NOTES
HYPERCALCEMIA & HYPOCALCEMIA

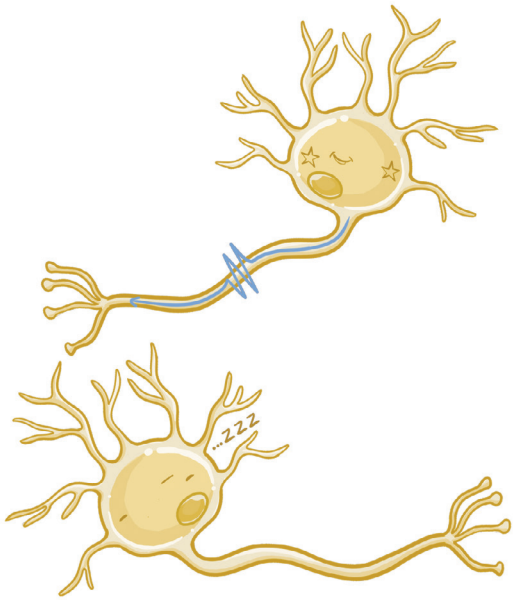
GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Calcium concentrations in the blood falling outside of the normal reference range
- Hypocalcemia: < 8.5mg/dL
- Hypercalcemia: > 10.5mg/dL

SIGNS & SYMPTOMS

- Variations that are mild, or slow in onset, usually asymptomatic
- Hypercalcemia → less excitable neurons and associated symptoms across multiple systems
- Hypocalcemia → more excitable neurons and associated symptoms across multiple systems



DIAGNOSIS

LAB RESULTS

- Blood calcium levels
- Determination of underlying cause (blood tests for levels of)
  - Parathyroid hormone, vitamin D, albumin, phosphorus, magnesium

OTHER DIAGNOSTICS

ECG

- Identify associated organ dysfunction

TREATMENT

MEDICATIONS

Hypercalcemia

- Lower blood calcium levels
  - Rehydrate, loop diuretics, glucocorticoids, bisphosphonates or calcitonin, dialysis

Hypocalcemia

- Raise calcium levels
  - Calcium gluconate
  - Vitamin D supplementation

HYPERCALCEMIA

osms.it/hypercalcemia

PATHOLOGY & CAUSES

- High blood calcium (> 10.5mg/dL)
- True hypercalcemia due to elevation of free ionized calcium (not protein-bound, which is 40–45% of total calcium)

CAUSES

Excessive bone resorption

- Hyperparathyroidism
  - Most common cause
  - Increased osteoclastic bone resorption
  - Overactive parathyroid → releases more parathyroid hormone → stimulates osteoclasts → osteoclasts break down bone → release calcium into blood
- Thyrotoxicosis
  - Thyroid hormone mediated increase in bone reabsorption
- Malignant tumors
  - Can secrete parathyroid hormone-related protein (PTHrP)
  - Can cause osteoblast cells to die
  - Can also cause overstimulation of osteoclasts → lytic bone lesions
  - Can directly invade bone
- Uncommon causes
  - Immobilisation, Paget disease of bone, anti-oestrogen treatment, hypervitaminosis A (retinoic acid → dose dependent increase in bone resorption)

Excessive calcium absorption

- Excess vitamin D
  - Stimulates active intestinal absorption, resorption from bone and increased renal reabsorption
- Diet or excessive supplementation
  - When intake exceeds 2 grams daily, passive transport may also lead to hypercalcemia
- Medications
  - Thiazide diuretics (increase calcium reabsorption in distal tubule of kidney)
  - Lithium (increase calcium reabsorption from the loop of Henle, also interferes with normal hypercalcemic feedback on the parathyroid gland)
  - Calcium carbonate supplementation
- Milk-alkali syndrome
  - Extra calcium from diet, alkali found in antacids)
  - Hypercalcemia, metabolic alkalosis, renal insufficiency

Insufficient excretion

- Adrenal insufficiency (e.g. Addisonian crisis)
- Adrenal failure (e.g. rhabdomyolysis)

False hypercalcemia / pseudohypercalcemia

- Hyperalbuminemia → ↑ albumin → ↑ protein-bound calcium → ↑ total calcium
  - Free ionized calcium concentrations remain the same (hormonal regulation)
  - Total calcium high, free ionized calcium normal
  - *Rare cause:* dehydration

COMPLICATIONS

- Calcium oxalate kidney stones (hypercalciuria, fluid loss)
- Osteoporosis (depletion of calcium stores in bone)
- Renal failure
- Cardiac arrhythmias
- Confusion, dementia, coma

SIGNS & SYMPTOMS

- Many individuals asymptomatic
- Slow chronic onset, better tolerated
- Neurological
  - Neurons less excitable
  - Blurred vision, slow or absent reflexes
  - *Central nervous system:* fatigue, anxiety, confusion, hallucinations, stupor
- Cardiovascular
  - Arrhythmias, shortened QT interval, bradycardia, hypertension
- Musculoskeletal
  - Generalized muscle weakness, bone pain, weak bones
- Gastrointestinal
  - Anorexia, nausea and vomiting, constipation
- Renal
  - Hypercalciuria, polyuria, polydipsia, kidney stones, distal renal tubular acidosis, nephrogenic diabetes insipidus, renal insufficiency

DIAGNOSIS

LAB RESULTS

- High calcium levels in blood > 10.5mg/dL
- Calcium levels must be corrected for albumin levels or measure free ionized calcium
  - *Albumin:* may be ↑ in pseudohypercalcemia
- *Parathyroid hormone:* ↑ or ↓
- *PTH-related hypercalcemia:* primary hyperparathyroidism and familial hyperparathyroidism
- *Non-PTH-related hypercalcemia:* primary malignancy, intoxication of vitamin D, granulomatosis
- *PTH-related peptide:* may ↑ in certain malignancies
- *Vitamin D:* may be ↑ in intoxication
- *Phosphate:* ↑ or ↓ depending if PTH-dependent (high in renal insufficiency, hypoparathyroidism, low in vitamin D deficiency)
- *Magnesium:* hypercalcemia may ↓ Mg levels

OTHER DIAGNOSTICS

ECG

- Bradycardia
- Atrioventricular block
- Shortening of QT interval
- Osborn wave (positive deflection at junction between QRS complex and ST segment)

TREATMENT

MEDICATIONS

- *Main goal:* lower calcium levels in blood
- *Rehydrate:* increases urinary excretion of calcium
- *Loop diuretics:* inhibit calcium reabsorption, so more is excreted
- *Glucocorticoids:* decrease gastrointestinal calcium absorption
- *Bisphosphonates or calcitonin:* inhibit osteoclasts, prevent bone resorption
- *Dialysis:* if renal failure is present, consider hemodialysis or peritoneal dialysis

MNEMONIC

The effects of hypercalcemia

Stones: renal or biliary calculi

Bones: bone pain

Groans: abdominal pain/ nausea

Thrones: polyuria

Psychiatric overtones: depression, anxiety, coma, insomnia

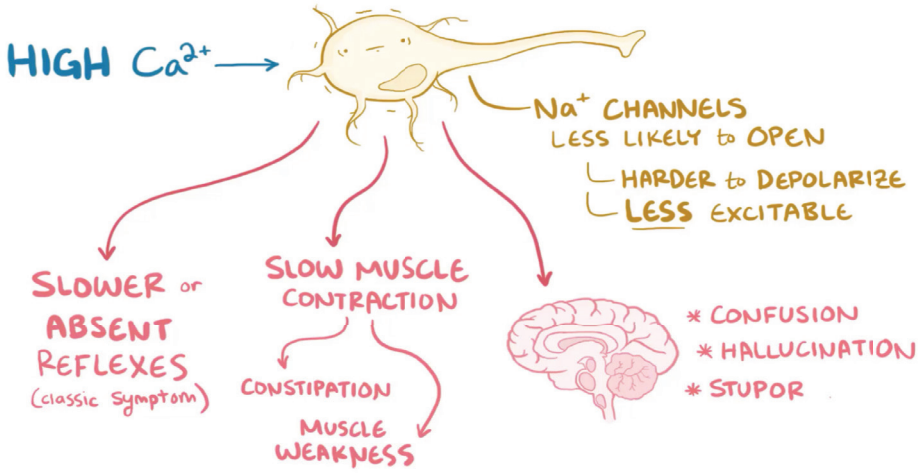


Figure 111.1 Illustration of the potential sequelae of hypercalcemia.

HYPOCALCEMIA

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PATHOLOGY & CAUSES

- Low blood calcium (< 8.5mg/dL)

CAUSES

Less calcium entering blood

- Most common cause
- *Low vitamin D:* deficient diet, malabsorption, cirrhosis, lack of sunlight, chronic renal failure
- *Hypoparathyroidism:* low levels or low activity of parathyroid hormone
  - Hypomagnesemia (Mg serum concentration < 1mg/dL) can facilitate parathyroid hormone resistance via suppressing secretion
- *Pseudohypoparathyroidism type 1A:* kidney unresponsive to parathyroid hormone
  - *Pseudohypoparathyroidism:* end-organ parathyroid hormone resistance
- Inhibition of bone resorption (uncommon)
  - Medications such as bisphosphonates, calcitonin and denosumab
  - Often occurs in setting of vitamin D deficiency, hypoparathyroidism and parathyroid hormone resistance

Too much calcium leaving blood

- *Kidney failure:* nephron doesn't effectively reabsorb calcium
- *Tissue injury:* burns, rhabdomyolysis, tumor lysis syndrome
- *Acute pancreatitis:* free fatty acids bind to ionized calcium
- Inflammatory processes (eg. sepsis and severe illness)
  - Up to 90% of critically-ill individuals, or those that have had major surgery develop hypocalcemia
- Too many blood transfusions → additives bind to ionised calcium → additives in blood (citrate, ethylenediaminetetraacetic acid (EDTA) chelate (bind) to calcium → complexed calcium, an inactive molecule
- *Hyperphosphatemia:* results in calcium being deposited in bone and extraskeletal tissue
- *Calcium complex formation:* formation of complexes → reduced availability of ionized

calcium for cellular processes
    - Foscarnet, drug for treatment of refractory herpes and cytomegalovirus
    - Fluoride poisoning, causes hypocalcemia partially due to formation of fluorapatite

False hypocalcemia / pseudohypocalcemia

- *Hypoalbuminemia (low albumin):* loss of bound calcium
    - Hormonal regulation means free ionized calcium concentrations stay essentially the same
    - Less overall calcium due to less bound calcium, but free ionized calcium levels remain the same

COMPLICATIONS

- Osteopenia, osteoporosis, cardiovascular collapse, vasogenic shock (calcium required in vascular smooth muscle contraction), cardiac arrhythmias, seizures, tetany, basal ganglia calcification, parkinsonism, hemiballismus, choreoathetosis

Figure 111.2 Trousseau's sign of latent tetany.

SIGNS & SYMPTOMS

- Neurological → neurons hyperexcitable
    - Involuntary contraction of muscles
    - Chvostek's sign (facial muscles twitch after facial nerve lightly finger tapped 1cm/0.39in below zygomatic process)
    - Trousseau's sign (blood pressure cuff occludes brachial artery → pressure makes nerve fire → muscle spasm makes wrist and metacarpophalangeal joints flex)
    - Muscle cramps
    - Abdominal pain
    - Perioral tingling (tingling around mouth)
    - Paresthesias (abnormal sensation felt on skin, eg. tingling, tickling, prickling, numbness, burning)
    - Carpopedal spasm (spasmodic contraction of muscles in hands, feet, ankles, wrists)
    - Hyperactive deep tendon reflexes
    - Seizures (extreme cases)
- *Cardiovascular:* decrease in rate, strength of contractions
    - Hypotension
    - Heart failure
    - Arrhythmias

DIAGNOSIS

LAB RESULTS

- Low level of calcium in blood (< 8.5mg/dL)
- Calcium levels must be corrected for albumin levels or measure free ionized calcium
    - Albumin may be low in pseudohypocalcemia
- PTH-related hypocalcemia
    - ↓ : hypoparathyroidism
    - ↑ : kidney disease, vitamin D deficiency, pseudohypoparathyroidism
- *Non-PTH-related hypocalcemia:* hypomagnesemia
- *Autosomal dominant hypocalcemia:* mutation in calcium-sensing receptor gene
- PTH
    - ↑ in kidney disease, vitamin D deficiency, pseudohypoparathyroidism
    - ↓ in hypoparathyroidism
- Vitamin D
    - Hypocalcemia may be caused by ↓ vitamin D (which ↑ PTH secretion)
- Phosphate
    - ↑ in hypoparathyroidism (in absence of kidney disease) or pseudohypoparathyoidism (PTH resistance)
    - ↓ in secondary hyperparathyroidism

- Normal in setting of hypocalcemia: hypomagnesemia/mild vitamin D deficiency

- *Magnesium:* ↓ levels can cause hypocalcemia

OTHER DIAGNOSTICS

ECG

- Prolonged QT segment
- Prolonged ST segment
- Arrhythmias (torsades de pointes, atrial fibrillation)

TREATMENT

MEDICATIONS

- *Main goal:* normalize calcium levels
  - Calcium gluconate
  - Vitamin D supplementation

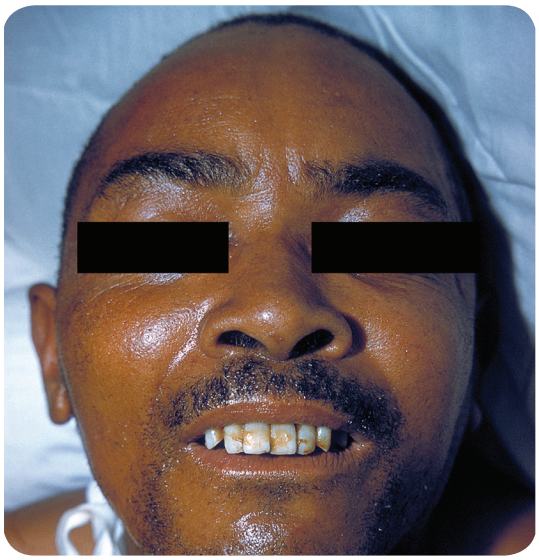

Figure 111.3 Hypocalcemia can can cause tetany, seen here in the face of this individual.