Hypocalcaemia

Neil Gittoes

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 an intensive care environment. An understanding of the physiological basis of calcium homeostasis 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 risks for serious errors in management. It may be an asymptomatic laboratory finding or a life-threatening metabolic disturbance. Acute hypocalcaemia can result in severe symptoms that require rapid admission to hospital and correction with intravenous calcium. In contrast, when hypocalcaemia develops slowly, even if quantitatively severe, patients can be surprisingly free of classical symptoms. This article will cover essential aspects of physiological regulation of calcium and offer 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; osteomalacia; parathyroid hormone; pseudohypoparathyroidism; vitamin D deficiency

Calcium homeostasis

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 (8.4–10.4 mg/dl)). 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. PTH also stimulates renal production of active 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D. 1,25-dihydroxyvitamin D acts on the gastrointestinal tract to increase calcium absorption. Vitamin D is derived primarily through synthesis in the skin with a small contribution from dietary intake. Skin synthesis requires exposure to ultraviolet (UV) light and is considerably reduced by skin pigmentation.

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What's new?

- Parathyroid hormone (PTH) therapy shows promise as an effective and potentially safer form of therapy for hypoparathyroidism. It is currently not licensed for this indication and more research is required
- Proton pump inhibitors are recognized causes of severe hypomagnesaemia, which inhibits PTH release and may cause severe hypocalcaemia
- Molecular characterization of more cases of 'idiopathic' hypoparathyroidism allows informed genetic counselling and screening

Presentation of hypocalcaemia

Symptoms of hypocalcaemia are mediated through neuromuscular excitability and comprise muscle twitching, spasms, tingling/numbness and carpopedal spasm, progressing to tetany, seizures, and cardiac dysrhythmias.[1] The development of neuromuscular excitability depends on both the 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 may be surprisingly free of symptoms. Chronic hypocalcaemia can be associated with neuropsychiatric symptoms, cataract formation and occasionally raised intracranial pressure. Chvostek's sign is a poor discriminator of hypocalcaemia; Trousseau's sign is more specific.[2]

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

Parathyroid destruction: hypocalcaemia due to hypoparathyroidism is most frequently caused by parathyroid damage during thyroid or parathyroid surgery.[3] Hypoparathyroidism may also occur as isolated or syndromic autoimmune conditions.[4] Antibodies directed at parathyroid tissue may also be found in some cases of autoimmune hypoparathyroidism.[5]

Developmental parathyroid disorders: isolated hypoparathyroidism has complex inheritance patterns.[6] Hypoparathyroidism also features as part of a number of syndromes (e.g. the DiGeorge sequence).[7]

Reduced PTH secretion: constitutive activation of the CaSR is seen in autosomal dominant hypocalcaemic hypercalciuria (ADHH), which results in mild hypocalcaemia with hypoparathyroidism. An acquired form, due to autoimmune activation of the parathyroid and renal CaSR, has also been described.[8]

Vitamin D deficiency

Hypocalcaemia may 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.[9]

Causes of hypocalcaemia

Hypocalcaemia with inappropriately low serum parathyroid hormone (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 calcium-sensing receptor (CaSR) causing constitutive activation
- Autoimmune activation of the CaSR
- Hypomagnesaemia
- 'Hungry bone' disease following parathyroidectomy

Hypocalcaemia with secondary hyperparathyroidism

Vitamin D deficiency

- Low ultraviolet 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[17]

- Intravenous bisphosphonates (and other drugs that inhibit 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, post-massive transfusion

Table 1

Reduced exposure to UV light, especially in the presence of pigmented skin, may cause vitamin D deficiency (osteomalacia). Vitamin D requirements also increase during and after pregnancy and low maternal vitamin D is associated with hypocalcaemia in breastfed children.

Patients with small intestinal diseases may 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.[10]

Resistance to PTH

A biochemical pattern similar to hypoparathyroidism occurs in the presence of high plasma PTH and is due to tissue resistance to PTH (pseudohypoparathyroidism, PHP). PHP is a genetically heterogeneous condition with some patients having skeletal abnormalities (Albright's hereditary osteodystrophy, AHO) that can occur in other family members independent of any abnormality of serum calcium (termed pseudo-pseudohypoparathyroidism).[6]

'Resistance' to vitamin D

The identification of rare cases of rickets 'resistant' to vitamin D treatment led to the finding of very rare anomalies of vitamin D metabolism and of the vitamin D receptor. Such conditions present early in life with hypocalcaemia and rickets.[11]

Investigation of hypocalcaemia

Measurement of PTH concentration is most informative when investigating the aetiology of hypocalcaemia. Along with a standard biochemical profile, in the context of the clinical history, all but the most idiosyncratic causes of hypocalcaemia can be determined (Figure 1).

With intact parathyroid function, hypocalcaemia causes PTH hypersecretion. Low or inappropriately 'normal' PTH concentrations with hypocalcaemia indicate hypoparathyroidism. A high PTH in the presence of normal renal function suggests deficiency of vitamin D or calcium malabsorption. PTH concentration can also be inappropriately normal in hypomagnesaemia[12] or when the CaSR displays increased sensitivity.

Raised serum alkaline phosphatase suggests osteomalacia, though metastatic cancer, with sclerotic metastases should also be considered. PTH stimulates renal phosphate clearance, so serum phosphate is low in non-parathyroid disease but high with PTH deficiency. Renal function should be measured because the kidney is central to several aspects of calcium homoeostasis. Serum magnesium is important for synthesis and release of PTH. In hypomagnesaemia, release of PTH is inhibited, leading to (potentially severe) hypocalcaemia.

Treatment of hypocalcaemia

Hypocalcaemia requiring acute intervention (largely determined by the speed of onset and biochemical severity of hypocalcaemia) is managed via a generic approach; longer term management depends on the clinical context and aetiology of hypocalcaemia.

Acutely presenting hypocalcaemia

Neuromuscular irritability with hypocalcaemia signals a requirement for prompt management with intravenous calcium. Even in asymptomatic patients with adjusted serum calcium less than 1.9 mmol/litre (7.6 mg/dl), early intervention and in-patient management should be considered.[13] A treatment algorithm for acute hypocalcaemia in adults is proposed in Figure 2. Calcium gluconate 10% (diluted in 50–100 ml glucose 5%), 10–20 ml, is infused slowly over 10 minutes with ECG monitoring (can be repeated). Continuous administration of a dilute solution of calcium (calcium gluconate 10%, 100 ml, in glucose 5% or sodium chloride 0.9%, 1 litre, at an initial infusion rate of 50 ml/hour, aiming to maintain serum calcium at the lower end of the reference range) is often necessary to prevent recurrent hypocalcaemia. Oral calcium supplements are initiated and, if PTH is deficient or non-functional, calcitriol (1 μg/day) is administered. In patients with hypomagnesaemia-related hypocalcaemia, magnesium replacement is required. With milder degrees of hypocalcaemia, treatment depends on the underlying cause.