on Bone

- Rubin et al., Osteopor Int 2009, JBMR 2011
  - 64 adults, 100 mcg QOD x 2 years
  - INCREASED spine BMD, DECREASED radius BMD by DXA
  - Persistently increased bone turnover markers
  - Increased trabecular bone with tunneling, bone formation rate, mineralizing surface, and cortical porosity
- Sikjaer et al., JBMR 2011
  - 62 adults, placebo-controlled, 100 mcg QD x 6 months (hypercalcemic)
  - DECREASED areal BMD at hip, spine, and total body with NO change in distal radius by DXA
  - Bone markers extremely elevated
  - Decreased trabecular density, increased tunneling, trend increased cortical porosity

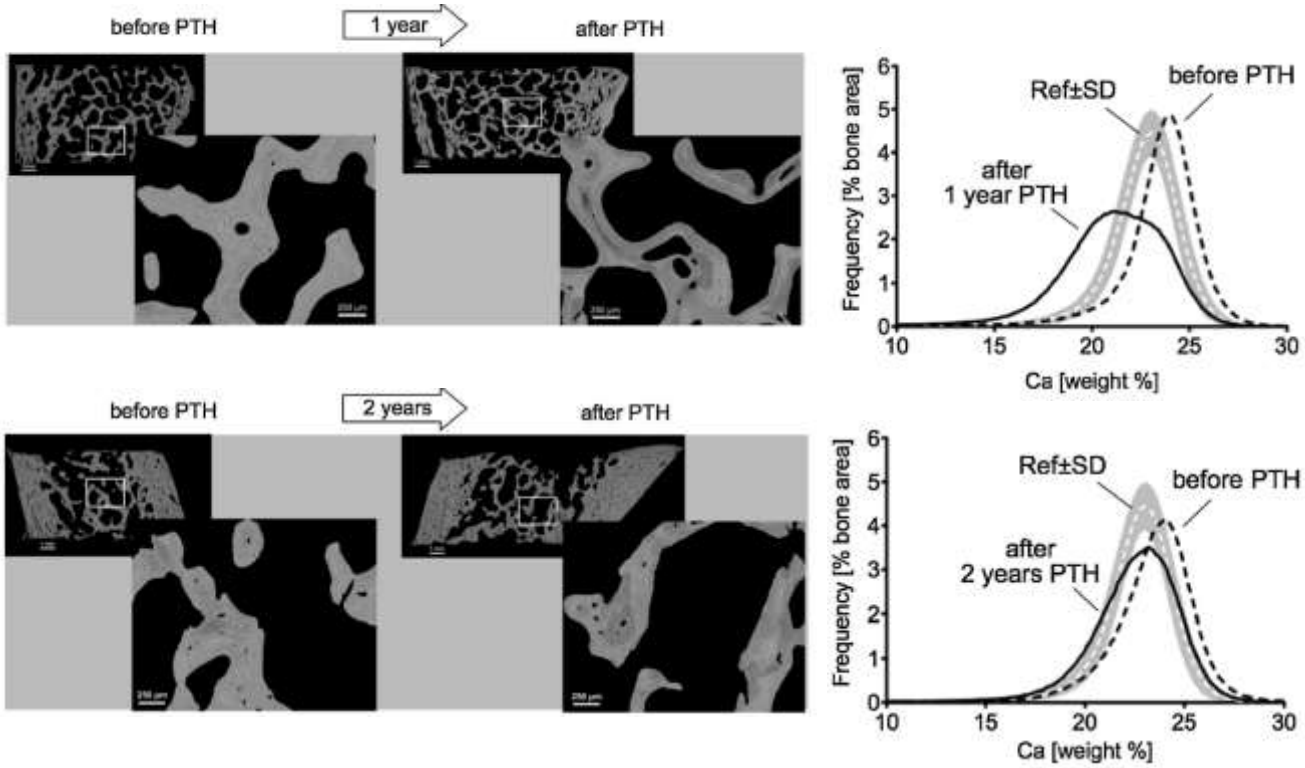
PTH 1-84 Bone Markers and DXA





Rubin, et al, JCEM, 2016

PTH 1-84 transiently decreases mineralization



Misof, et al, JBMR, 2016

LA- PTH (long-acting PTH)

- Mass General Hospital (Boston) and Chugai Pharmaceutical Co (Japan)
- Recent study - daily injections at different doses for 28 days in hypoparathyroid rats
- Results (excluding highest dose of drug):
  - longer effect on blood calcium
  - normalization of phosphate
  - normal urine calcium
  - no significant effects on bone

Shimizu, et al JBMR, 2016

PCO371 – PTH receptor activator

- Chugai Pharmaceutical Co (Japan)
- Daily oral PCO371 for 4 weeks in hypoparathyroid rats
- Results:
  - increased blood calcium
  - decreased alfacalcidiol (similar to calcitriol) requirements
  - decreased urine calcium

Tamura, et al Nature Communications, 2016

What happens when you stop PTH therapy?

Subjects

- 8 subjects, mean age 37 ± 13 y
- Duration of PTH therapy: 46 mo (19.8-61.3)
- PTH 1-34 dose 0.54 ± 0.23 mcg/kg/d

- The first patient to stop PTH became markedly hypocalcemic so a weaning protocol was developed

Gafni, et al JBMR, 2015;30(11): 2112-2118.

Weaning Regimen

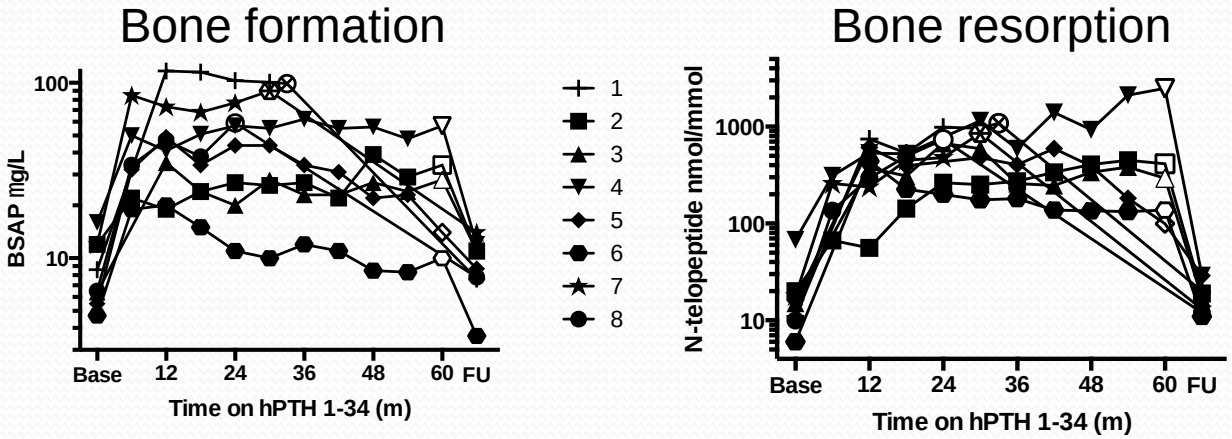
	Before PTH	While on PTH
Calcium (mg/d)	1425 ± 656	514 ± 565
Calcitriol (mcg/d)	0.69 ± 0.22	0

- Calcium and calcitriol doses were started at about twice the pre-PTH doses
- Serum calcium was checked 1-2 times per week
- PTH weaning was started once calcium level approached 9 mg/dL (2.25 mmol/L)
- PTH dose was gradually decreased and calcium and calcitriol were adjusted to maintain a calcium level of 7.6-9 mg/dL (1.9-2.25 mmol/L)
- Mean duration of PTH weaning: 60 ± 34 days
- Mean time between start of wean and follow-up visit 6.3 ± 1 month

Why?

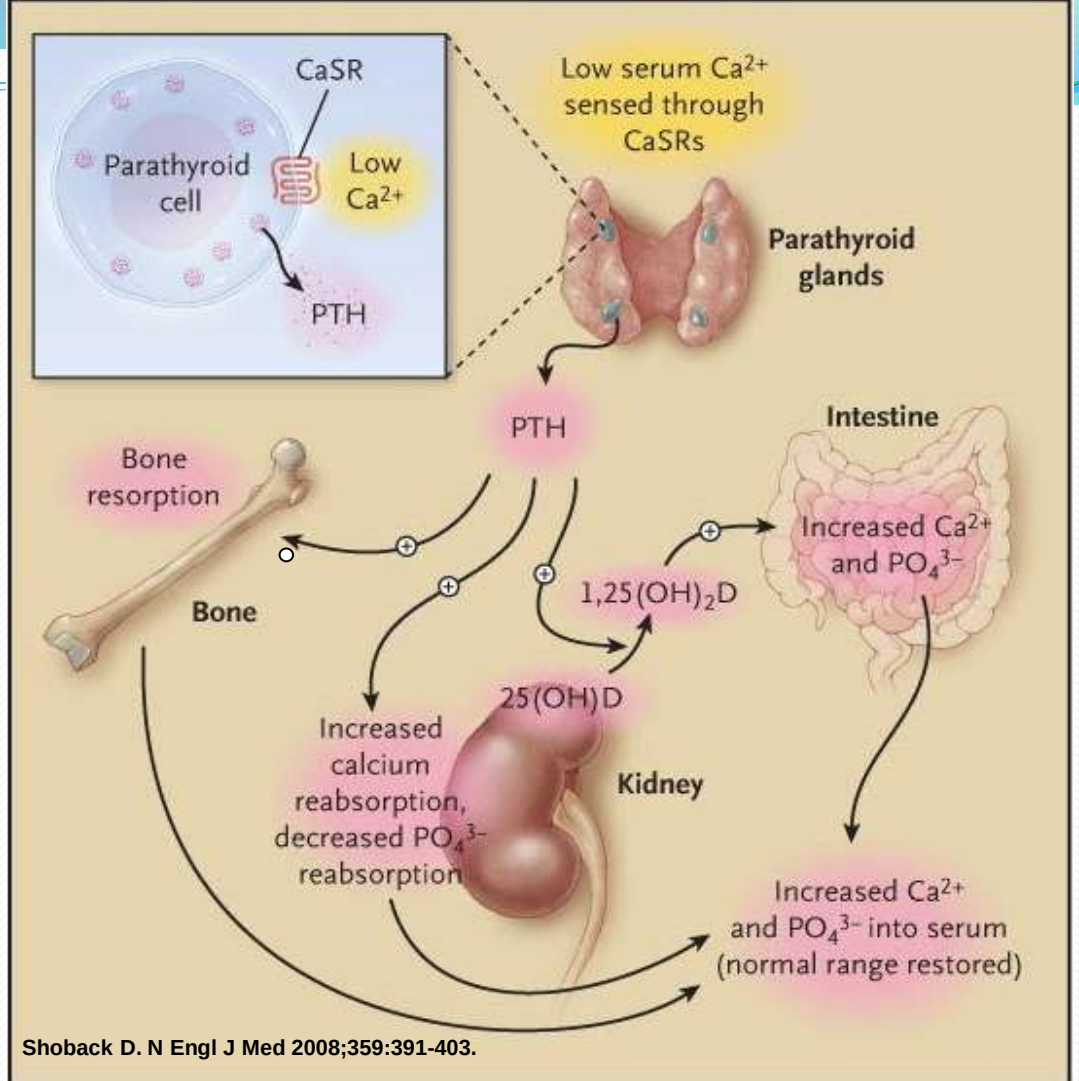
Hungry bone syndrome?

Bone turnover is high while on PTH 1-34

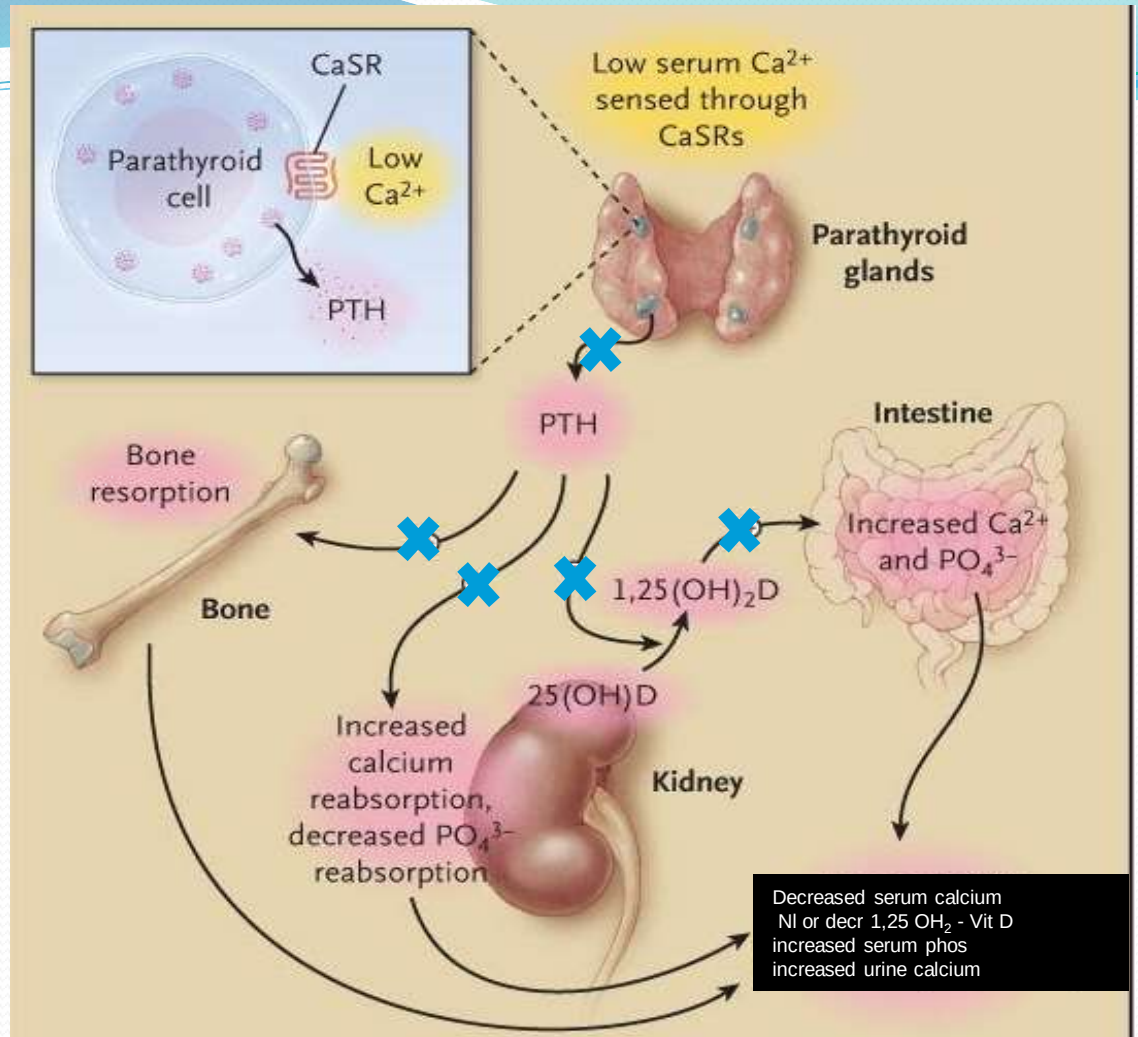


- If the PTH is stopped abruptly while the bone is still active, much of the calcium from diet and supplements gets deposited into the bone
- Extra calcium and calcitriol is needed to prevent hypocalcemia
- Bone density rose sharply at the 6 month follow-up visit, with the exception of the 1/3 radius

Gafni, et al JBMR, 2015;30(11): 2112-2118.



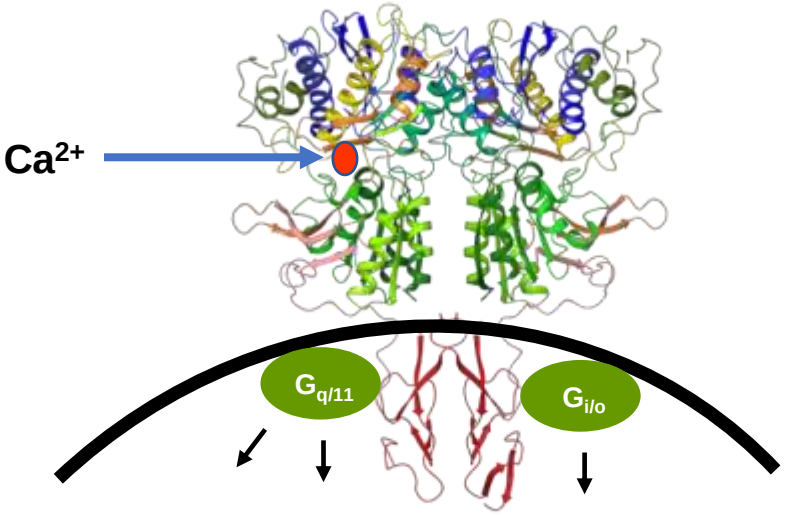
Shoback D. N Engl J Med 2008;359:391-403.



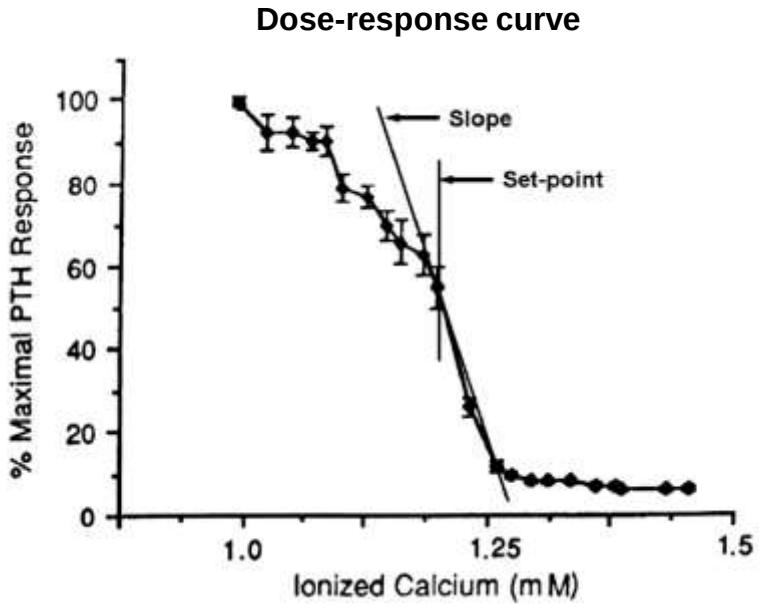
Shoback D. N Engl J Med 2008;359:391-403.

The CaSR: Master Regulator of Ca^{2+}

"Calciostat"



G protein-coupled receptor

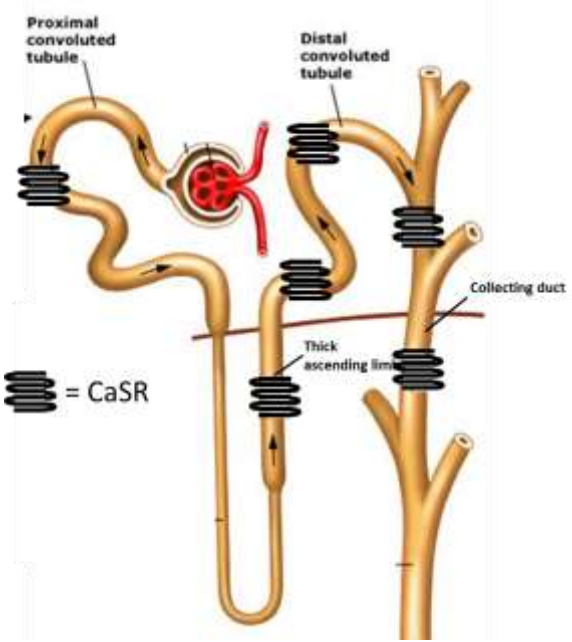


Ed Nemeth, FEBS Lett 1993 ; Brown, Nature, 1993

Renal Regulation of calcium by the Calcium-sensing receptor

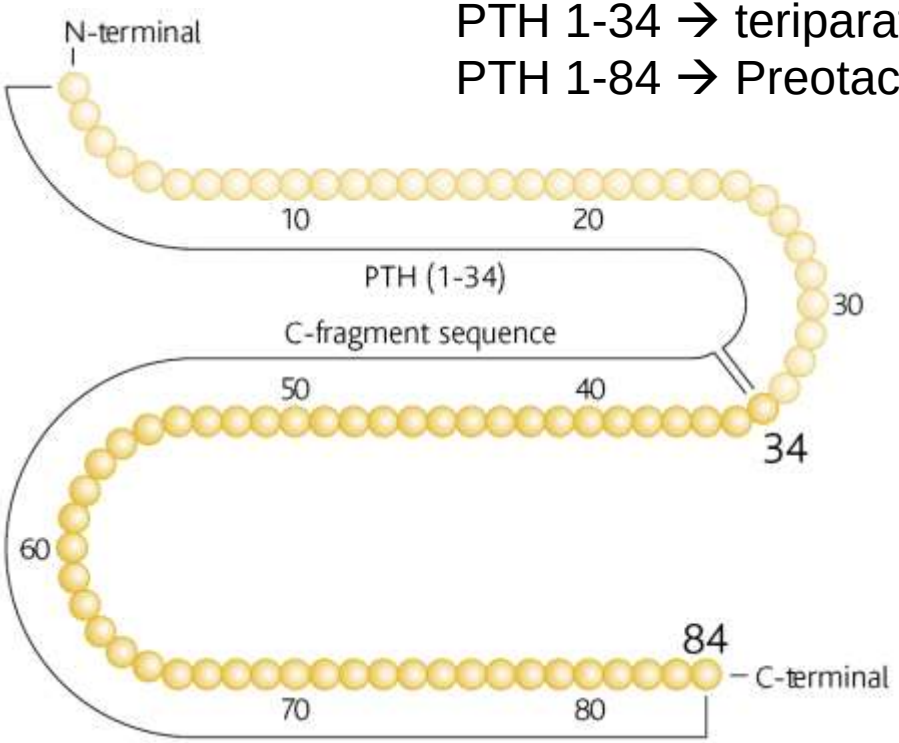
- When blood Ca is low, CaSR holds on to Ca
- When blood Ca is high, CaSR dumps Ca in urine
- Silently calcifying the kidney with overtreament

- Gain-of-function mutations in CaSR cause autosomal dominant hypoparathyroidism
- for level of blood Ca, urinary Ca is higher
- ↑ ↑ risk of renal complications



What about replacement PTH?

PTH 1-34 → teriparatide, Forteo/Forsteo™
PTH 1-84 → Preotact/Natpara/Natpar™



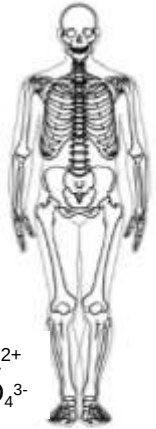
Parathyroid Hormone – It's All About the Calcium!

Tissues

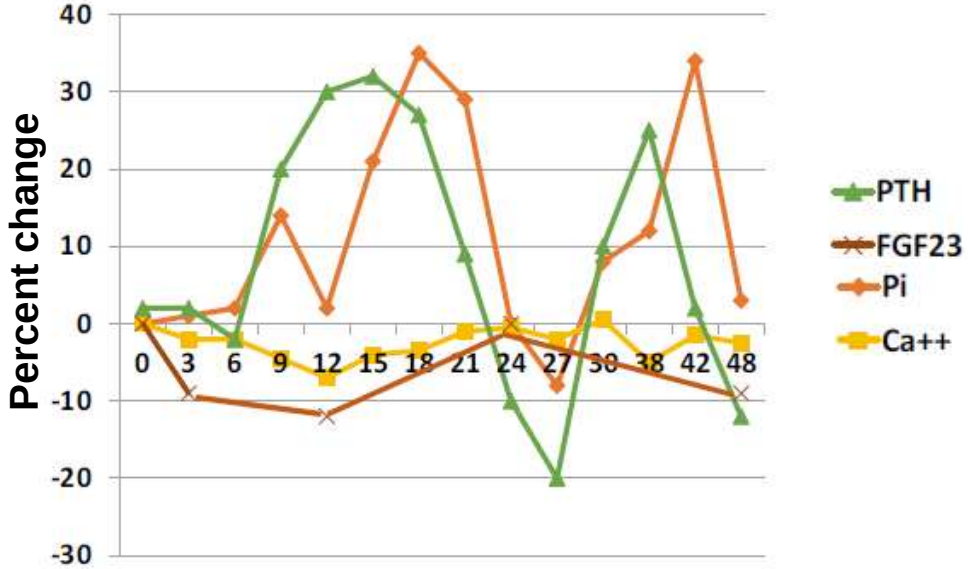
Calcium is critical for:

- Neural function
- Muscle function
- Cell signaling
- Cofactor

Skeleton



> 1 kg Ca^{2+}
1.6 kg PO_4^{3-}



Peacock, Cal Tiss Intl, 2020

PTH = parathyroid hormone
FGF23 = fibroblast growth factor 23
Pi = inorganic phosphate

Effect of PTH on Urine Citrate/Renal calcification

- 31 hypoparathyroid subjects, aged 16-60 (mean 39.5 y)
- Synthetic PTH 1-34 BID for up to 5 years
  - NO calcitriol
  - Calcium supplements if diet inadequate
- Doses titrated to maintain blood calcium 7.6-9 mg/dL (1.9-2.25 mmol/L)
- Renal CT and ultrasound looking for nephrolithiasis (NL) and nephrocalcinosis (NC)

- Timepoints:
  - Baseline
  - 6 months on PTH
  - Last visit on PTH
  - Follow-up (FU) after PTH

Gafni…Collins, JBMR 2018

Summary of PTH 1-34 Therapy

- Can effectively manage hypocalcemia; effects on hypercalciuria are variable
- Induces marked hypocitraturia, potentially increasing renal morbidity
- Increases bone turnover and cortical porosity
- Bone effects variable - anabolic in trabecular bone; catabolic in cortical bone
- Discontinuation is associated with a hungry bone syndrome
- Given the lack of long-term data, PTH therapy should be reserved for patients with refractory hypocalcemia

Gafni and Collins, NEJM, 2019
Yao, et al, JBMR 2022
Khan et al, JBMR 2022