Hypocalcaemia

What is hypocalcaemia?

The normal range for total serum calcium is 2.1-2.6 mmol/L (normal range is quoted for guide only - ranges vary between laboratories) [1] .

Derangements above (hypercalcaemia) and below (hypocalcaemia) this level interfere with the normal function of most body cells but nerve and muscle cells in particular.

In the hypocalcaemic state, about 40% of plasma calcium is bound to albumin. It is the unbound, ionised fraction of calcium that is important physiologically and the level for serum calcium is usually reported as both uncorrected and corrected (where adjustment is made for changes in albumin levels).

Extracellular calcium-sensitive receptors (CaSRs) have been identified which enable the parathyroid gland and other tissues involved in calcium homeostasis (principally bone and kidney) to monitor and regulate calcium levels. Activating genetic mutations have been identified which cause a hypocalcaemic syndrome of varying severity, termed 'autosomal dominant hypocalcaemia or hypoparathyroidism' as well as Bartter's syndrome type V [2] [3] .

Adjusting calcium level for albumin

- Approximate 'correction': add 0.1 mmol/L to calcium concentration for every 4 g/L that albumin is below 40 g/L and a similar subtraction for raised albumin.
- This does not replace measurement of ionised calcium concentration.

- Special care should be taken where the measured albumin concentration is less than about 20 g/L, because of the known inaccuracy of albumin measurement at low levels.
- Other factors affect calcium binding - for example, plasma proteins in myeloma.

Epidemiology

Evidence for overall incidence is sparse. The condition spans all ages and both sexes. It has a prevalence of 18% in all patients in hospital and 85% in the intensive care unit [4] .

Hypocalcaemia presentation

Hypocalcaemia symptoms

Hypocalcaemia symptoms generally correlate with the magnitude and rapidity of the fall in serum calcium: mild hypocalcaemia (2.00-2.12 mmol/L) can be asymptomatic, whereas acute symptoms of neuromuscular irritability can develop in the more severe form (<1.9 mmol/L) [4] .

- Paraesthesia (usually fingers, toes and around mouth).
- Tetany.
- Carpopedal spasm (wrist flexion and fingers drawn together).
- Muscle cramps.

Hypocalcaemia signs

- **Chvostek's sign** (also called Weiss' sign, Schultze-Chvostek sign or facialis phenomenon) is a feature of latent tetany and may be seen in hypocalcaemia or normocalcaemia (in anxious patients):
    - When the course of the facial nerve is tapped (as it passes in front of the ear, below the zygomatic arch), muscular spasm is provoked. This is seen as twitching of the face, mouth or nose.
    - It was named by František Chvostek, an Austrian physician (1835-1884).

- **Trousseau's sign** occurs in patients with hypocalcaemia (or hypomagnesaemia) and results from enhanced neuromuscular excitability:
    - To elicit this sign, inflate a blood pressure cuff to a pressure above the patient's systolic level and maintain the pressure for several minutes.
    - Look for carpopedal spasm which involves flexion at the wrist, flexion at the metacarpophalangeal joints, extension of the interphalangeal joints and adduction of the thumbs and fingers.
    - Patients may also experience paraesthesia of the fingers and there may be muscle fasciculations.
    - It is said to occur before the other signs of hypocalcaemia and is both specific and sensitive. However, it is less sensitive than Chvostek's sign (tapping on the facial nerve).
    - The Trousseau-von Bonsdorff test is an extension of Trousseau's sign. As soon as the cuff is deflated, the patient is asked to take deep breaths at a rate of 40 per minute and carpopedal spasm is induced in hypocalcaemia.
- Seizures.
- Prolonged QT interval which may progress to ventricular fibrillation (VF) or heart block.
- Laryngospasm.
- Bronchospasm.

With prolonged hypocalcaemia

- Subcapsular cataract.
- Papilloedema.
- Abnormal teeth.
- Ectopic calcification (for example, in basal ganglia may cause extrapyramidal neurological symptoms).
- Dementia and confusion.

Hypocalcaemia causes (aetiology)

Causes of hypocalcaemia fall into two main classes.

With low parathyroid hormone (PTH) levels (hypoparathyroidism) [5]

- Parathyroid agenesis - alone or along with other abnormalities - eg, DiGeorge's syndrome.
- Parathyroid destruction - due to surgery, radiotherapy, infiltration by metastases or systemic disease (eg, amyloidosis, sarcoidosis).
- Autoimmune disorder.
- Reduced parathyroid secretion - due to gene defects, hypomagnesaemia, neonatal hypocalcaemia (may be due to maternal hypercalcaemia), hungry bone disease (after parathyroidectomy), mutation in CaSR.

With high PTH levels (secondary hyperparathyroidism)

- Vitamin D deficiency - due to nutritional lack, malabsorption, liver disease, receptor defects.
- Vitamin D resistance (rickets) - renal tubular dysfunction (Fanconi's syndrome) or receptor defect.
- PTH resistance - pseudohypoparathyroidism, hypomagnesaemia.

Important other causes of hypocalcaemia

- Hyperventilation.
- Drugs - calcium chelators (citrate in blood transfusion); bone resorption inhibitors (bisphosphonates, calcitonin); drugs affecting vitamin D (phenytoin, ketoconazole), foscarnet.
- Acute pancreatitis.
- Acute rhabdomyolysis - usually in relation to crush injuries.
- Malignancy - tumour lysis (following chemotherapy) or osteoblastic metastases (most common in prostate and breast cancers).
- Toxic shock syndrome.

- COVID-19 infection - there is a high incidence of hypocalcaemia in patients with severe infection. Ionised calcium estimation has been suggested as a means of identifying patients who require hospitalisation [6] .

The most common causes are hypoparathyroidism (frequently following surgery), vitamin D deficiency or abnormal metabolism, chronic kidney disease and hypomagnesaemia.

Hypocalcaemia is extremely common in patients in hospital and correlates with the severity of their illness [7] .

Differential diagnosis [4]

	Serum phosphate	Serum parathyroid hormone (PTH)	Serum alkaline phosphatase (ALP)	Other
Chronic kidney disease	Raised	Raised	Raised	Raised creatinine
Hypoparathyroidism	Raised	Low/undetectable	Normal	Normal vitamin D metabolites
Pseudohypoparathyroidism	Raised	Raised		
Vitamin D deficiency or malabsorption	Low	Raised	Raised	Low $25(OH)D_3$ levels

- Hypoalbuminaemia - correct for albumin.
- Consider drug therapy, malignancy, acute pancreatitis and rhabdomyolysis.

Investigations

- Is the patient really hypocalcaemic? (Ideally take fasting blood specimens, uncuffed - remove tourniquet after needle in vein but before taking blood sample.) Ensure use of an adjusted calcium value.

- Exclude chronic kidney disease (check U&Es), acute pancreatitis (check amylase), rhabdomyloysis (check serum creatine kinase).
- Estimate serum magnesium and phosphate.
- Estimate serum PTH.
- Evaluate vitamin D metabolism.
- Perform an ECG to exclude dysrhythmias and prolonged QT interval.

Always assess the patient clinically. Patients vary: some may be symptomatic within the normal reference range since there are narrow individual ranges within the normal reference range.

Management[1] [4]

Acute hypocalcaemia

- Treat where symptomatic (seizures, tetany) or at high risk of complications with a serum calcium <1.90 mmol/L.
- Give 10 ml (2.25 mmol) of calcium gluconate 10% by slow intravenous (IV) injection. Repeat as necessary or follow with infusion of calcium gluconate 10% infusion - 40 ml (9 mmol)/24 hours.
- Oral calcium preparations may need to be given as supplements to IV treatment or where IV access is difficult.
- Monitor serum calcium concentrations regularly to judge response.
- If it is likely to be persistent, give vitamin D by mouth.
- If hypomagnesaemic, it is necessary to correct the magnesium level before the hypocalcaemia will resolve.

Persistent hypocalcaemia

- Initially, supplementary calcium (10-20 mmol calcium bd-qds) and vitamin D; however, calcium may be discontinued once stabilised.
- Calcitriol (oral $1,25(OH)_2D_3$) is more expensive than the parent vitamin D compounds, vitamin D_2 (ergocalciferol) and vitamin D_3, but is used first-line in patients with renal impairment because it does not require hydroxylation by the kidney for activation.

- Closely monitor the patient's serum and urine concentration. In some hypoparathyroid individuals, calcium levels may remain permanently unstable and it is important that the maintenance dose be regularly monitored.and adjusted.

Prevention

- Ensure adequate dietary intake or consider supplementation in those with necessary dietary exclusions - eg, lactose-intolerant [8] .
- To avoid hypocalcaemia in patients on total parenteral nutrition, ensure magnesium and calcium levels are checked at least weekly and more frequently if the patient is acutely unwell.
- Giving $1,25(OH)_2D_3$ and calcium for several days before elective subtotal parathyroidectomy may prevent extreme hypocalcaemia.

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