Hypocalcaemia

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Abstract

Hypocalcaemia is encountered in all areas of clinical practice: in primary care, where vitamin D deficiency is often the cause, and in unselected secondary care, where hypocalcaemia has a prevalence of 18%, rising to 85% in intensive care environments. An understanding of the physiological basis of calcium homoeostasis is essential to deciphering the cause of underlying hypocalcaemia. Awareness of the clinical presentation, differential diagnosis and treatment of hypocalcaemia is important. Hypocalcaemia is potentially life-threatening and carries risk of serious errors in management. It can be an asymptomatic laboratory finding or a life-threatening metabolic disturbance. Acute hypocalcaemia can result in severe symptoms that indicate a medical emergency requiring rapid admission to hospital and correction with intravenous calcium. In contrast, when hypocalcaemia develops slowly, even if it is quantitatively severe, patients can be surprisingly free of classical symptoms. This article covers essential aspects of the physiological regulation of calcium and offers practical clinical advice on investigating, diagnosing and treating common (and less common) causes of hypocalcaemia. Treatment advice is proposed for acute hypocalcaemia, vitamin D deficiency and management of hypoparathyroidism.

Keywords Calcium; calcium-sensing receptor; hypocalcaemia; hypomagnesaemia; hypoparathyroidism; MRCP; osteomalacia; parathyroid hormone; pseudohypoparathyroidism; vitamin D deficiency

Key points

- Patients with symptomatic hypocalcaemia or an adjusted serum calcium <1.9 mmol/litre should be treated with intravenous calcium in a monitored environment
- Measurement of plasma parathyroid hormone (PTH) with a standard biochemical profile allows the aetiology of hypocalcaemia to be deciphered in most cases
- Patients with hypoparathyroidism should be monitored long term for hypercalciuria and nephrolithiasis
- Thiazide diuretics can be employed to reduce hypercalciuria
- Severe and chronic, but not mild, vitamin D deficiency causes hypocalcaemia
- PTH therapy is now approved by the FDA and EMA for the treatment of chronic hypoparathyroidism in patients who cannot be adequately treated on standard therapies. Its exact positioning in treatment of hypoparathyroidism is yet to be determined and the potential for influencing chronic disease outcomes is also to be clarified
- Molecular characterization of 'idiopathic' hypoparathyroidism cases allows informed genetic counselling and screening

Calcium homoeostasis

Calcium is critical for many fundamental cellular functions, and extracellular calcium homoeostasis is tightly regulated (typical reference range for serum calcium 2.10–2.60 mmol/litre). Calcium sensing occurs via the calcium-sensing receptor (CaSR), which modulates parathyroid hormone (PTH) synthesis and secretion. PTH stimulates calcium reabsorption in the kidney and calcium release from bone.

Vitamin D is derived primarily through synthesis in the skin with a small contribution from dietary intake. Skin synthesis of colecalciferol (vitamin D_3) from 7-dehydrocholesterol requires exposure to ultraviolet (UVB) light and is considerably reduced by skin pigmentation. Colecalciferol is bound to vitamin D-binding protein and is converted to 25-hydroxyvitamin D (25OHD) in the liver. PTH stimulates renal production of active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) from 25OHD, via the action of 1α-hydroxylase. $1,25(OH)_2D$ acts on the gastrointestinal tract to increase calcium absorption.

Presentation of hypocalcaemia

Clinical features of hypocalcaemia are mediated through neuromuscular excitability and comprise muscle twitching, spasms, tingling/numbness (classically peri-oral and digital) and carpopedal spasm, progressing to tetany, seizures, and cardiac dysrhythmias. The development of neuromuscular excitability depends on both absolute serum concentration of calcium and how rapidly it falls. Rapid falls in calcium are often associated with symptoms, whereas patients with hypocalcaemia of gradual onset can be surprisingly symptom-free. Chronic hypocalcaemia can be associated with neuropsychiatric symptoms, cataract formation and occasionally raised intracranial pressure.

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Chvostek's sign (eliciting facial muscle spasm by tapping the skin over the parotid gland and facial nerve) is a poor discriminator of hypocalcaemia; Trousseau's sign (inducing carpopedal spasm by inflating a blood pressure cuff on the arm) is more specific.

Causes of hypocalcaemia

Hypocalcaemia can be broadly categorized into conditions associated with a quantitative deficiency of PTH (hypoparathyroidism) and those where there is secondary hyperparathyroidism (Table 1).

Hypoparathyroidism

PTH deficiency results in reduced production of $1,25(OH)_2D$ with subsequent renal calcium loss and reduced intestinal absorption.

Parathyroid destruction: hypocalcaemia resulting from hypoparathyroidism is most frequently caused by parathyroid damage during thyroid or parathyroid surgery. Hypoparathyroidism can also occur as isolated or syndromic autoimmune conditions. In addition, antibodies directed at parathyroid tissue can be found in some patients with autoimmune hypoparathyroidism.

Developmental parathyroid disorders: isolated hypoparathyroidism has complex inheritance patterns. Hypoparathyroidism also features as part of a number of syndromes (e.g. DiGeorge syndrome or 22q11.2 deletion syndrome, characterized by features including hypoparathyroidism, hypoplasia of the thymus, congenital heart disease, palate defects and learning disabilities).

Reduced parathyroid hormone secretion: constitutive activation of the CaSR from mutations at 3q21.1 results in mild hypocalcaemia with hypoparathyroidism in autosomal dominant hypocalcaemia type 1. Presentation can be on routine screening or with symptomatic hypocalcaemia, with nephrocalcinosis or ectopic calcifications. A Bartter-like phenotype (Bartter syndrome type V) also exists, which is associated with renal salt-wasting and hypokalaemic metabolic alkalosis. Autosomal dominant hypocalcaemia type 2 is associated with gain-of-function mutations in the G protein α-11 subunit (19p13.3), which acts as a signalling partner for CaSR. An acquired form, caused by autoimmune activation of the parathyroid and renal CaSR, has also been described.[1]

Proton pump inhibitor-associated hypomagnesaemia

Proton pump inhibitors (PPIs) are used widely for the treatment of peptic ulcers and related diseases. Their use can be associated with hypomagnesaemia, in addition to hypoparathyroidism, hypocalcaemia and hypokalaemia. Features typically resolve within days of discontinuation of the PPI.

Vitamin D deficiency

Hypocalcaemia can be seen as a consequence of severe and chronic vitamin D deficiency, but frankly low serum calcium is not a feature of mild vitamin D deficiency/insufficiency. Reduced exposure to UV light, especially in the presence of pigmented skin, can cause vitamin D deficiency (osteomalacia). Vitamin D requirements also increase during and after pregnancy, and low maternal vitamin D is associated with hypocalcaemia in breast-fed children.

Patients with diseases of the small intestine can have suboptimal absorption of dietary calcium and vitamin D, and are at particular risk of hypocalcaemia. Severe hypocalcaemia has also been reported in patients with pre-existing vitamin D deficiency who are given intravenous bisphosphonates, which prevent stimulation of bone resorption by elevated plasma PTH.

Rickets and osteomalacia: nutritional rickets has been defined by defective chondrocyte differentiation and mineralization of the growth plate and osteoid, caused by vitamin D deficiency and/or low calcium intake in children. This can be associated with skeletal deformities and growth failure. In contrast, osteomalacia represents reduced mineralization of osteoid in mature bone following growth plate fusion.[2] Rickets is associated with vitamin D deficiency, with an increased incidence in individuals with serum 25OHD concentrations <30 nmol/litre. Radiological features include growth plate widening and metaphyseal cupping, with affected groups having an increased fracture risk.

Causes of hypocalcaemia

Hypocalcaemia with inappropriately low serum PTH

Destruction of parathyroid glands

- Surgery, autoimmune, radiation, infiltration

Abnormalities of parathyroid development

- Isolated hypoparathyroidism
  - Autosomal recessive, autosomal dominant or X-linked
- Syndromes of hypoparathyroidism associated with developmental anomalies
  - e.g. DiGeorge sequence

Reduced PTH secretion/function

- Mutations of the CaSR causing constitutive activation
- Autoimmune activation of the CaSR
- Hypomagnesaemia
- 'Hungry bone' disease following parathyroidectomy

Hypocalcaemia with secondary hyperparathyroidism

Vitamin D deficiency

- Low UV exposure, poor diet, malabsorption, chronic renal disease, enzyme-inducing drugs

Resistance to PTH

- Pseudohypoparathyroidism
- Hypomagnesaemia

Resistance to vitamin D

- Mutations in vitamin D receptor, mutations in 1α-hydroxylase enzyme

Miscellaneous

Following drug treatment

- Intravenous bisphosphonates (and other drugs inhibiting bone turnover) in untreated vitamin D deficiency
- Gadolinium salts used in magnetic resonance imaging
- Foscarnet
- Osteoblastic metastases, hyperphosphataemia, acute pancreatitis, acute rhabdomyolysis, acute severe illness, tumour lysis, hyperventilation, after massive transfusion.

Table 1

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