

## Hypercalcemia — Causes and Treatment

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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**. 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

## Calcium regulation

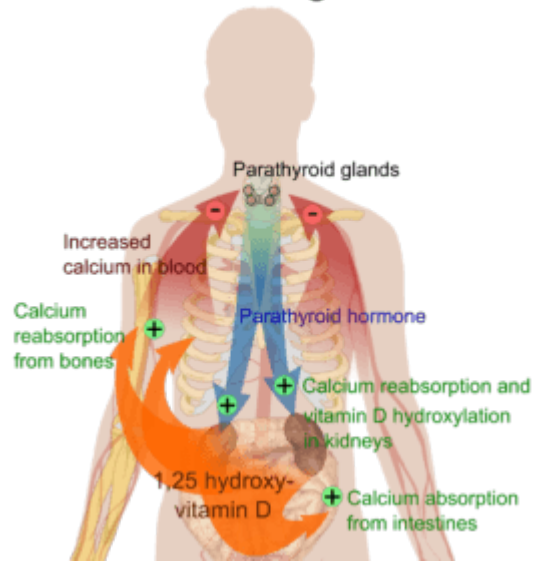


Image: "Overview of calcium regulation," by Mikael Häggström. License: Public Domain

There are **4 parathyroid glands** situated at the back of the thyroid gland. They have chief cells producing **parathyroid hormone (PTH)**, which plays a major role in calcium metabolism by regulating serum calcium level.

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

The **normal calcium level** in the body is **between 2.2-2.6 mmol/L**. When the serum calcium levels are low, PTH secretion is increased to raise the calcium levels to the normal range. PTH increases the 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 excretion of phosphate.

## 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 the **elderly females**.

# Etiology of Hypercalcemia

## Causes of hypercalcemia

Hypercalcemia is a common condition, which is caused by a number of very different diseases. Some of these causes are discussed below.

### 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. Malignancy usually causes **severe hypercalcemia**. The 2 ways that malignancy can cause hypercalcemia are:

**Bone metastasis:** Metastasis from breast, multiple myeloma, prostate, lymphoma, thyroid and [lungs](#), etc. The metastasis to the bone activates osteoclast activity, thus releasing calcium to the serum.

**PTH-like peptides:** These are commonly secreted from squamous cell carcinoma, mainly of 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 the normal cases of sarcoidosis.

### Prolonged immobilization

People who have been **bed-bound for a couple of years** develop a mild hypercalcemia. This is a benign condition and often does not require any 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 is 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 analogues 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 1<sup>st</sup> 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

Several serum calcium and phosphate levels should be performed to get a diagnosis of hypercalcemia. To find the cause of hypercalcemia other tests are done. 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)<sub>2</sub>D) in granulomatous diseases
5. Serum Angiotensin Converting Enzyme: raised levels in sarcoidosis
6. Evaluate for bone metastasis
7. Consider immobilization
8. Hydrocortison suppression test: Administering to the patient 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 analogues
- 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 more 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 keep them hydrated. However, there is a **risk of fluid overload**. So, if the patient develops crackles in the lungs or edema of the legs, give them a shot of Furosemide to reduce the fluid in the body.

**Note:** Never give IV fluids and furosemide together as this will make the person more dehydrated and will worsen the serum calcium levels.

#### 2. IV bisphosphonates

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

This is the treatment of choice for hypercalcemia of malignancy or an undiagnosed cause. **Pamidronate** is preferred as it is long acting, and the effect lasts at least for 2 weeks. The only problem with this drug is that it takes about 24 to 48 hours for it to start working. Zoledronate is an alternative.

**Calcitonin** can be given together with Pamidronate. Calcitonin inhibits resorption of the bone and increases the renal excretion of calcium. The effect of calcitonin begins within a couple of hours and wears off after about 2 days. Therefore when Calcitonin and Pamidronate are given together, calcitonin begins to act within a couple of hours and after 2 days, as its effect wears off, the bisphosphonate is activated.

#### 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)<sub>2</sub>D).

#### 4. Mobilize the patient

## References

Kumar & Clark, 2012. Clinical medicine. 8<sup>th</sup> ed.

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