Advances in the Management of Hypoparathyroidism

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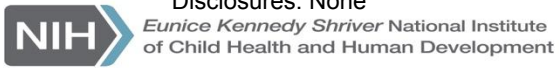
Disclosures: None



APS-1 Symposium

July 7, 2023

Hypoparathyroidism

- Low levels of PTH lead to hypocalcemia and hyperphosphatemia
- Main clinical symptoms are tetany, tingling, muscle cramps, and seizures
- Common etiology:
  - Children: genetic variants
  - Adults: damage to parathyroid gland from neck surgery
- Estimated prevalence: 30 per 100,000 individuals worldwide.

PTH, parathyroid hormone.

Mannstadt M, et al. *Nat Rev Dis Primers*. 2017;3:17055.

Hypoparathyroidism is one of the few hormonal insufficiencies not treated with replacement of its missing hormone

Conventional therapy (FDA approved)

- Active vitamin D (calcitriol; alphacalcidol)
- Calcium
- Magnesium
- Multiple pills taken 2-4 times daily

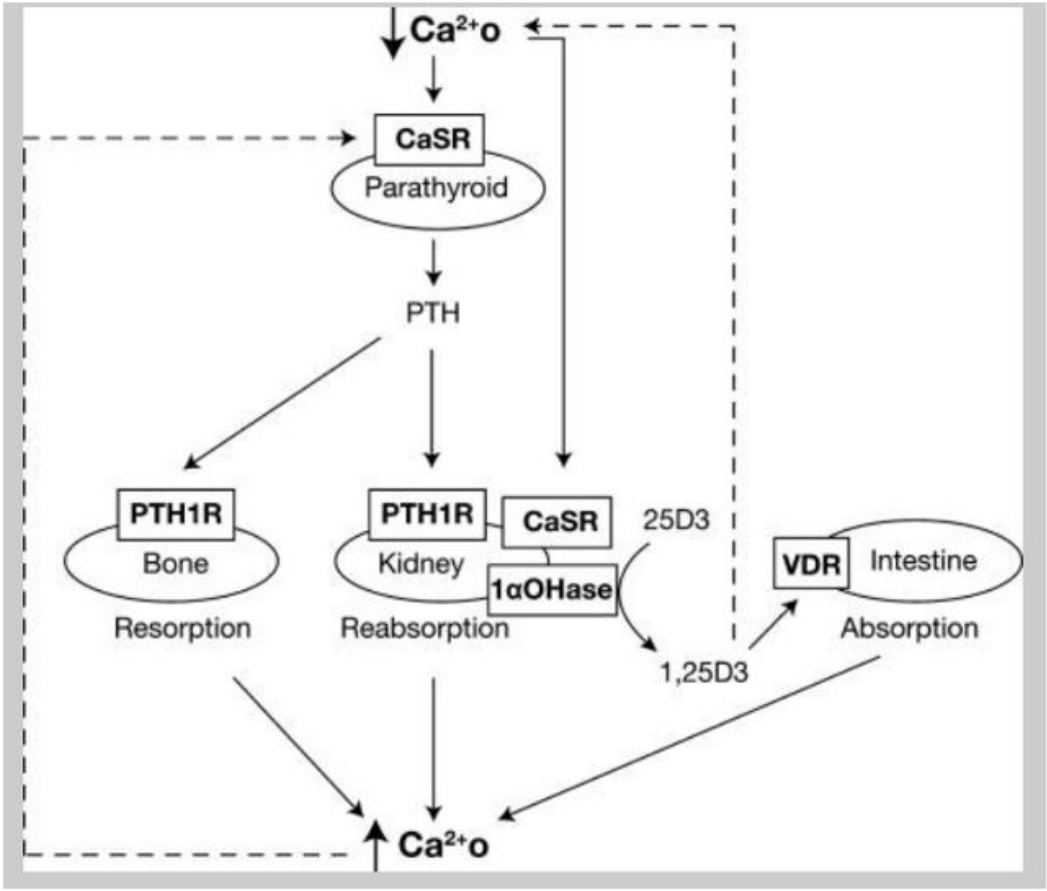
Treatment Challenges Associated with Conventional Therapy

- Relies entirely on the GI tract to raise serum calcium
- Vitamin D analogs have no direct effect on kidney to reabsorb calcium
- High urinary calcium leads to kidney damage, renal insufficiency

Hypoparathyroidism

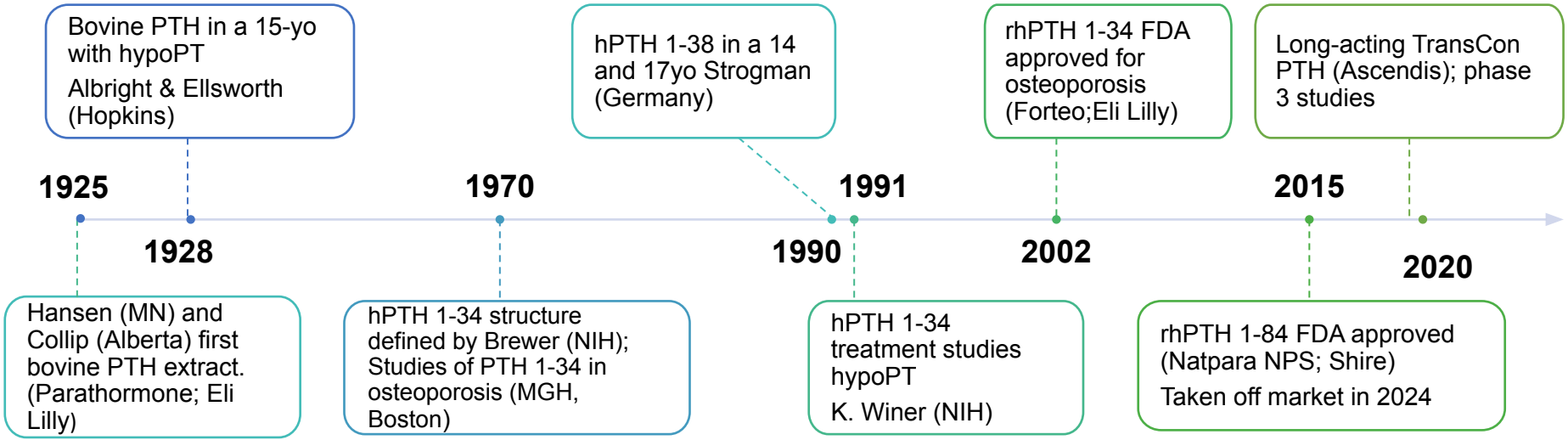
HypoPT leads to a loss of PTH-mediated:

- renal calcium reabsorption
- phosphaturia
- vitamin D synthesis
- bone turnover



Hannan J Mol Endo. 2016

Key Milestones in the Development of PTH as a Therapy for Hypoparathyroidism



hPTH: human parathyroid hormone; hypoPT, hypoparathyroidism; rhPTH, recombinant human parathyroid hormone.

Baseline Clinical Characteristics of Patients With HypoPT Followed Over 27 Years

192 patients with hypoPT:

- 50% children
- 64% female
- 25% post-surgical (96% Adults)
- 62% hereditary/familial

	Entire Cohort	APS-1	CaR*	Post-surgical	Idiopathic
Numbers of Patients	192	90	21	49	32
Female	123	55	16	41	11
Male	69	35	5	8	21
Children (2-19 years)	97	64	13	2	18
Adults (20-74 years)	95	26	8	47	14
Age (years) at baseline	26	18	18	47	23
Age (years) at disease onset	15 ± 17	6 ± 4	7 ± 12	38 ± 13	13 ± 13
Duration of Disease (mean ± SD years)	11 ± 11	12 ± 13	11 ± 6	9 ± 10	10 ± 9
Duration on Protocol (mean ± SD years)	3 ± 5	4 ± 6	5 ± 4	2 ± 3	3 ± 4

APS-1, autoimmune polyglandular syndrome type 1; CaR, gain-of-function mutation in the *CaSR* gene; hypoPT: hypoparathyroidism.

Winer KK, et al. *Bone*. 2021;149:115977.

Baseline Imaging of ~50% of Patients With HypoPT on Conventional Therapy Showed Renal or Brain Calcifications

Baseline imaging at baseline:

- Renal calcifications
  - APS-1: 60%
  - CaR: 100%
  - PS: 20%
- Brain calcifications
  - APS-1: 50%
  - CaR: 80%
  - PS: 0%

Etiology of HypoPT	Entire cohort	APS-1	CaR	Post-surgical	Idiopathic/ Familial
Kidney imaging	145	70	21	35	19
Nephrocalcinosis	77	42	21	7	7
Brain imaging	55	34	10	6	5
Brain calcification	29	17	8	0	4

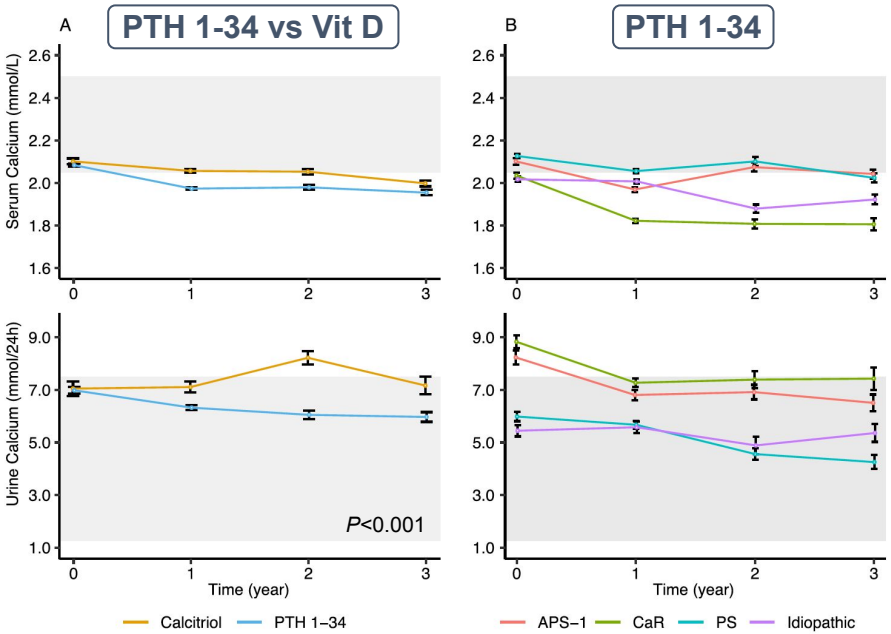
APS-1, autoimmune polyglandular syndrome type 1; CaR, gain-of-function mutation in the *CaSR* gene; hypoPT, hypoparathyroidism; PS, post-surgical.

Winer KK, et al. *Bone*. 2021;149:115977.

Comparative 3-Year Profile of Serum and Urine Calcium Levels With Twice-Daily PTH vs. Conventional Therapy

Pooled analysis of serum and urine calcium in 112 adults and children with hypoPT:

- 3-year follow-up
- PTH maintains average urine calcium in the normal range
- Response to twice-daily PTH injections varies by etiology



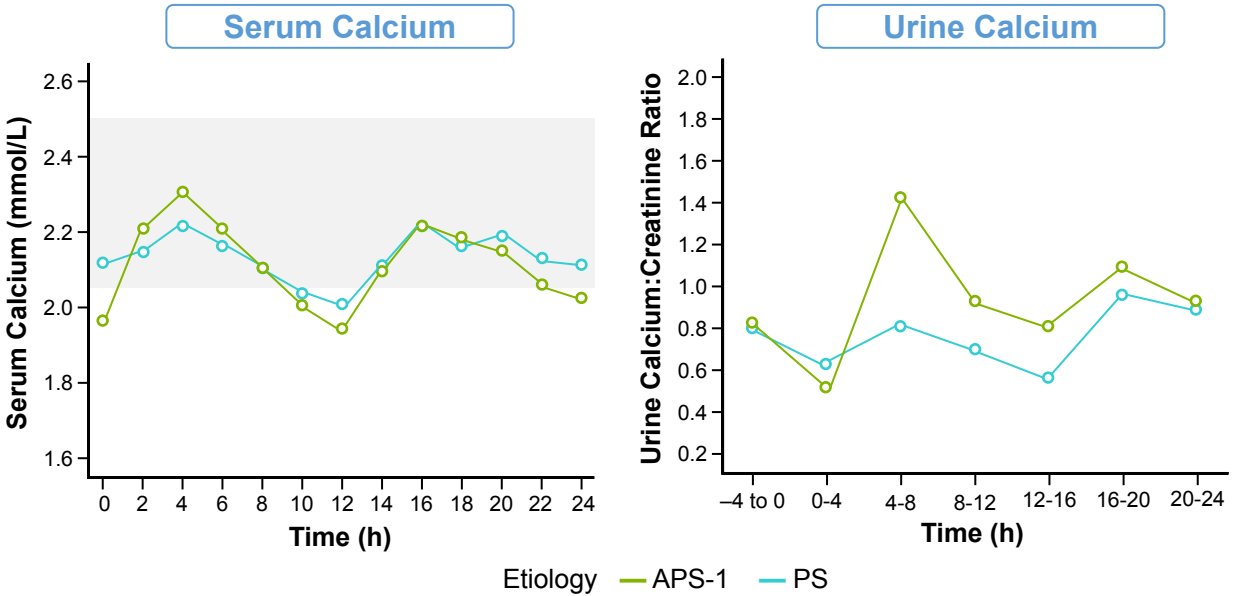
APS-1, autoimmune polyglandular syndrome type 1; CaR, gain-of-function mutation in the *CaSR* gene; hypoPT, hypoparathyroidism; PS, post-surgical; PTH, parathyroid hormone.

Winer KK, et al. *Bone*. 2021;149:115977.

Calcium Patterns in Response to Twice-Daily PTH 1-34: U-Calcium differs Post-Surgical vs APS-1 Etiologies

Pooled analysis in 35 patients with hypoPT:

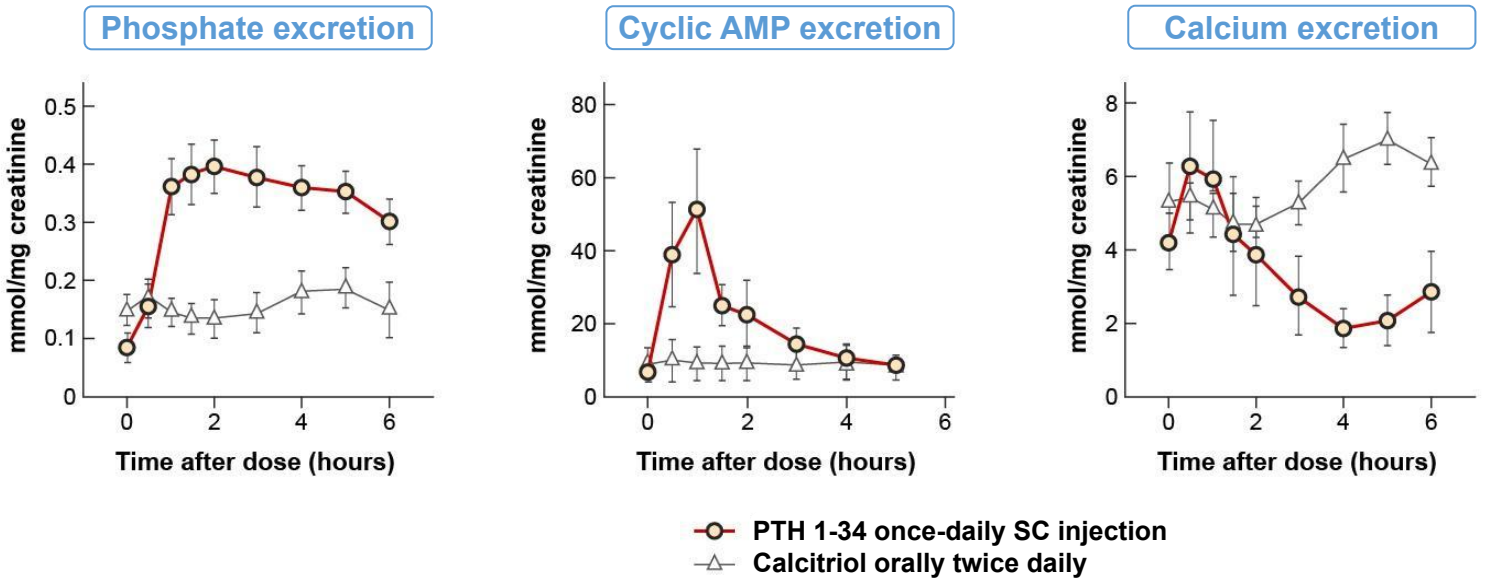
- 24-h response to twice-daily PTH injections (t = 0, 12 h)
- Etiologies: 13 APS-1, 22 PS



APS-1, autoimmune polyglandular syndrome type 1; hypoPT, hypoparathyroidism; PD, pharmacodynamic; PS, post-surgical; PTH, parathyroid hormone.

Winer KK, et al. *Bone*. 2021;149:115977.

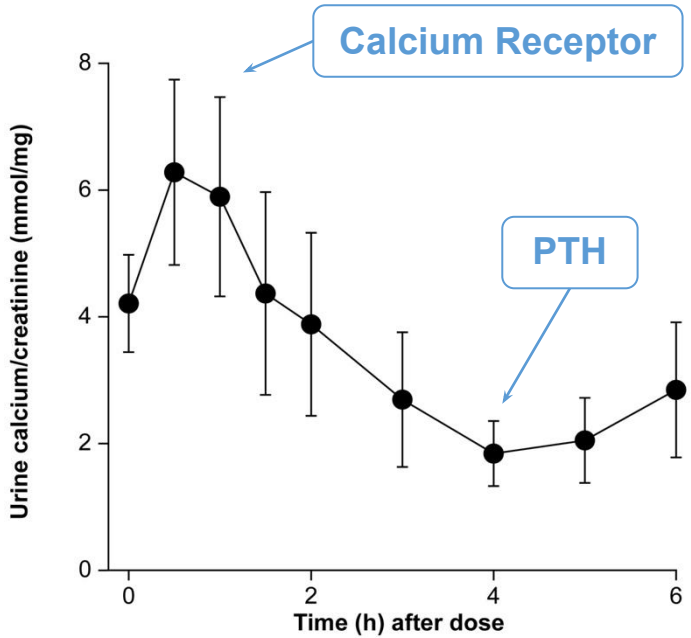
Comparative Pharmacodynamic (PD) Responses to PTH 1-34 vs Calcitriol in Patients With HypoPT



AMP, adenosine monophosphate; hypoPT, hypoparathyroidism; PTH, parathyroid hormone.

Winer KK, et al. *JAMA*. 1996;276(8):631-636.

PTH Induces a Biphasic Response in Calcium Excretion



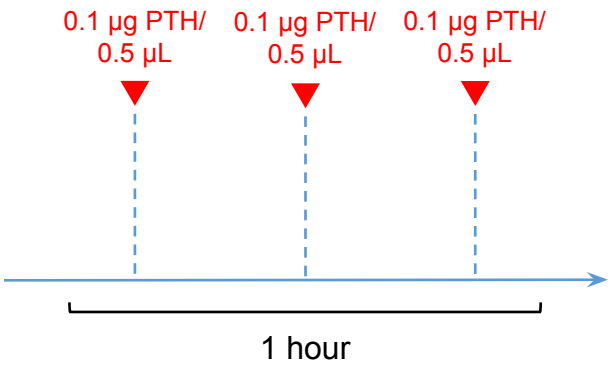
- Magnitude of the initial rise in UCa is PTH-dose dependent
- Hypothesis: Hypercalciuria could be mitigated by increasing injection frequency with smaller PTH doses
- Twice daily injections led to a reduction of PTH dose by 50%

Normal PTH Physiology May Be Replicated by Delivery of PTH Microboluses by Pump

Hypothesis: PTH given via pump will mimic normal physiology and maintain blood and urine calcium within a narrow range of normal.

Example:

- 7.2 µg PTH/day
- 3 pulses/hour



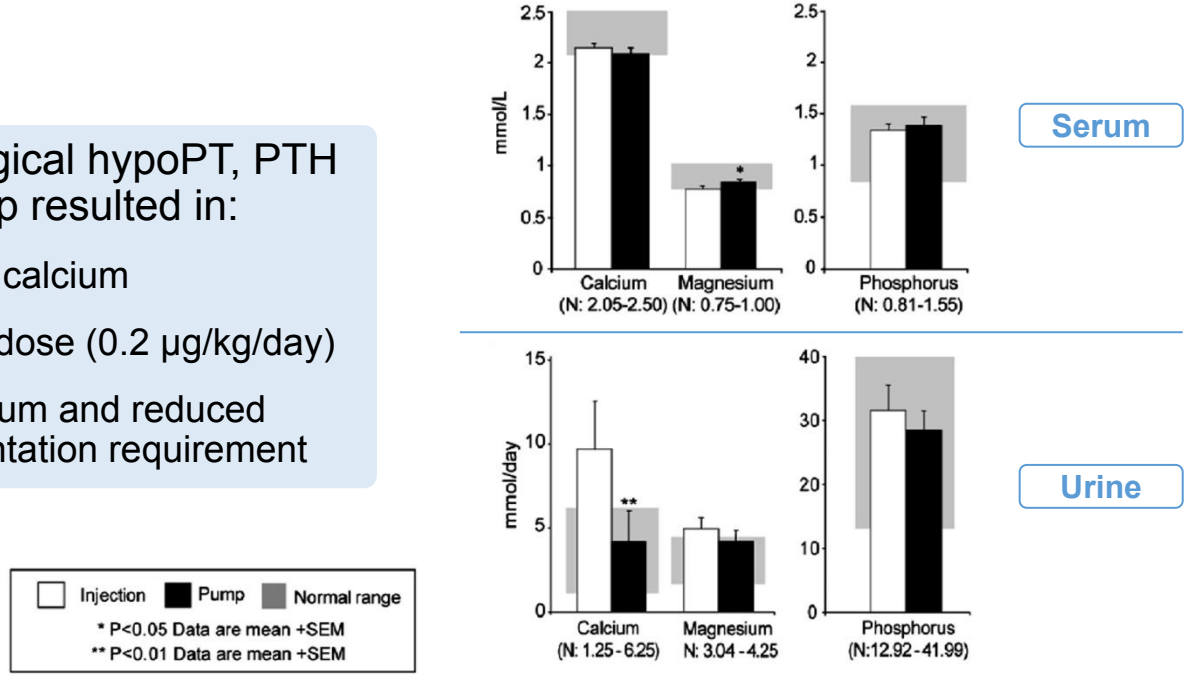
Omnipod® insulin pump (Insulet) for PTH delivery

PTH, parathyroid hormone.

Pump Delivery of PTH 1-34 Produces Normal Serum and Urine Minerals

In adults with post-surgical hypoPT, PTH 1-34 delivered by pump resulted in:

- 50% reduction in urine calcium
- 65% reduction in PTH dose (0.2 µg/kg/day)
- Higher serum magnesium and reduced magnesium supplementation requirement

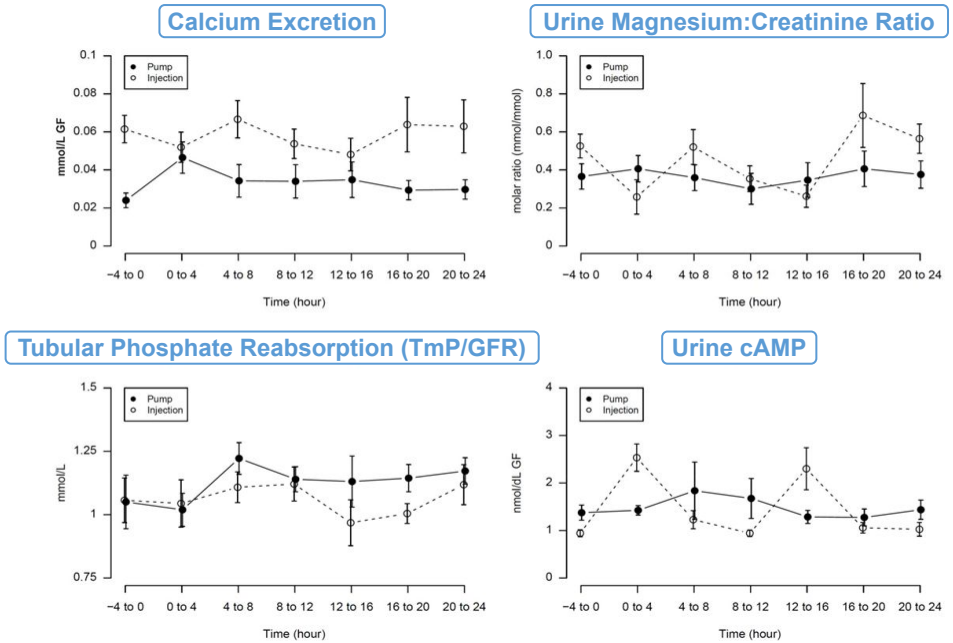


BID, twice daily; hypoPT, hypoparathyroidism; PTH, parathyroid hormone; SC, subcutaneous; SEM, standard error of the mean; TmP, tubular maximum reabsorption of phosphate.

Winer KK, et al. *J Clin Endocrinol Metab*. 2012;97(2):391-399.

Pump Delivery of PTH 1-34 Produces Improved Circadian Patterns in Urine Excretion vs Twice-Daily SC Injections

- 8 adults with post-surgical hypoPT
- Reduced fluctuation for urinary calcium, magnesium, phosphate, and cAMP (*P*<0.01 pump vs twice-daily PTH)

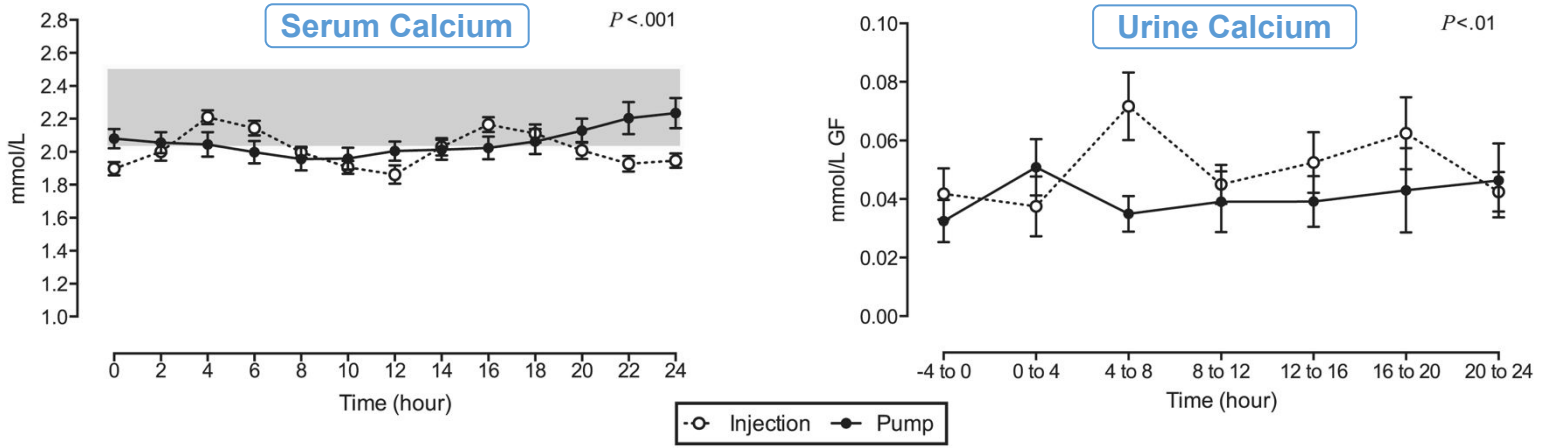


cAMP, cyclic adenosine monophosphate; GFR, glomerular filtration rate; hypoPT, hypoparathyroidism; PTH, parathyroid hormone; SC, subcutaneous; TmP, tubular maximum reabsorption of phosphate.

Winer KK, et al. *J Clin Endocrinol Metab*. 2012;97(2):391-399.

Pump Delivery of PTH 1-34 Produces Improved Serum and Urine Calcium Profiles vs Twice-Daily SC Injections

- 7–20-year-old patients with APS-1 (n=5) or ADH (n=7)
- Pump delivery improved serum and urine calcium with minimal fluctuations



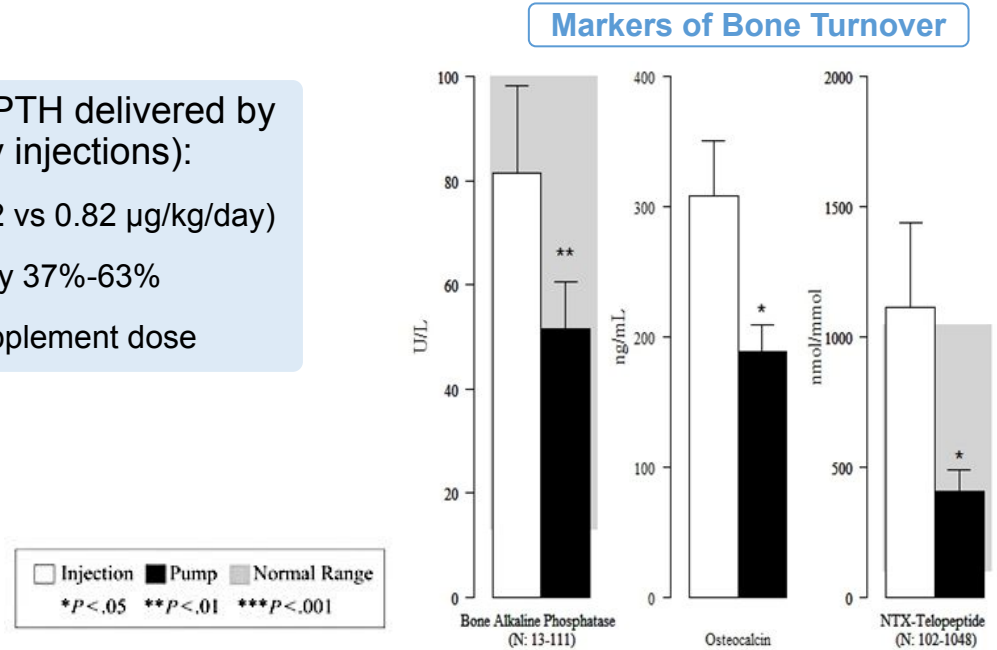
ADH, autosomal dominant hypocalcemia; APS-1, autoimmune polyglandular syndrome type 1; PTH, parathyroid hormone; SC, subcutaneous.

Winer K, et al. *J Pediatr*. 2014;165(3):556-563.

Pump Delivery of PTH 1-34 Reduces Markers of Bone Turnover vs Twice-Daily SC Injections

In children with APS-1 or ADH, PTH delivered by pump resulted in (vs. twice-daily injections):

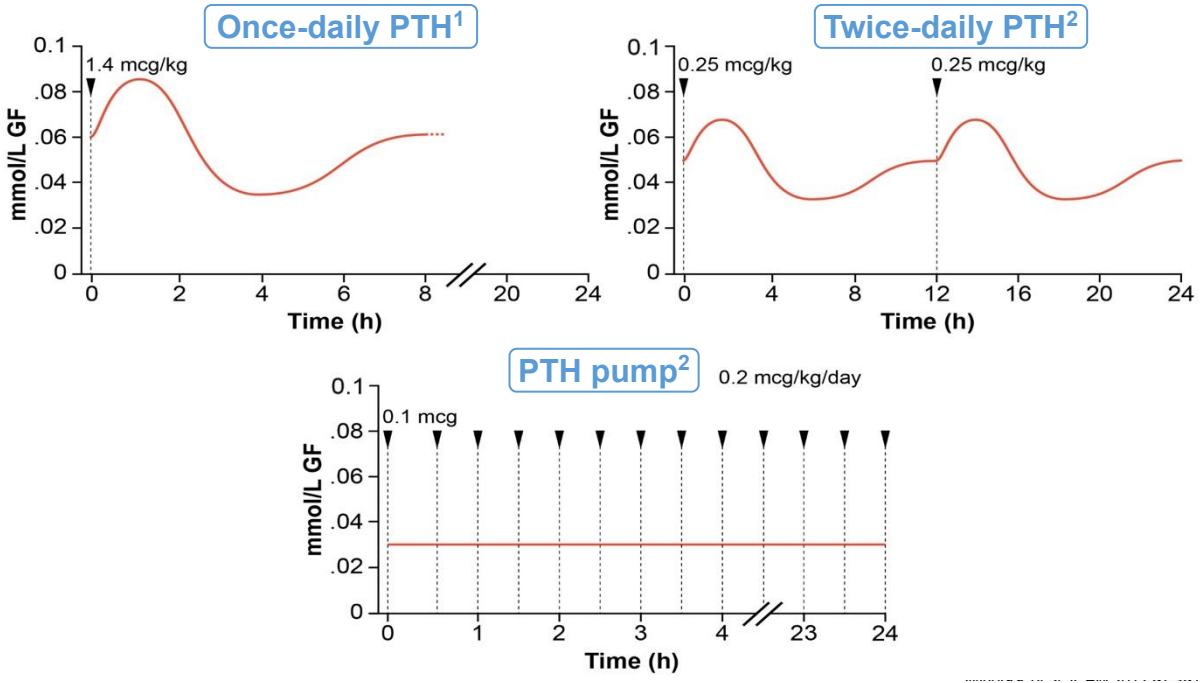
- 60% Reduction in PTH dose (0.32 vs 0.82 µg/kg/day)
- Bone turnover markers reduced by 37%-63%
- 40% reduction on magnesium supplement dose



ADH, autosomal dominant hypocalcemia; APS-1, autoimmune polyglandular syndrome type 1; PTH, parathyroid hormone; SC, subcutaneous.

Winer K, et al. *J Pediatr*. 2014;165(3):556-563.

Increase in PTH 1-34 Injection Frequency Reduces Dose and Urine Calcium Excretion



GF, glomerular filtrate; PTH, parathyroid hormone.

1. Winer KK, et al. *JAMA*. 1996;276(8):631-636. **2.** Winer KK, et al. *J Clin Endocrinol Metab*. 2012;97(2):391-399.

Long-term Effects of PTH 1-34 Therapy in Adults and Children With HypoPT

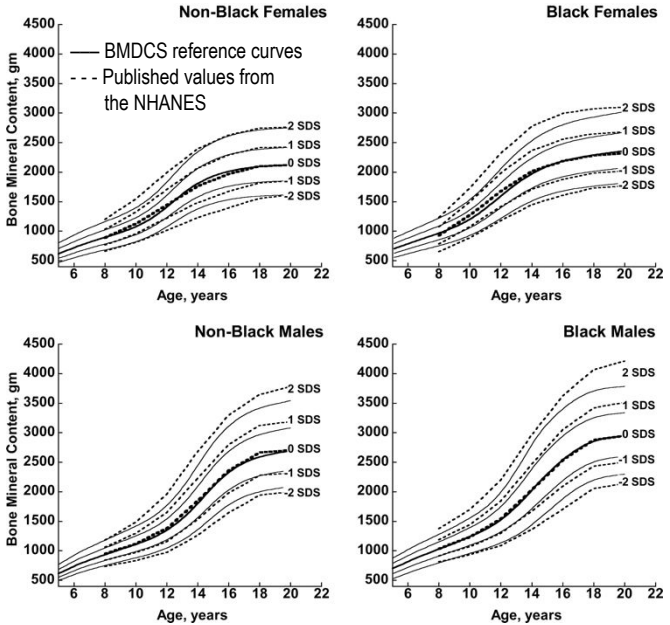
Risk Factors for Osteoporosis in APS-1

1. Malabsorption leading to poor weight gain and linear growth
2. GH deficiency
3. Hypogonadism, delayed puberty, irregular menses in women
4. Chronic inflammation
5. Use of pharmacological doses of corticosteroids[1]

1. Hardy RS, et al. *Endocr Rev*. 2018;39(5):519-548.

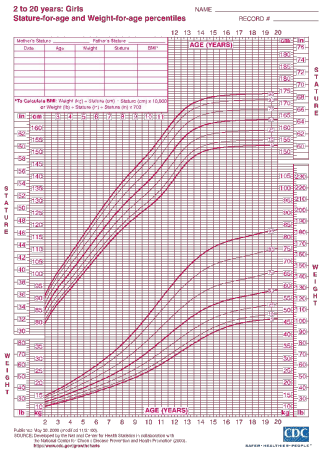
Bone Growth Reference Curves Resemble CDC Percentile Growth Charts

Reference Curves for Bone Density[1]

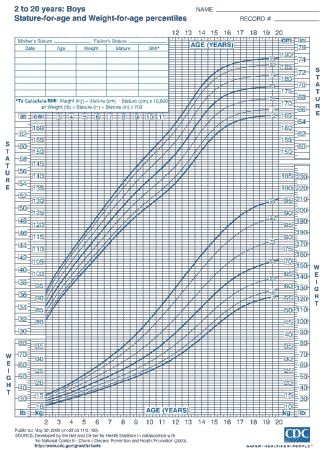


CDC Percentile Growth Charts[2]

Girls (2-20 Years Old)



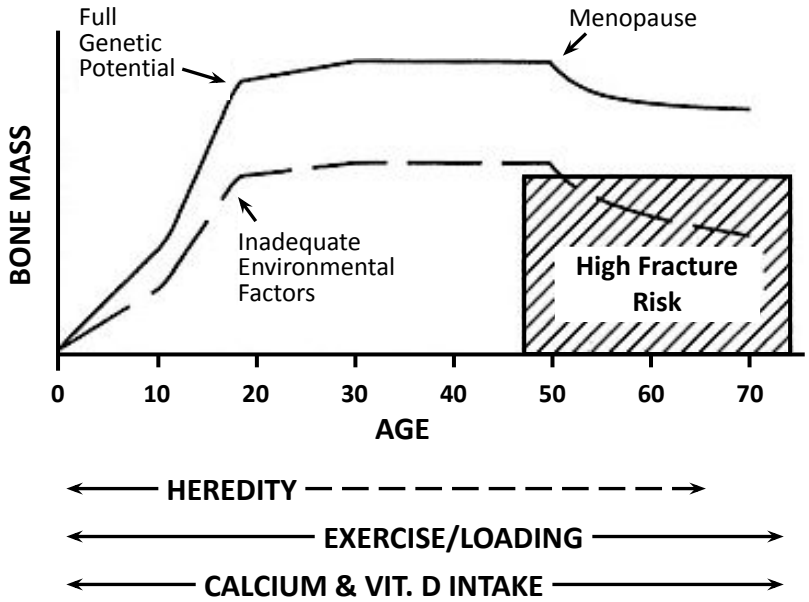
Boys (2-20 Years Old)



BMC, bone mineral content; BMDCS, Bone Mineral Density in Childhood Study; NHANES, National Health and Nutrition Examination Surveys.

1. Zemel BS, et al. *J Clin Endocrinol Metab*. 2011;96(10):3160-3169. **2.** CDC Growth Charts. https://www.cdc.gov/growthcharts/clinical_charts.htm

Bone Mass Life-Line in Women: Normal vs Compromised Peak Bone Mass Development

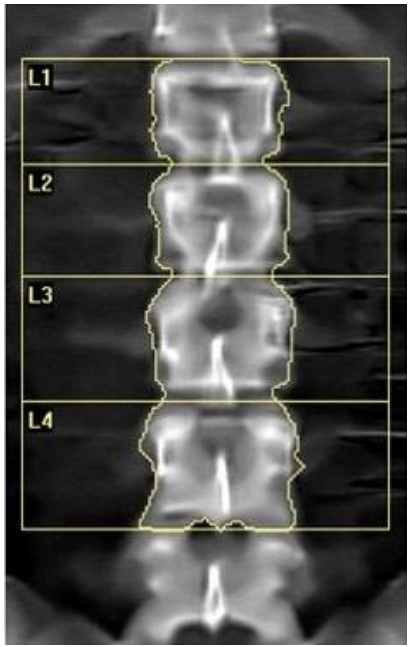


Heaney RP, et al. *Osteoporos Int.* 2000;11(12):985-1009.

DXA Is Used to Evaluate Bone Mineral Density

- Compared to reference norms
- In children, normal bone acquisition tracks along percentiles
- Abnormal scans are red flag for change in medical management

DXA of lumbar spine



DXA, dual energy X-ray absorptiometry.

Source: https://www.monash.edu/medicine/scs/research/bone-muscle/clinical-imaging-service/dxa

Bone Turnover Markers Reflect the Activity of Osteoclasts and and Osteoblasts

Resorption Markers

C-terminal telopeptide

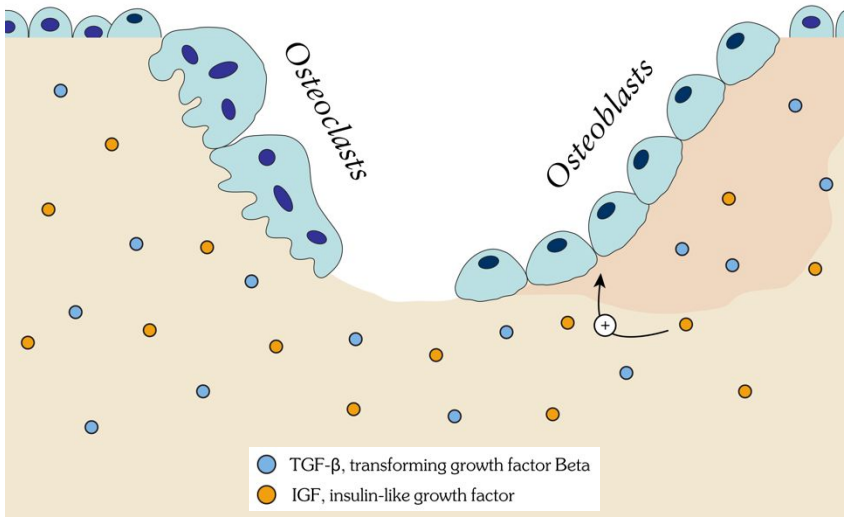
N-telopeptide (urine)

Formation Markers

Alkaline phosphatase

Osteocalcin

P1NP



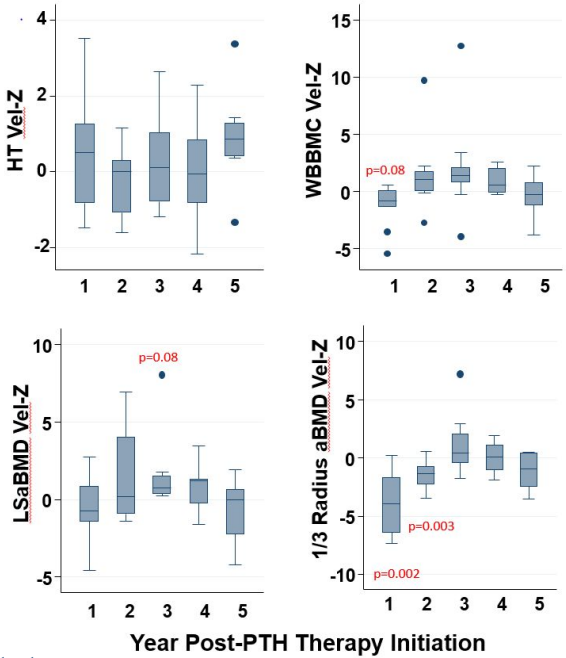
Schini M Endocrine Reviews 2023

Modified from: https://en.wikipedia.org/wiki/Bone_remodeling#/media/File:Bonemetabolism.svg

PTH 1-34 Therapy Provided Linear Growth and Bone Mineral Accrual in Children With HypoPT

Observational study in 14 children aged 7-16 years with hypoPT (APS-1 or CaR) receiving twice-daily PTH 1-34

- Normal height velocity
- Normal bone accrual velocity
  - Whole body
  - Lumbar Spine
  - Distal Radius-suboptimal bone accrual velocity in year 1



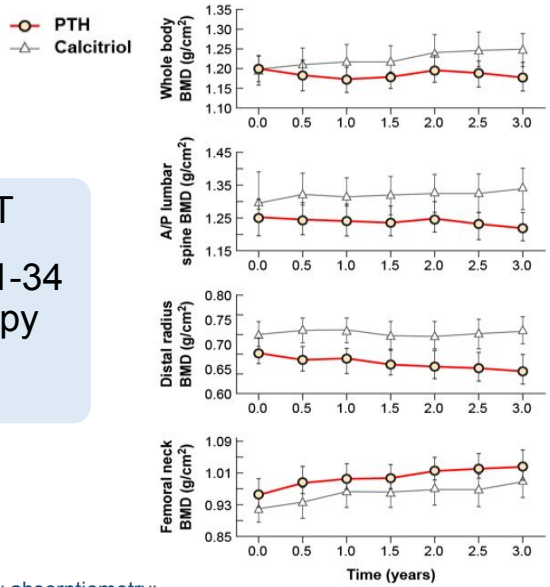
aBMD, areal bone mineral density; HT, annualized height velocity; hypoPT, hypoparathyroidism; LS, lumbar spine; PTH, parathyroid hormone; VeL-Z, velocity Z scores; WBBMC, whole body bone mineral content.

Winer K, et al. *J Pediatr*. 2018;203:391-399.

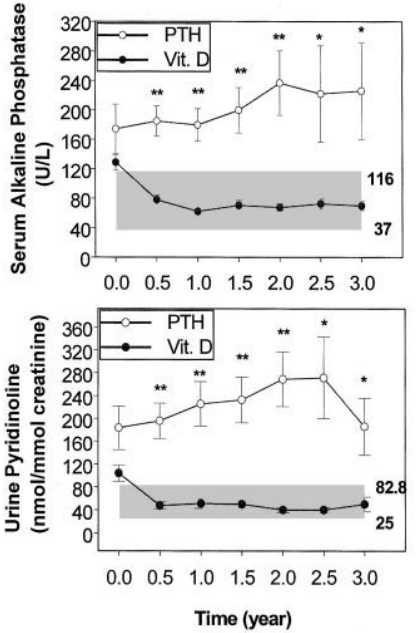
PTH 1-34 Showed no Difference in BMD vs Conventional Therapy

- 27 adults with hypoPT
- Twice-daily SC PTH 1-34 vs conventional therapy
- 3-year follow-up

BMD by DXA: PTH similar to vit. D



Bone markers remain elevated for 3 years



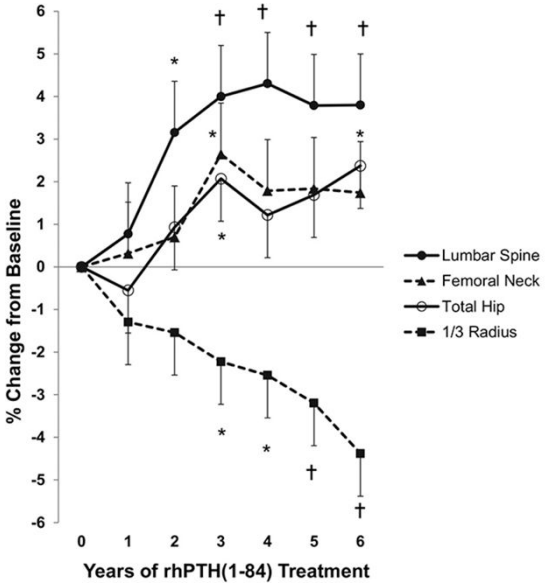
BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; hypo-PT, hypoparathyroidism PTH, parathyroid hormone; SC, subcutaneous.

Winer KK, et al. *J Clin Endocrinol Metab*. 2003;88(9):4214-4220.

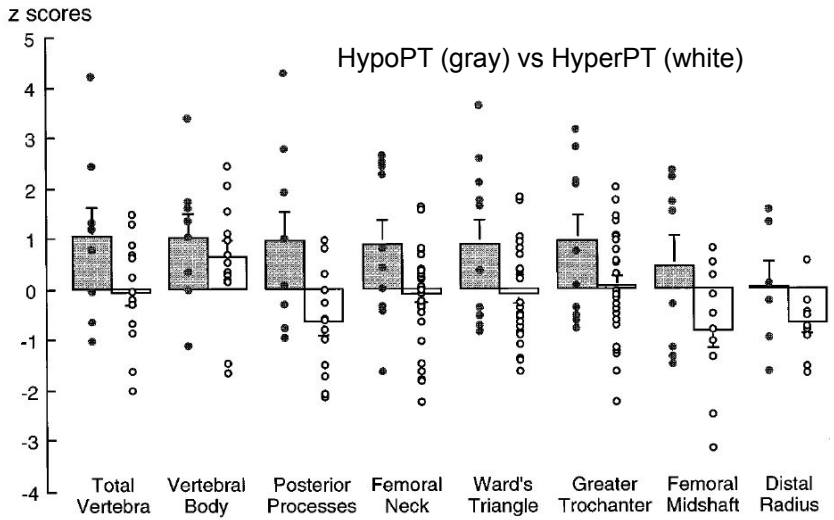
Bone density in patients with hypoparathyroidism

PTH 1-84 dosing:

- 100 µg QD or QOD for 3 years
- Lower doses of 50 µg and 75 µg introduces thereafter 3 years



Hypoparathyroidism is associated with elevated bone density in adults



HypoPT, hypoparathyroidism; PTH, parathyroid hormone, QD, once daily; QOD, once every other day.

1. *J Clin Endocrinol Metab*. 2016;101(7):2742. **2.** *J Clin Endocrinol Metab*. 1999;84(2):718-722.

Summary

- Hypoparathyroidism due to APS-1 is often refractory to conventional therapy
- PTH 1-34 given by twice-daily injections reduced mean calcium excretion compared to calcitriol therapy
    - Responses to PTH differed according to etiology.
- Twice-daily SC PTH produced normal linear growth and bone accrual in children
- Pump therapy produced the most physiologic profile of serum calcium, urine calcium excretion, and markers of bone turnover with a reduced PTH dose.
- Response to PTH delivered by pump was similar across etiologies.

APS-1, autoimmune polyglandular syndrome type 1; PTH, parathyroid hormone; SC, subcutaneous.

Emerging Therapies For Patients With HypoPT

Long-acting PTH

- TransCon™ PTH: PTH 1-34 transiently conjugated to linker and carrier molecule, which increases the half life of the PTH peptide (phase 3, adults; Ascendis)[1]

- LA-PTH: PTH/PTHrP hybrid molecule (AZP-3601); single injection calcemic effects last 48 hours (Amolyt)[2]

HypoPT, hypoparathyroidism; LA, long-acting; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein.

1. Khan AA, et al. *J Bone Miner Res*. 2023 Jan;38(1):14-25. **2.** Shimizu M, et al. *J Bone Miner Res*. 2016;31(7):1405-1412.

Thank You