Hypoparathyroidism:

Now that you have it, what do you do?

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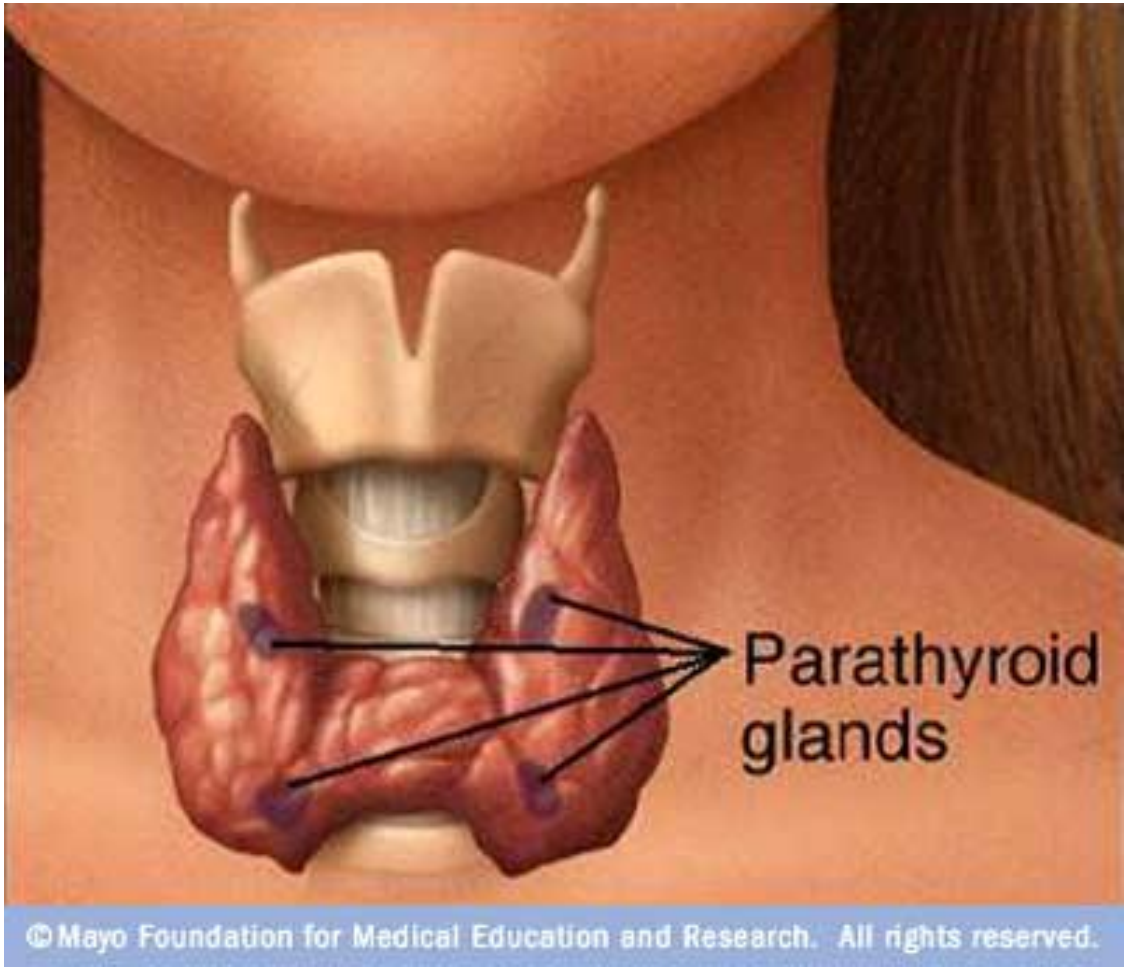
No conflicts of interest

Overview

- Parathyroid glands and PTH
- Causes of hypoparathyroidism
- Symptoms and potential complications
- Lab diagnosis and monitoring
- Treatment
  - Goals of treatment
  - Current and future treatment regimens

What are the parathyroid glands?



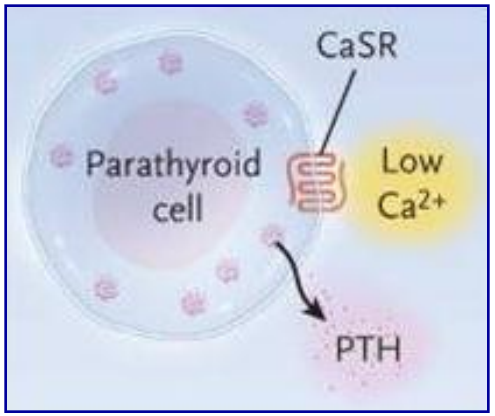
What does parathyroid hormone do?

Parathyroid hormone (PTH) orchestrates the body's calcium homeostasis

- Maintains the calcium level in the blood within in narrow physiologic range
  - Normal total Ca ≈ 8.6-10.2 mg/dL
  - Critical for neuromuscular function
    - Muscle contraction
    - Nerve transmission
    - Bone mineralization

How does PTH control calcium?

If the blood calcium level decreases . . .

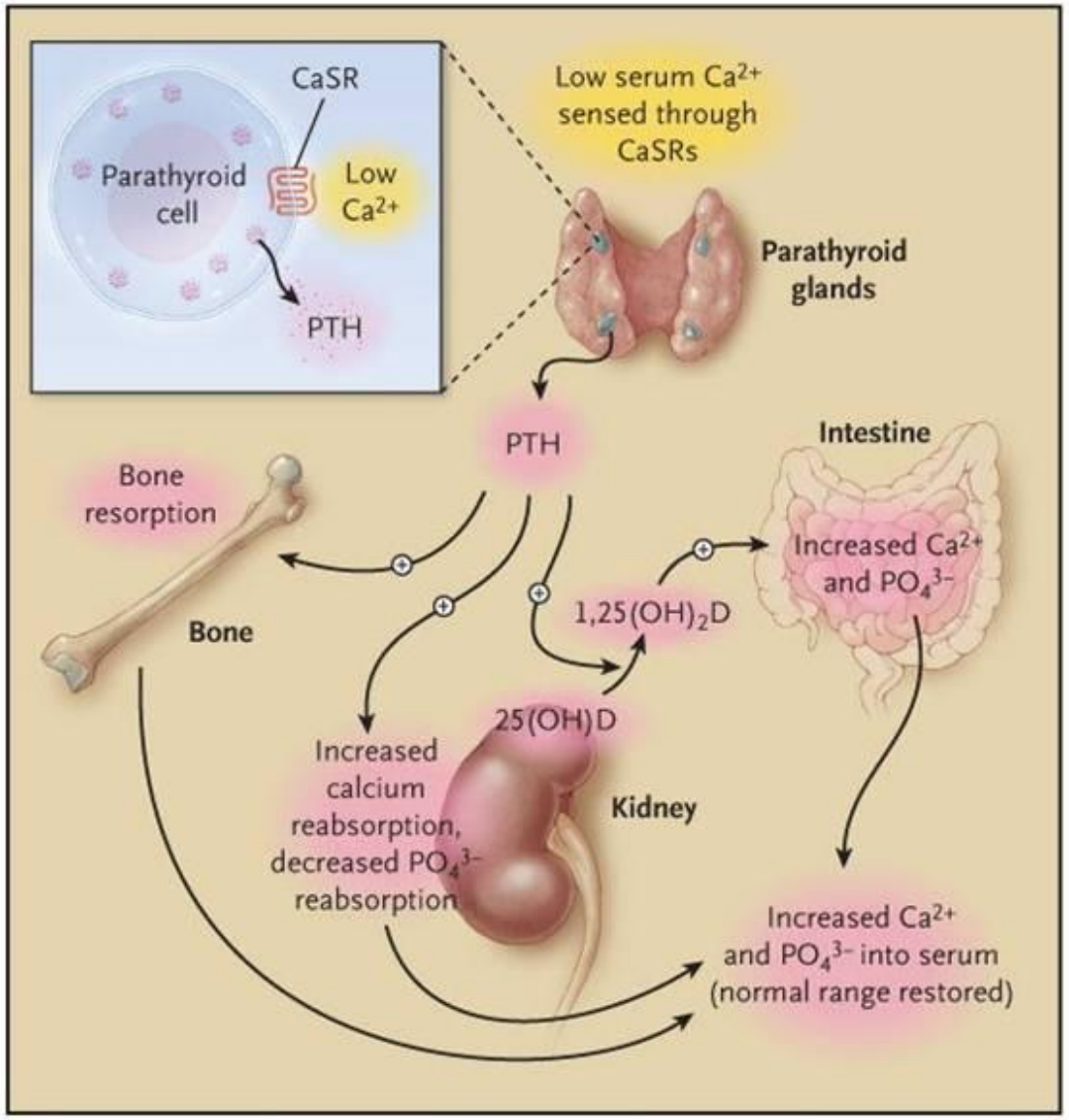


. . . then the parathyroids secrete more PTH . . .

PTH increases the calcium level through its effects on

- Kidney: ↑ Ca reabsorption, ↑ activated vit D
- Intestine: activated vit D ↑s Ca absorption
- Bone: Ca mobilized from the skeleton

Normal calcium homeostasis



But what happens the body cannot produce enough PTH?

Blood calcium level low →

Inadequate PTH production →

- Too little activated vitamin D
- Not enough Ca absorbed in the gut
- Kidney can't hold on to Ca
- Skeletal Ca not mobilized

→ Blood calcium level stays low

Hypoparathyroidism = Hypocalcemia (low blood calcium level) with low or “inappropriately normal” PTH

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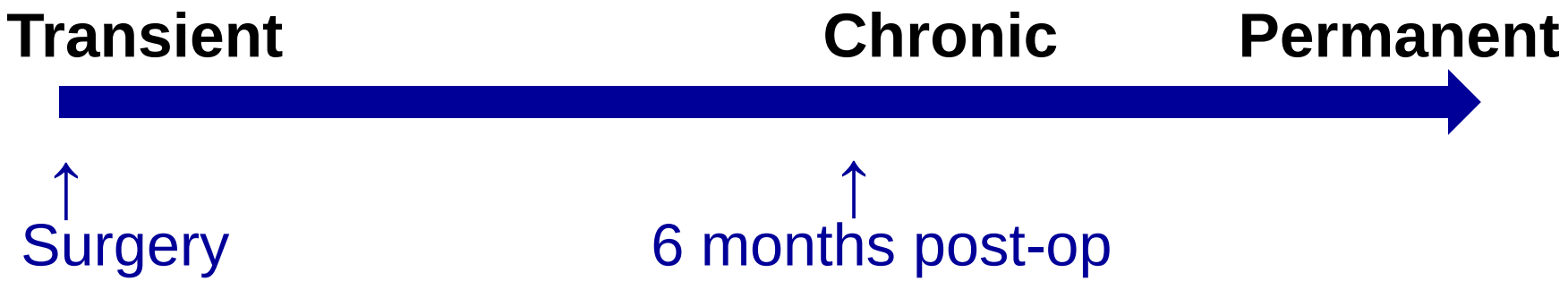
Causes of hypoparathyroidism

- Accidental damage to or removal of parathyroid glands during surgery
- Genetic or developmental
  - Parathyroid glands not formed properly
  - Impaired parathyroid function
- Autoimmune
- Extensive radiation to the neck
- Infiltrative (e.g., copper, iron, infection)
- Low magnesium

Surgical hypoparathyroidism

- Accidental removal of or damage to the parathyroid glands or their blood supply
  - Highest risk operations: completion thyroidectomy, total thyroidectomy with neck dissection
  - Partial more common than complete



Surgical hypoparathyroidism

- Transient hypoparathyroidism: Common
  - 7% to 46% of total thyroidectomies
  - Parathyroid gland “stunning”
  - Recovery in days to weeks (or longer)
- Permanent hypoparathyroidism
  - Lower incidence with experienced endocrine surgeons, high-volume centers
    - 0.9% to 1.6% of thyroid operations
    - Earlier reports: as high as 6.6%

Bilezikian et al., 2011; Shoback, 2008

Measures surgeons can take

- Discuss risks with you pre-operatively
- Monitor serum Ca level peri-operatively
  - Low serum Ca or PTH level post-op (in hospital) warrants close attention
- Monitor for symptoms/signs of low Ca
- Treat post-operatively with calcium ± vitamin D when appropriate (hopefully temporarily)

Kim et al., 2011; Asari et al., 2008

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Symptoms

- Largely related to hypocalcemia
- Depend on timing (acute vs. chronic) and severity
  - Chronic hypocalcemia may have few if any symptoms despite low Ca levels
- Highly variable, individual

Symptoms: Acute

Neuromuscular irritability

- Tingling (paresthesias) of lips, fingers, toes
- Muscle cramping/twitching, especially hands (“claw”) and feet
  - Severe = tetany
- Airway spasms
- Seizures, altered consciousness, coma
- Heart arrhythmia

Chvostek's sign

Images in Clinical Medicine

Chvostek's Sign and Carpopedal Spasm

Ganesh Athappan, M.D., and Venkatesh Kumar Ariyamuthu, M.D.

N Engl J Med 2009; 360:e24 April 30, 2009

Trousseau’s sign

Images in Clinical Medicine
Trousseau's Sign
Michael E. Meininger, M.D., and Jason S. Kendler, M.D.
N Engl J Med 2000; 343:1855

Symptoms: Chronic

Tingling, cramping/twitching, but also:

- Generalized fatigue
- “Brain fog”
- Insomnia
- Depression ± anxiety
- Headaches
- Bone pain
- Dry skin, hair loss

Potential complications

- Cataracts
- Congestive heart failure
- Calcium deposits in the brain
  - Basal ganglia, parkinsonism
- Other soft tissue calcification
- Kidney complications
  - Kidney stones, chronic kidney disease

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Calcium levels: Total vs. ionized (free)

- Physiologically active calcium is the ionized (free) calcium (~50% of total)
- Most of bound Ca is bound to albumin
  - *If your albumin level is low, your doctor will adjust your measured total calcium level upward*
    - *(A measured total Ca of 7.7 mg/dL with an albumin of 3.0 g/dL is ≈ a total Ca of 8.5 mg/dL)*
- iCa may be checked in conditions expected to affect binding to albumin

Lab diagnosis

- Serum calcium
- Albumin
- Intact PTH
- 1,25-dihydroxyvitamin D (activated vit D)
- Phosphate
- Magnesium

- If serum calcium level is high and PTH is low, diagnosis may be unclear

Monitoring

- Serum calcium
- Albumin
- Phosphate
- Urinary calcium (24-hour)
- 25-hydroxyvitamin D
- Serum PTH may be rechecked if hypo-parathyroidism is hoped to be transient

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Goals of treatment: Acute crisis

Symptomatic hypocalcemia can be an emergency (e.g., tetany, airway spasm) → goals are to raise Ca level and resolve symptoms

- IV calcium infusion
- Magnesium repletion if necessary

Goals of treatment: Chronic

- Serum calcium in the low-normal range
  - Calcium
  - Vitamin D
- Avoid high urinary calcium (= hypercalciuria)
  - Prevent kidney complications
- Avoid high serum phosphate
  - Avoid high calcium-phosphate product (minimize calcium deposits)

Current treatment options

- Calcium
- Calcitriol (activated vitamin D)
- Ergocalciferol, cholecalciferol (D_2 & D_3)
- Thiazide diuretics
- Low phosphate diet
- Phosphate binders

Calcium

- Calcium carbonate or calcium citrate
  - Calcium citrate better absorbed in people with low stomach acid
  - Take calcium carbonate with meals
- Amount needed varies (1 - 9 grams/day)
  - Dosed 2-4 times daily
  - Recognize difference between mg carbonate/citrate and mg elemental Ca
- Potential side effects: constipation

Calcitriol

- Activated vitamin D = $1,25(OH)_2D$
- Improves intestinal calcium absorption
  - Also increases phosphate absorption
- Doses vary (0.25 - 2.0 mcg/day)
- Short duration of action

Ergocalciferol, cholecalciferol

- Vitamin D_2 and D_3
- Require some PTH to be converted to active vitamin D (calcitriol)
- Longer lived (last weeks in the body)
- Doses vary (~800 IU - 50,000 IU/day)
  - Regimen may depend on vitamin D level in blood (25-hydroxyvitamin D level)

Goals of treatment: Chronic

- Serum calcium in the low-normal range
  - Calcium
  - Vitamin D
- Avoid high urinary calcium (= hypercalciuria)
  - Prevent kidney complications
- Avoid high serum phosphorus
  - Avoid high calcium-phosphorus product (minimize calcium deposits)

Thiazide diuretics

- Include hydrochlorothiazide (HCTZ), chlorthalidone
- Decrease urinary calcium excretion
- May help to limit amount of vit D needed to maintain normal serum calcium level
- Side effects:
  - Increased urination
  - Low blood potassium level (may need supplement)

Measures to lower phosphorus

- Low phosphorus diet
  - Limit intake of beans, cola, organ meats
  - Balance need for calcium with avoidance of phosphate with respect to dairy
- Phosphate binder medications
  - Bind to phosphate in gut and limit its absorption
  - Calcium carbonate or citrate
  - Sevelamer, lanthanum

PTH replacement therapy

- Not FDA-approved for hypoparathyroidism, but under investigation
- PTH(1-84) = full-length molecule, or
  PTH(1-34) = first 34 amino acids (teriparatide)
  - Both currently in use as treatment for osteoporosis: PTH(1-34) FDA-approved and PTH(1-84) approved in Europe

PTH replacement therapy

- Potential to reduce calcium and calcitriol requirements
  - Potential to decrease risk of high urinary calcium (= hypercalciuria)
  - Potential to decrease risk of accidental high serum calcium (= hypercalcemia)
  - Potential to decrease risk of soft tissue calcium deposits
  - Potential for more physiologic bone metabolism

PTH replacement therapy

- Subcutaneous injection

- Clinical trial protocols have considered injections every other day, to twice daily

Examples of PTH clinical trials

- PTH(1-34) twice daily vs. calcitriol in 27 adults: PTH(1-34) maintained serum Ca in the low-normal or mildly low range over 3 years
- PTH(1-84) every other day in 30 adults: Average calcium dose decreased from 3030 ± 2325 mg to 1661 ± 1267 mg; average calcitriol dose decreased, too

Winer et al., 2003; Rubin et al., 2010

Examples of PTH clinical trials

- PTH(1-84) once daily vs. placebo added to conventional therapy in 62 adults
  - 6 months
  - Those on PTH(1-84) reduced calcium and active vitamin D doses by 75% and 73%, respectively
  - Frequent hypercalcemia during titration

Sikjaer et al., 2011

Continued research needed

- What is the best PTH dosing regimen (i.e., twice daily, every other day)?
- Exactly how should calcium and calcitriol doses be decreased when therapy is started?
- What are the long-term effects of PTH replacement therapy?

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Hypoparathyroidism Association
www.hpth.org