Autosomal Dominant Hypocalcemia

Mary Scott Roberts, MD
Clinical Development
Calcilytix Therapeutics

ICD-10 Coordination and Maintenance Committee
September 14, 2022

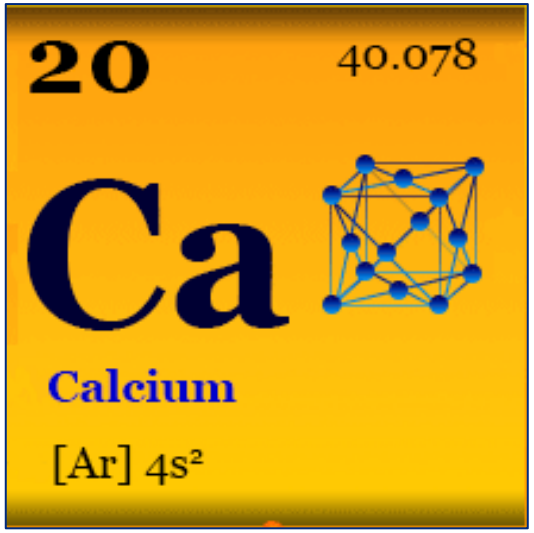
bridgebio

Executive Summary

- Calcium is an essential mineral and plays a critical role within several functions in the body.
- Parathyroid hormone (PTH) is the most important regulator of calcium levels in the blood.
- Autosomal dominant hypocalcemia (ADH) is a genetic form of hypoparathyroidism, that is characterized by low levels of calcium in the blood (hypocalcemia).
- Hypocalcemia affects multiple organs which include the musculoskeletal, renal and nervous systems.
- Although the two conditions are interrelated, ADH clinically identifies a form of hypoparathyroidism, rather than a form of hypocalcemia.

Role of Calcium

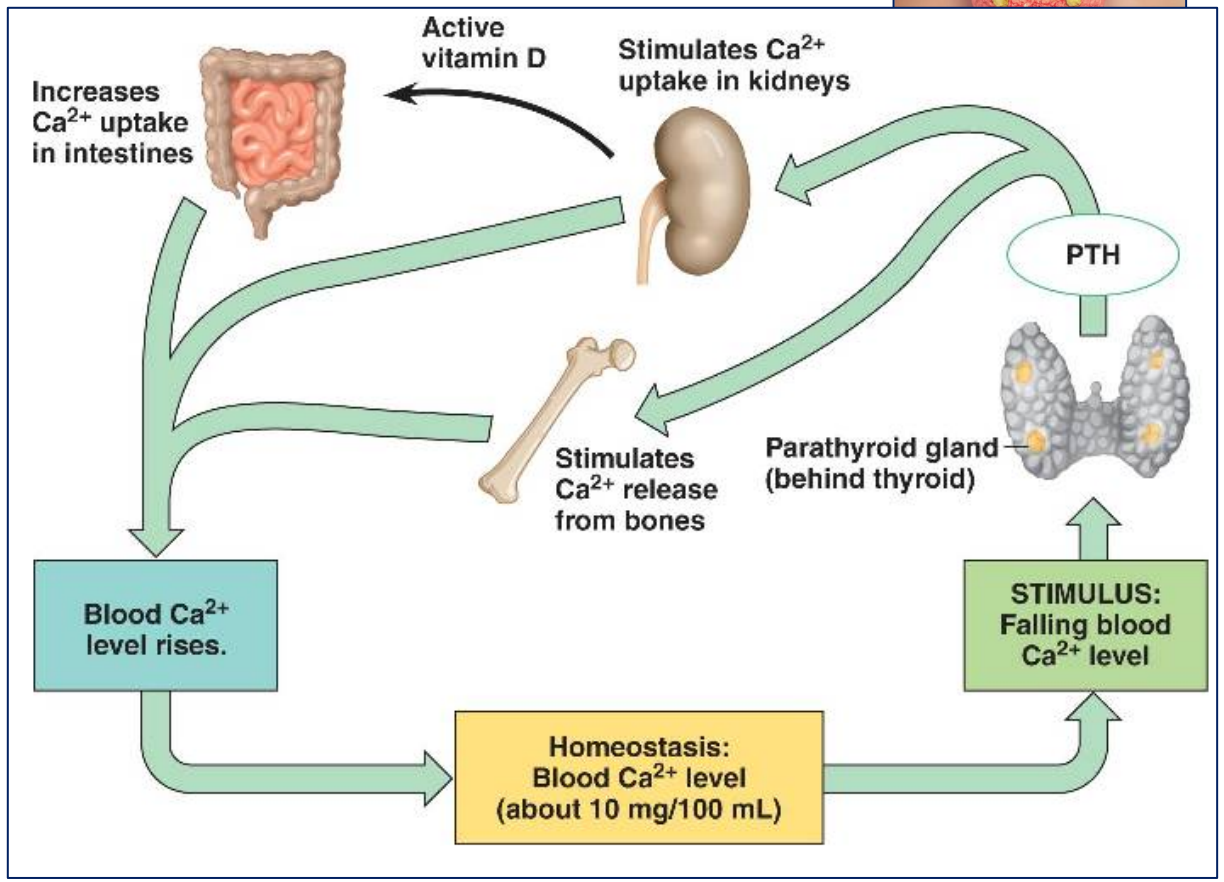
- Calcium is the most abundant mineral in the body.
- It plays a key role in:
  - ✓ Strengthening bones and teeth
  - ✓ Muscle contraction
  - ✓ Nerve conduction
  - ✓ Normal functioning of multiple enzymes
  - ✓ Blood clotting
  - ✓ Maintaining normal heart rhythm
- Because of its wide-ranging effects, the body maintains tight control over calcium levels in the blood.



Beto JA. The role of calcium in human aging. *Clin Nutr Res*. 2015;4(1):1-8. doi:10.7762/cnr.2015.4.1.1

Hypocalcemia

- Hypocalcemia is low levels of calcium in the blood.
- The body uses a feedback loop to keep blood calcium within a normal range.
  - The parathyroid glands produce PTH with several effects:
    - ✓ Bones release calcium.
    - ✓ Kidneys reabsorb calcium from urine filtrate.
    - ✓ Intestines increase absorption of calcium.



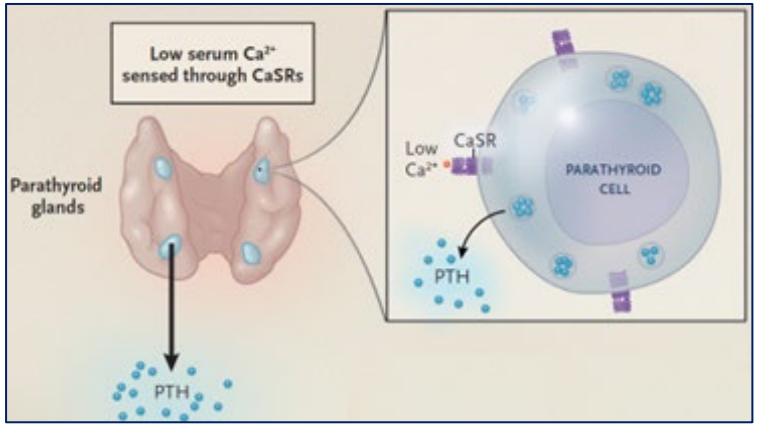
Khan M, Jose A, Sharma S. Physiology, parathyroid hormone. StatPearls Publishing; 2022.

Autosomal Dominant Hypocalcemia ADH

ADH is a genetic disorder of calcium metabolism, mediated by hypoparathyroidism.

ADH1

- This is caused by genetic mutations that alter the calcium-sensing receptor (CaSR) on the surface of parathyroid cells and renal tubules.



ADH2

- This less common type is caused by mutations in the *GNA11* gene, which impacts CaSR function.

The effect is that the body senses and interprets even very low levels of calcium as normal, preventing the feedback loop from increasing blood calcium levels.

Gafni RI, Collins MT. Hypoparathyroidism. N Engl J Med. 2019;380(18):1738-1747. doi:10.1056/NEJMcp1800213
Roszko KL, Bi RD, Mannstadt M. Autosomal Dominant Hypocalcemia (Hypoparathyroidism) Types 1 and 2. Front Physiol. 2016;7:458. Published 2016 Oct 18. doi:10.3389/fphys.2016.00458

Symptoms and Manifestations of ADH

- Although some people are asymptomatic, ADH has a variety of symptoms and manifestations which can range from mild to severe to debilitating.
- Multiple organ systems may be impacted by hypocalcemia, particularly the musculoskeletal, nervous, and renal systems.

Musculoskeletal System

- ✓ Spasms of the hands and feet (carpopedal spasms)
- ✓ Prickling and tingling sensations (paresthesia)
- ✓ Bronchospasm and laryngospasm, which can lead to respiratory arrest
- ✓ Impaired cardiac contractility and arrhythmias

Goltzman, D. Clinical manifestations of hypocalcemia. UpToDate. March 12, 2021. Accessed August 16, 2022. https://www.uptodate.com/contents/clinical-manifestations-of-hypocalcemia

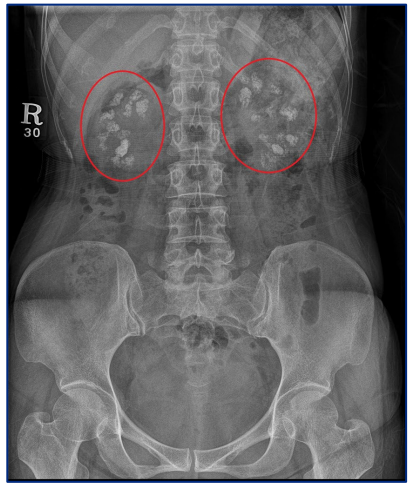
Symptoms and Manifestations of ADH, cont.

Nervous System

- ✓ Seizures
- ✓ Cognitive impairment
- ✓ Abnormal movement, gait, and coordination
- ✓ Calcifications of the basal ganglia of the brain

Renal System

- ✓ Hypercalciuria (high calcium levels in urine)
- ✓ Nephrolithiasis (kidney stones) and nephrocalcinosis (calcification of kidney tissue)
- ✓ Chronic kidney disease, including renal failure

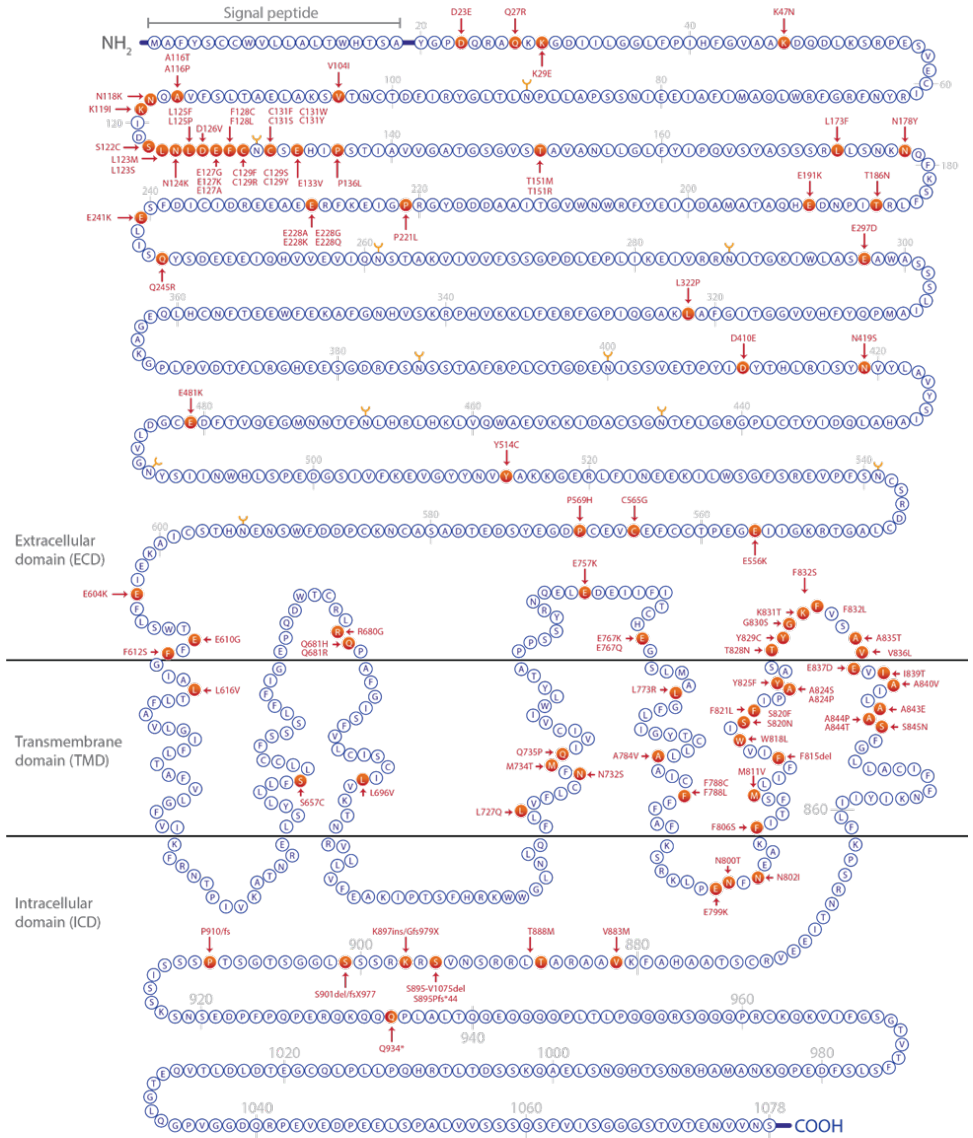


Roszko KL, Stapleton Smith LM, Sridhar AV, et al. Autosomal Dominant Hypocalcemia Type 1: A Systematic Review. J Bone Miner Res. 2022;10.1002/jbmr.4659. doi:10.1002/jbmr.4659

Diagnosis

- ADH is definitively diagnosed by genetic testing.
- Median age at diagnosis of hypocalcemia-related disorder is 4 years.
- Median age at diagnosis of ADH1 is about 25, although it ranges widely.
- Prevalence of ADH1 in the US is not known but is estimated at 3.9 per 100,000.

CaSR amino acid sequence with known activating variants →●



Roszko KL, Stapleton Smith LM, Sridhar AV, et al. Autosomal Dominant Hypocalcemia Type 1: A Systematic Review. J Bone Miner Res. 2022;10.1002/jbmr.4659. doi:10.1002/jbmr.4659

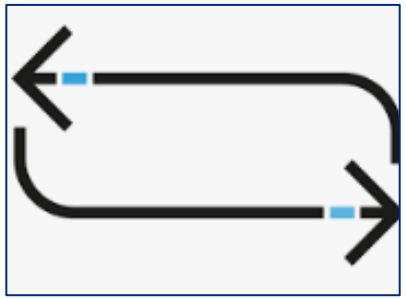
Treatment

- Treatment of ADH is directed at hypocalcemia.
  - ✓ People with ADH routinely take calcium supplements.
  - ✓ On an urgent basis, when acute symptoms are present, IV calcium may be infused.
  - ✓ Prescription level active vitamin D is also given to improve gut calcium absorption.
- As needed, associated symptoms and manifestations are also treated directly.
  - ✓ Antiepileptics may be given for seizures.
  - ✓ Renal dialysis may be needed for renal failure.

Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. Nat Rev Dis Primers. 2017;3:17055. Published 2017 Aug 31. doi:10.1038/nrdp.2017.55
Sastre A, Valentino K, Hannan FM, et al. PTH Infusion for Seizures in Autosomal Dominant Hypocalcemia Type 1. N Engl J Med. 2021;385(2):189-191. doi:10.1056/NEJMc2034981

Paradoxical Effects of Treatment

- Chronic use of calcium and active vitamin D can actually worsen hypercalciuria.
- Increases in urine calcium are strongly associated with development of calcifications in the kidneys.
- Chronic treatment can increase the risk of basal ganglia calcification in the brain.
- The level of treatment must be continuously balanced against the significant risk of complications.



✓ Due to the narrow range of parameters, people with ADH often remain symptomatic despite currently available treatments.

✓ To preclude complications, treatment may be avoided in completely asymptomatic persons.

Babey M, Brandi ML, and Shoback D, Conventional Treatment of Hypoparathyroidism, Endocrinol Metab Clin N Am 47 (2018) 889–900. https://doi.org/10.1016/j.ecl.2018.07.012

Life-Long Monitoring

- Persons diagnosed with ADH require monitoring for the rest of their lives.
- The degree of monitoring varies depending on each person's stability and symptomatology.

Stable (at a minimum)

- ✓ Serum calcium level once or twice annually
- ✓ Annual 24-hour urine to monitor indicators of renal function, eg, creatinine, calcium excretion
- ✓ Renal imaging every five years; no specific schedule for brain imaging

Symptomatic

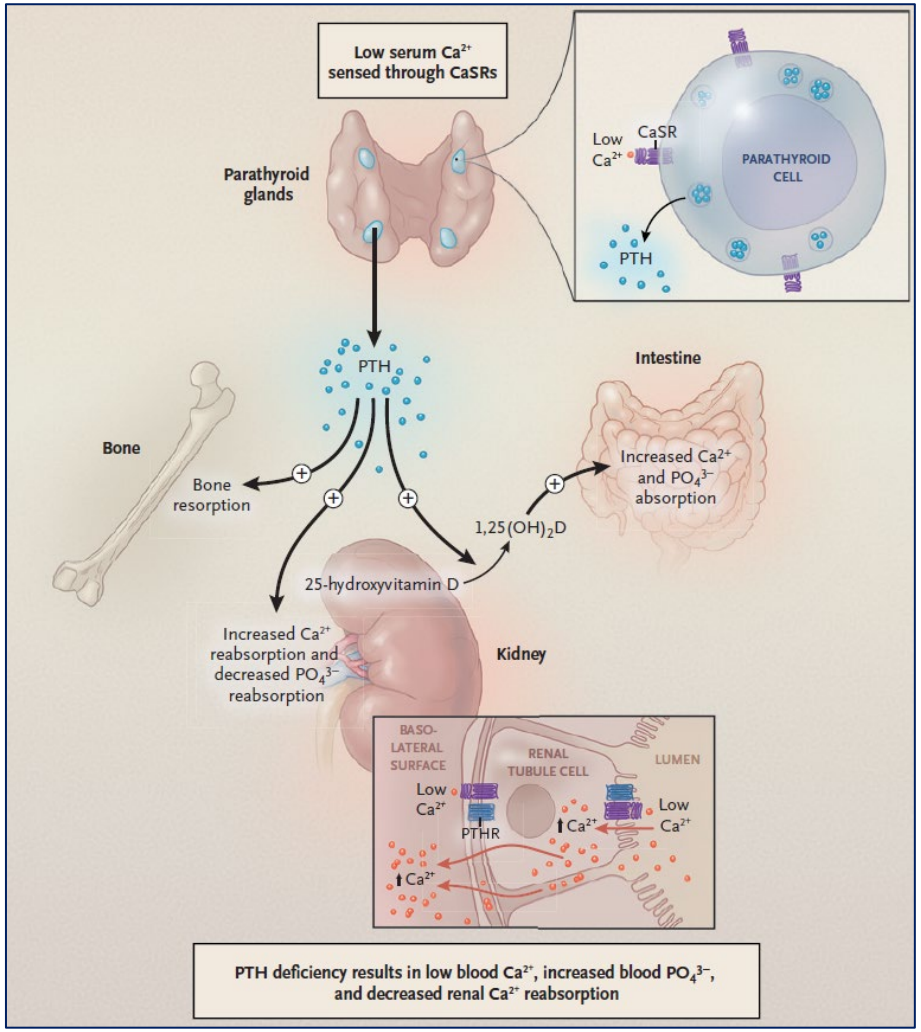
- ✓ Frequent serum calcium levels, eg, when dosages are being adjusted
- ✓ Frequent renal function monitoring, eg, for individuals experiencing or at high risk for renal complications
- ✓ Regular imaging, eg, for known calcifications or impaired function

Babey M, Brandi ML, and Shoback D, Conventional Treatment of Hypoparathyroidism, Endocrinol Metab Clin N Am 47 (2018) 889–900. https://doi.org/10.1016/j.ecl.2018.07.012
Brandi ML, Bilezikian JP, Shoback D, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. J Clin Endocrinol Metab. 2016;101(6):2273-2283. doi:10.1210/jc.2015-3907

Hypocalcemia–Hypoparathyroidism

- Hypoparathyroidism and hypocalcemia are intertwined.
- ADH clinically identifies a form of hypoparathyroidism, rather than a form of hypocalcemia.

Clinical Questions?



Gafni RI, Collins MT. Hypoparathyroidism. N Engl J Med. 2019;380(18):1738-1747. doi:10.1056/NEJMcp1800213
Brandi ML, Bilezikian JP, Shoback D, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. J Clin Endocrinol Metab. 2016;101(6):2273-2283. doi:10.1210/jc.2015-3907