

Hypocalcemia — Definition and Treatment

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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. Hypocalcemia is the condition in which the serum calcium levels in the blood are low. The presentation of the patients with hypocalcemia can vary from asymptomatic to life-threatening situations.



Definition of Hypocalcemia

Calcium regulation

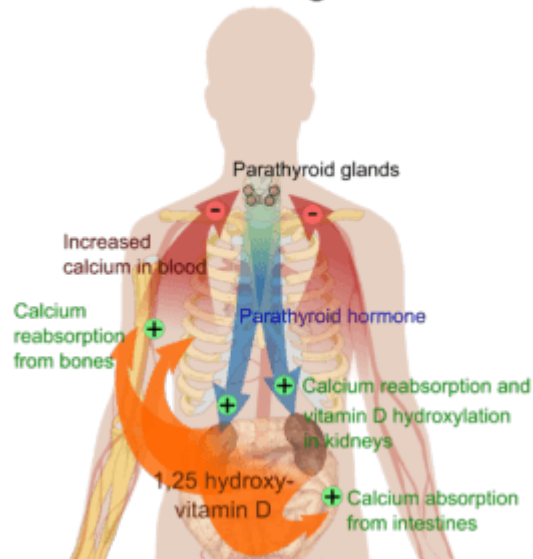


Image: "Overview of calcium regulation," by Mikael Häggström. License: Public Domain

Hypocalcemia is a medical condition in which the **serum calcium level is low**. The normal serum total calcium level in the body is between 2.2–2.6 mmol/L (8.5 – 10.2 mg/dL).

40-45% of serum total calcium is bound to proteins, predominantly albumin, while 55-60% is present in the ionized form. Although serum **total calcium** is often measured, it is actually the serum **ionized calcium** that is physiologically active, and its low concentrations should be labeled as hypocalcemia.

Etiology of Hypocalcemia

The causes of hypocalcemia include, besides **inadequate oral intake of calcium**, the following:

Vitamin D deficiency

Vitamin D is a major hormone responsible for calcium hemostasis, as well as an increase in intestinal calcium absorption. Adequate sunlight exposure physiologically converts skin cholesterol into vitamin D in healthy individuals. The deficiency of vitamin D can be a result of several causes such as intestinal malabsorption, less exposure to sunlight, [renal failure](#) and severe liver disease.

The kidney and liver contain enzymes that are necessary to activate vitamin D into its functional form, **1,25-dihydroxycholecalciferol**, also simply called **calcitriol**. In end-stage kidney and liver disease, there will be dysfunction of both these organs that would lead to reduced activation of vitamin D and, therefore, **reduced absorption of calcium from the small intestine** resulting in hypocalcemia.

Intestinal malabsorption due to diseases such as [celiac disease](#) and chronic pancreatitis results in reduced absorption of ingested vitamin D from the [small intestine](#).

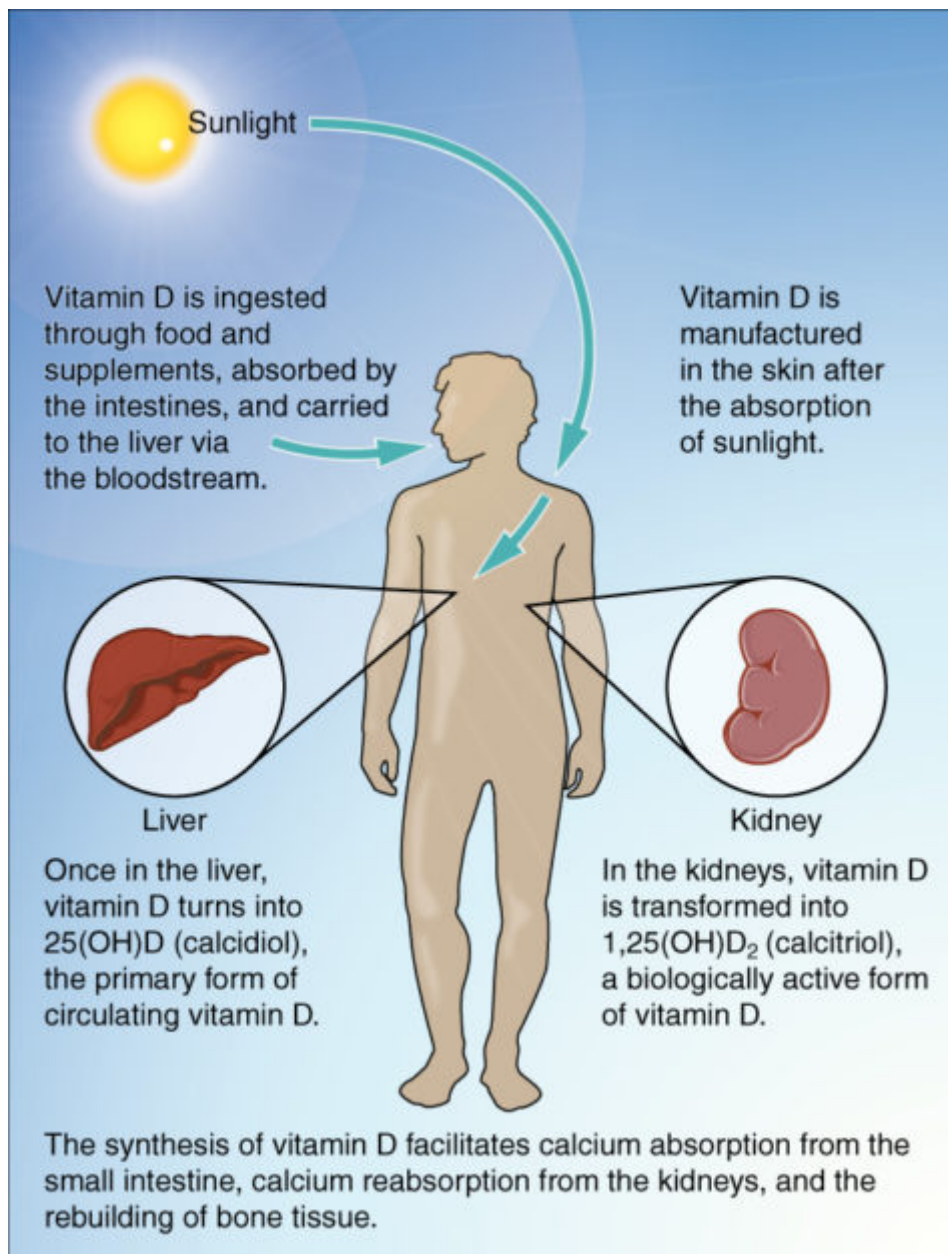


Image: "Synthesis of vitamin D," by OpenStax College - Anatomy & Physiology, Connexions Website. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Hypoparathyroidism

Hypoparathyroidism is an endocrine disorder in which our body does not produce an adequate **parathyroid hormone**. Parathyroid hormone (PTH) is secreted by the parathyroid glands. These are four glands which, as their name suggests, lie parallel to the thyroid gland. PTH plays a key role in the **regulation of serum calcium levels**. It **elevates** the levels of calcium in the blood, which is usually achieved by:

1. **Mobilization of calcium** as well as phosphate from the **bone** into the extracellular fluid, then into the blood
2. **Reduction of calcium excretion** from the **kidney**, thus retention of calcium in the blood
3. **Increased activation of inactive vitamin D3**, which is another hormone that is important in the maintenance of normal calcium levels in the **blood**.

In cases where hypoparathyroidism is present, these functions performed by PTH are absent or insufficient, resulting in **hypocalcemia**. Hypoparathyroidism can occur following a variety of causes, as described below.

Damage to the parathyroid glands. This can occur during thyroid surgery, which happens to be the **most common** cause of hypoparathyroidism. Hypoparathyroidism is, however, not that common a complication of thyroidectomies, as only a small percentage of patients present with hypoparathyroidism in the post-thyroidectomy period.

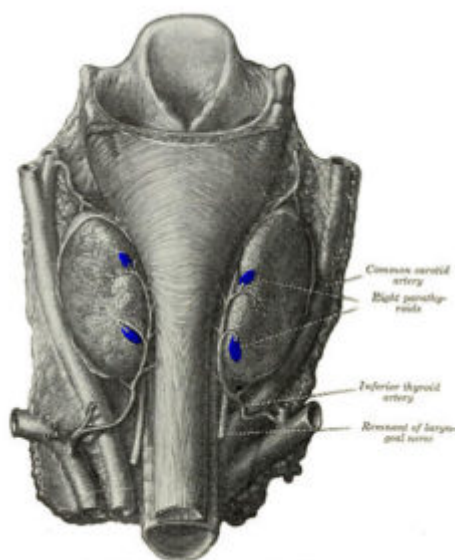


FIG. 1177.—Parathyroid glands. (Halsted and Ersson.)

[Image](#): "Thyroid and parathyroid glands from Gray's Anatomy," by CFCF - Own work, License: [CC BY-SA 3.0](#)

Damage to the parathyroid glands can also occur in surgery aimed at treating laryngeal malignancies or other neck tumors. It can also result following **extensive irradiation to the neck region**, face, and mediastinum.

Congenital causes of hypoparathyroidism are relatively rare, including the well-known **DiGeorge syndrome**. This syndrome manifests with congenital **cardiac** defects, **abnormal** facies characterized by micrognathia, broad nasal bridges and a long face, absent **thymus** with T-cell immune dysfunction, **cleft lip/palate** and neonatal **hypocalcemia**. This syndrome occurs due to the deletion of a part of chromosome 22, more specifically at chromosome 22q11.2 and can be remembered by a mnemonic **CATCH-22**.

Autosomal dominant familial hypoparathyroidism is another cause of hypoparathyroidism that may be congenital, although the presentation may be seen in adulthood. Affected patients may present with hypoparathyroidism, **deafness** (usually sensorineural) and may demonstrate symptoms associated with other conditions, for example, **diabetes mellitus**.

Autoimmune polyendocrine syndrome type 1 is a rare autoimmune disorder that affects multiple endocrine glands, including parathyroid glands, demonstrating their insufficient functioning.

Parathyroid gland infiltration. This may be seen in conditions such as **hemochromatosis** and **Wilson's disease**, in which there is an accumulation of abnormal levels of iron and copper, respectively, in several glands, including the parathyroid gland resulting in hypoparathyroidism.

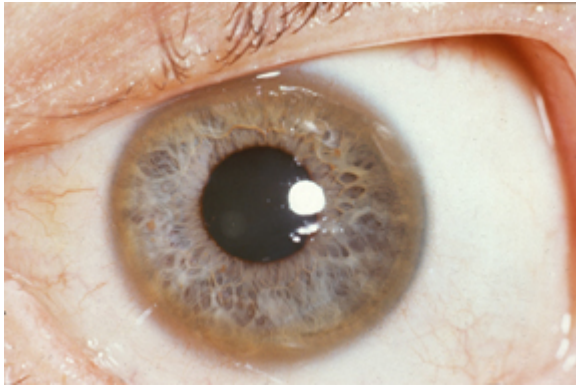


Image: "Kayser-Fleischer ring: copper deposition in Descemet's membrane of the cornea. These rings can be either dark brown, golden, or reddish-green, are 1 to 3 mm wide, and appear at the corneal limbus. With rare exceptions, they are diagnostic of inherited hepatolenticular degeneration—Wilson's disease. This 32-year-old patient complained of longstanding difficulty speaking. He also had a tremor," by Herbert L. Fred, MD, Hendrik A. van Dijk - <http://cnx.org/content/m15007/latest/>, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Pseudohypoparathyroidism is an autosomal recessive disorder with end-organ **resistance to parathyroid hormone** owing to a mutation in a G protein (GNAS).

Parathyroid hormone is secreted normally, but the end organs, especially the **kidney** and **bones**, are resistant to the biological actions of PTH. This leads to hypocalcemia, hyperphosphatemia and raised serum concentration of the parathyroid hormone.

Patients with pseudohypoparathyroidism may have typical features such as obesity, short stature, rounded face, short 4th and 5th metatarsals and metacarpals as well as subcutaneous calcification. When these features are present the condition is called **Albright's Hereditary Osteodystrophy**.

There is no symptomatic relief upon administration of PTH.

Hypomagnesemia may reduce the sensitivity of parathyroid glands and decrease the secretion of PTH, resulting in **PTH-dependent hypocalcemia**. This hypocalcemia is rapidly corrected following the administration of magnesium. Therefore, magnesium levels should be checked in patients with hypoparathyroidism.

Malabsorption

Calcium is absorbed passively throughout the intestine, and **actively** at the **duodenum** and **jejunum**. In malabsorptive diseases, such as celiac disease and chronic pancreatitis, calcium will not be absorbed into the body properly, resulting in hypocalcemia.

Large blood transfusions

Most blood products including fresh frozen plasma and platelets contain **high concentrations of citric acid** to prevent coagulation. During major blood transfusions, this citrate **binds to calcium** in the serum thus lowering the ionized plasma calcium concentration.

Acute pancreatitis

Acute pancreatitis releases the pancreatic enzymes, including lipases, into the circulation. Lipase breaks down triglycerides into **free fatty acids that bind with serum calcium**,

resulting in hypocalcemia.

Alkalosis

In alkalosis, increased calcium attaches to serum proteins in the exchange of hydrogen ions. This may decrease the levels of ionized calcium in the blood.

Rhabdomyolysis

In rhabdomyolysis, the lysed muscle cells release enzymes that chelate calcium, thus resulting in hypocalcemia.

Clinical Features of Hypocalcemia

Most cases of hypocalcemia are asymptomatic. The symptoms depend upon the severity of the condition, although the exact concentration at which symptoms appear is yet to be determined, and so is the rapidity with which hypocalcemia occurs (i.e., acute or chronic setting).


Neuromuscular irritability

A normal calcium level is important to maintain a normal neuromuscular function. Hypocalcemia increases the neuronal excitability by increasing the permeability of its membranes to sodium ions. Most severe forms of hypocalcemia present with **tetany**. Symptoms of tetany can be mild or severe.

Paresthesia, numbness, especially in the perioral region, and muscle cramps are all mild symptoms of tetany, whereas carpopedal spasms, seizures, and laryngospasms indicate severe tetany. Bronchospasms, hypotension and reduced cardiac contractility are other features of neuromuscular irritability. Behavioral changes such as impaired intellectual capacity, depression and personality changes may also occur.

In children, hypocalcemia may present with a **classical triad** of **convulsions, stridor** – due to spasms affecting the glottis – and **carpopedal spasms**. In carpopedal spasms, the [hand](#) attains a characteristic posture that involves adduction of the thumb and flexion at the metacarpal phalangeal joints.

The two common clinical signs of hypocalcemia are:

-  [Image](#): “A hand being held similarly to Trousseau’s sign,” by Huckfinne. License: Public Domain

Chvostek sign – if you tap over the facial nerve, the patient develops twitching of the ipsilateral facial muscles.

- Trousseau’s sign** – a sphygmomanometer cuff is applied and inflated above the systolic pressure for 3 minutes. This will induce a tetanic spasm of the fingers and wrist.

Both these signs are evident of latent tetany.

Electrocardiogram (ECG)

The ECG may show QT interval prolongation with an increased risk of **ventricular arrhythmias** and decreased cardiac contractility, which may present with heart failure, hypotension, syncope, and angina.

Differential Diagnosis of Hypocalcemia

Absent parathyroid hormone

- Hereditary hypoparathyroidism
- Idiopathic hypoparathyroidism
- Syndromes associated with hypoparathyroidism (DiGeorge's syndrome, autoimmune polyendocrine syndrome type 1, etc.)
- Acquired hypoparathyroidism (surgery, radiation)
- Hypomagnesemia

Ineffective parathyroid hormone

- [Chronic renal failure](#):
- Vitamin D deficiency (decreased dietary intake, decreased exposure to sunlight, intestinal malabsorption)
- Pseudohypoparathyroidism

Overwhelmed parathyroid hormone

- Severe acute hyperphosphatemia
- Tumor lysis
- [Acute renal failure](#)
- Rhabdomyolysis

Investigations for Hypocalcemia

The clinical history and the presentation are often diagnostic of hypocalcemia, which is then confirmed by **low serum calcium levels**.

However, the first thing to check in these patients is whether this is **true hypocalcemia**, or it is an effect from **low albumin levels**. As previously mentioned, about 40-45% of serum total calcium is bound to albumin, hence, albumin-deficient states may cause decreased serum total calcium while the physiologically active serum ionized calcium level may be normal.

Therefore, albumin levels should be checked along with the serum calcium levels. In case of low albumin, the serum calcium levels should be corrected. **The correction constitutes this: for every decrease in albumin by 1 g, there is a decrease in calcium by 0.8 mg/dL.** If the corrected calcium level becomes normal then the patient does not have true hypocalcemia and should be treated for low albumin instead. However, if calcium levels are still low after correction, then the patient has true hypocalcemia.

- **Serum parathyroid hormone levels** - if the parathyroid hormone levels are low in the serum, then it could be hypoparathyroidism. If it is high then the

hypocalcemia could be due to other causes, such as vitamin D deficiency, or pseudohypoparathyroidism.

- **Serum phosphate levels** - phosphate levels are often raised in hypocalcemic patients, especially if the underlying cause is hypoparathyroidism or renal failure. Serum phosphate levels may decrease in vitamin D deficiency.
- **Serum magnesium levels** - to exclude hypomagnesemia; severe hypomagnesemia will result in reduced secretion and activity of the parathyroid hormones, which will be reversed by magnesium replacement.
- **Serum vitamin D levels** - vitamin D levels will be low in vitamin D deficiency.
- **Serum creatinine and BUN** - to exclude any renal diseases.
- **X-rays of metacarpals** - shows short 4th and 5th metacarpals in pseudohypoparathyroidism.

Treatment of Hypocalcemia

The treatment of hypocalcemia depends on the underlying cause and its severity. The cause should be properly evaluated and addressed. For example, in vitamin D and parathyroid hormone deficiency, the respective hormones should be administered. Serum magnesium should be corrected in cases of hypomagnesemia.

Severe hypocalcemia

If the patient has any evidence of tetany, latent tetany, laryngospasms or muscle cramps, the patient should be given **intravenous calcium gluconate** or **calcium chloride**. It will readjust the calcium in serum as quickly as possible.

Mild hypocalcemia

If the patient has mild symptoms then only maintenance therapy is needed. These patients should be given **oral calcium carbonate 2-4 g/day** or **calcium citrate**. This is usually prescribed in conjunction with **vitamin D** if the vitamin D levels are subnormal. The best way to give vitamin D is in the active form, 1,25 hydroxycholecalciferol. It has the quickest action as it does not require hydroxylation by kidney and liver enzymes.

Patients with end-stage kidney disease develop hyperphosphatemia. When the phosphate levels increase, the calcium levels go down further. Therefore, these patients should have a **restricted diet** and **phosphate binders such as calcium carbonate and aluminum hydroxide** should be given to reduce the phosphate levels in the blood.

However, during the treatment, the serum calcium levels should be monitored regularly for hypercalcemia.

References

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

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