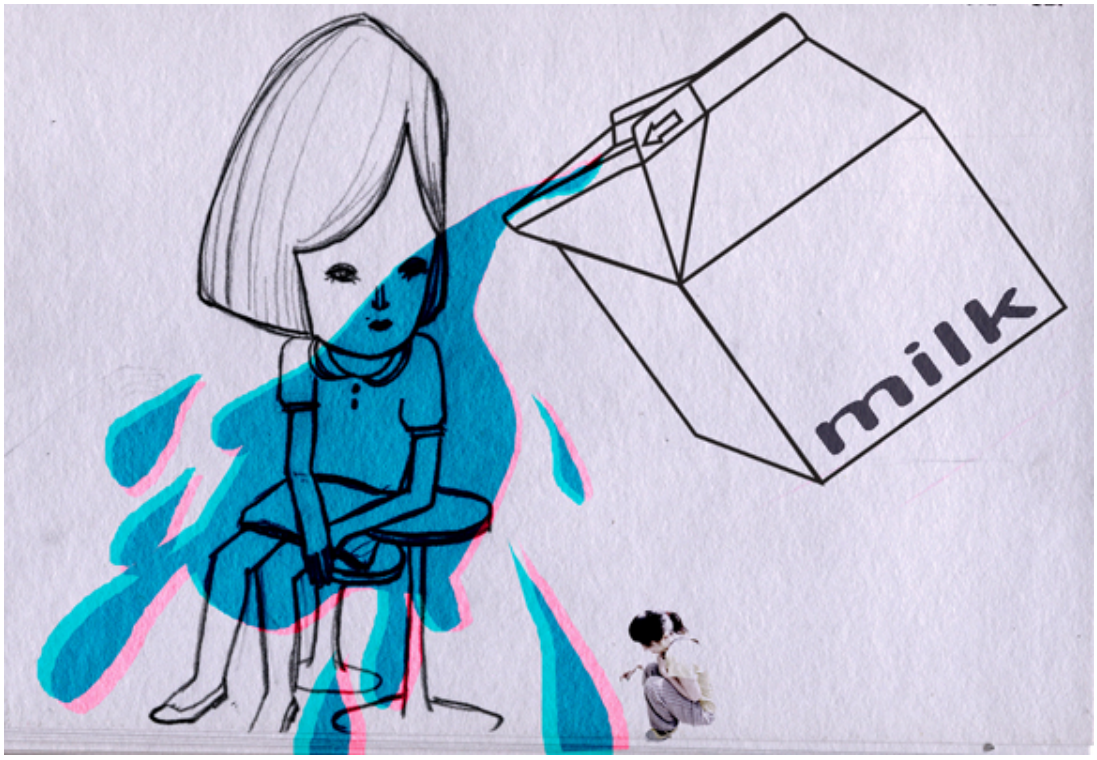
Hypercalcemia — Causes and Treatment

See online here

The normal calcium level in the body is between 2.2–2.6 mmol/L. The calcium levels are regulated by a hormone known as the parathyroid hormone (PTH) which is secreted by the parathyroid gland. If the body fails to maintain the calcium levels within the normal ranges, hypercalcemia or hypocalcemia results. This article focuses on hypercalcemia. Read on to learn about the causes, symptoms, diagnosis and management of hypercalcemia.



Definition of Hypercalcemia

Hypercalcemia is a condition in which the **serum calcium levels are abnormally high**. Normal serum calcium levels range from 2.2 to 2.6 mmol/L. Hypercalcemia can be:

- **Mild:** 2.6–2.9 mmol/L
- **Moderate:** 3.0–3.4 mmol/L
- **Severe:** > 3.4 mmol/L

Normal Calcium Metabolism

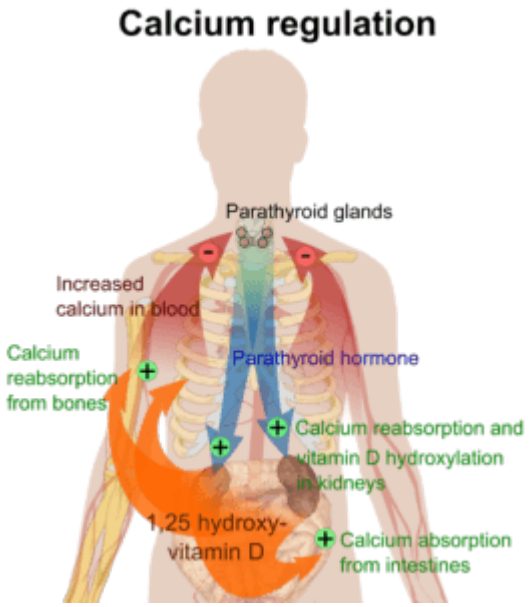


Image: “Overview of calcium regulation,” by Mikael Häggström. License: Public Domain

There are **four parathyroid glands** at the back of the thyroid gland. They have chief cells that produce **parathyroid hormone (PTH)**, which plays a major role in calcium metabolism by regulating serum calcium levels.

The roles of calcium in the human body include:

1. Formation and maintenance of bones and teeth
2. Blood clotting
3. Hormone release
4. Muscle contraction
5. Nerve and brain function
6. Enzymatic reaction

When serum calcium levels are low, the hypothalamus signals the parathyroid glands to increase PTH secretion and raise calcium levels to the normal range. PTH increases serum calcium levels by:

- increasing the osteoclastic resorption of the bone
- increasing the intestinal absorption of calcium
- increasing the synthesis of calcitriol, which, in turn, increases absorption of dietary calcium
- increasing the renal tubular reabsorption of calcium
- increasing phosphate excretion

Epidemiology

Spread of hypercalcemia

Hypercalcemia is a common condition and is often **detected incidentally**. Mild asymptomatic hypercalcemia occurs in about **1 in 1000 individuals,** with an incidence of hypercalcemia of about 25 to 30 per 100,000. Hypercalcemia is more common among **elderly females**.

Etiology of Hypercalcemia

Causes of hypercalcemia

Hypercalcemia is a common condition, which is caused by a number of very different diseases.

Primary hyperparathyroidism

This is one of the most common causes of hypercalcemia. **Primary hyperparathyroidism** and malignancies account for **more than 90%** of the cases of hypercalcemia. This is a benign condition, causing mild or moderate hypercalcemia.

Malignancy

This is the **second most common cause** of hypercalcemia. It is very important to exclude malignancy from a patient with hypercalcemia. Two types of malignancy usually cause **severe hypercalcemia**.

Bone metastasis: Certain cancers metastasize to the bones, including breast, prostate, thyroid, and lung, as well as multiple myeloma and lymphoma. This metastasis activates osteoclast activity, thus releasing calcium to the serum.

PTH–like peptides: These are commonly secreted from squamous cell carcinoma, mainly from the lungs or esophagus. The cancerous cells secrete PTH–like peptides, which act similarly to the parathyroid hormone by activating osteoclast activity to break down bones and release calcium to the blood.

Granulomatous diseases such as sarcoidosis, tuberculosis, etc.

Sarcoidosis is a very common condition, with patients developing hypercalcemia by **activating vitamin D synthesis via macrophages**. This usually occurs in the summer months when people are exposed to sunlight because then they absorb more vitamin D and activate more of it through the macrophages. This type of hypercalcemia is unique because it is treated with **glucocorticoids** just like normal cases of sarcoidosis.

Prolonged immobilization

People who have been **bedridden for a couple of years** develop mild hypercalcemia. This is due to a lack of weight-bearing activities, which leads to osteoclast activation and subsequent bone demineralization and hypercalcemia. It can develop after 4-6 weeks or can take months to appear. This is a benign condition and usually requires no treatment.

Hyperthyroidism

Hyperthyroidism also activates osteoclasts, thus increasing bone resorption and serum calcium.

Familial hypocalciuric hypercalcemia

As the name suggests, this **disease runs in families**. It is an **autosomal dominant condition** in which the kidney tubules are unable to get rid of the surplus calcium. Therefore, the calcium levels in the urine are reduced, while the serum calcium levels are raised. Patients with this disease may have a family history of (unnecessary) parathyroidectomy. The majority of the patients are asymptomatic therefore do not require any treatment.

Drugs

Thiazide diuretics, chronic lithium administration, vitamin D analogs, and vitamin A cause hypercalcemia. Other causes of hypercalcemia include adrenal insufficiency, pheochromocytoma, and parenteral nutrition.

Symptoms of Hypercalcemia

Hypercalcemia can be mild or severe. Mild hypercalcemia (calcium < 3mmol/L) is frequently asymptomatic. Severe hypercalcemia produces a number of symptoms. The clinical presentation can be either **acute or chronic**.

Acute presentation of hypercalcemia

- **GI symptoms:** Anorexia, nausea, vomiting, constipation, abdominal pain.
- **CNS symptoms:** Confusion, weakness, lethargy, hyporeflexia, altered mental status, coma.
- **CVS symptoms:** Hypertension, occasional bradycardia, and 1st-degree heart block; ECG changes such as shortened QT interval, J waves & widening T waves.
- **Renal symptoms:** Polyuria or nocturia, polydipsia (develop nephrogenic diabetes insipidus; these patients may develop severe dehydration), renal colic (nephrolithiasis).

Chronic presentation of hypercalcemia

- Osteoporosis with bone pain
- Nephrocalcinosis (deposition of calcium in renal parenchyma)
- Band keratopathy (corneal degeneration characterized by calcium deposition)
- Chondrocalcinosis
- Pancreatitis
- Hypertension

Investigations of Hypercalcemia

Hypercalcemia is diagnosed through blood tests to measure calcium and phosphate levels. Other tests will be required to determine its cause. The serum PTH is:

Very high

The most likely cause in this setting is **hyperparathyroidism**.

Normal or slightly increased

Check the urinary calcium levels. If 24-hour urinary calcium levels are less than 100mcg/d or single urinary calcium creatinine ratio is less than 0.01, suspect **familial hypocalciuric hypercalcemia**. Otherwise, **primary hyperparathyroidism** is the most likely cause.

Low or undetectable

This suggests that the parathyroid function is appropriate for the calcium levels. Therefore, further tests will be needed to determine the cause of hypercalcemia, including:

1. Protein electrophoresis or immunofixation to exclude myeloma
2. Serum TSH to exclude hyperthyroidism
3. 09:00 hours cortisol and/or ACTH test to exclude Addison's disease
4. Raised calcitriol (1, 25 $(OH)_2D$) in granulomatous diseases
5. Serum Angiotensin-Converting Enzyme (raised levels indicate sarcoidosis)
6. Bone metastasis evaluation
7. Consider immobilization as a possible cause
8. Hydrocortisone suppression test: Administering 40 mg of hydrocortisone 3 times daily for 10 days leads to suppression of plasma calcium levels in sarcoidosis, Vitamin D mediated hypercalcemia, and some malignancies

Differential Diagnosis of Hypercalcemia

High PTH

- Primary hyperparathyroidism
- Lithium therapy
- Tertiary hyperparathyroidism
- Ectopic PTH secretion (very rare)

Hypercalcemia of malignancy

- Multiple myeloma
- Metastasis to bone
- Breast cancer

High vitamin D levels

- Vitamin D intoxication – Iatrogenic or self-administered
- Granulomatous diseases, such as sarcoidosis or TB
- Lymphoma

Endocrine diseases

- Hyperthyroidism
- Addison's disease

Drugs

- Thiazide diuretics
- Vitamin A
- Vitamin D analogs
- Lithium therapy

Renal failure

- Severe secondary hyperparathyroidism
- Aluminum intoxication
- Milk-alkali syndrome

Management of Hypercalcemia

Treatment of acute severe hypercalcemia

Patients with acute severe hypercalcemia present with dehydration, nausea, vomiting, nocturia, and polyuria. **Immediate treatment** is compulsory if the patient is seriously ill or the serum calcium levels are greater than 3.5 mmol/L.

1. IV fluids

This is the **most important part of the treatment**. Many patients with hypercalcemia are dehydrated due to vomiting and nephrogenic diabetes insipidus. These patients require **at least 4–6L of fluid a day** to remain hydrated. However, there is a **risk of fluid overload**. Patients who develop crackles in the lungs or edema of the legs may be administered Furosemide to reduce the fluid in the body. If the edema is chronic, the dosage is usually 20-80 mg PO once daily. If pulmonary edema develops acutely, it may be administered 0.5-1 mg/kg (or 40 mg) IV over 1-2 minutes.

Note: Never give IV fluids and furosemide together because this will make the person more dehydrated and further increase serum calcium levels.

2. IV bisphosphonates

Bisphosphonates are an anti-resorptive agent that suppresses bone resorption and **pushes the serum calcium back into the bone, thus reducing serum calcium levels**.

Pamidronate is the treatment of choice for hypercalcemia due to malignancy or an undiagnosed cause. It is long-acting, and the effect lasts at least two weeks. The only problem with this drug is that it takes about 24 to 48 hours for it to take effect. Zoledronate is an alternative.

Calcitonin can be given together with Pamidronate. Calcitonin inhibits calcium resorption of the bone and increases renal excretion of calcium. The effect of calcitonin begins within about two hours and wears off after about two days. Therefore, when calcitonin and Pamidronate are given together, they work in tandem: calcitonin takes effect relatively quickly, and as it begins to wear off, Pamidronate begins to take effect.

3. Glucocorticoids

Glucocorticoids are effective in vitamin D mediated hypercalcemia, such as granulomatous diseases and vitamin D intoxication. Glucocorticoids act by inhibiting the

production of calcitriol (1, 25 (OH) $_2$D).

4. Mobilize the patient

References

Kumar & Clark, 2012. Clinical medicine. 8th ed.

Notes