Quick Reference for Residents:

Hypocalcemia: Evaluation

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Diagnostic approach to hypocalcemia

INTRODUCTION — Hypocalcemia has many causes. It can result from inadequate parathyroid hormone (PTH) secretion, PTH resistance, vitamin D deficiency or resistance, abnormal magnesium metabolism, and extravascular deposition of calcium, which can occur in several clinical situations.

The diagnostic approach to hypocalcemia involves confirming, by repeat measurement, the presence of hypocalcemia and distinguishing among the potential etiologies. The diagnosis may be obvious from the patient's history; examples include chronic kidney disease and postsurgical hypoparathyroidism. When the cause is not obvious or a suspected cause needs to be confirmed, other biochemical tests are indicated.

This topic will review the evaluation of patients with hypocalcemia. The clinical manifestations and treatment of hypocalcemia are discussed separately.
CONFIRM HYPOCALCEMIA — The first step in the evaluation of a patient with hypocalcemia is to verify with repeat measurement (total serum calcium corrected for albumin or ionized calcium) that there is a true decrease in the serum calcium concentration. If available, previous values for serum calcium should also be reviewed. If the patient has a low albumin-corrected serum calcium or ionized calcium concentration, further evaluation to identify the cause is indicated.

Hypoalbuminemia: Calcium correction — Calcium in serum is bound to proteins, principally albumin. As a result, the total serum calcium concentration in patients with low or high serum albumin levels may not accurately reflect the physiologically important ionized (or free) calcium concentration. Each 1 g/dL reduction in the serum albumin concentration will lower the total calcium concentration by approximately 0.8 mg/dL (0.2 mmol/L) without affecting the ionized calcium concentration and, therefore, without producing any symptoms or signs of hypocalcemia.

Therefore, a patient who has a serum albumin concentration that is 2 g/dL (20 g/L) below normal will have a fall in serum total calcium concentration of 1.6 mg/dL (0.4 mmol/L). If the measured serum total calcium concentration is 8 mg/dL (2 mmol/L), then the corrected value will be 9.6 mg/dL (2.4 mmol/L), which is normal. Thus, in patients with hypoalbuminemia or
hyperalbuminemia, the measured serum calcium concentration should be corrected for the abnormality in serum albumin (calculator 1) or for standard units (calculator 2).

**Ionized calcium** — If the diagnosis of hypocalcemia is in doubt, either because the patient's symptoms are atypical or the patient's serum calcium concentration is only slightly low, serum ionized calcium should be measured if a laboratory known to measure ionized calcium reliably is available. It is important to note that the affinity of calcium for albumin is increased in the presence of alkalosis. Thus, respiratory alkalosis may cause an acute decrease in ionized calcium.

**DETERMINING THE ETIOLOGY** — Hypocalcemia has many causes.

The etiology may be obvious from the patient's history and physical examination; examples include chronic kidney disease and postsurgical hypoparathyroidism. When the cause is not obvious or a suspected cause needs to be confirmed, other biochemical tests are indicated.

**Clinical clues** — The etiology of hypocalcemia may be obvious from the clinical history. A family history of hypocalcemia suggests a genetic cause. Chronic hypocalcemia is often seen in patients with an activating mutation of the calcium-sensing receptor and in pseudohypoparathyroidism.

On the other hand, acquired hypoparathyroidism is most often the result of postsurgical or autoimmune damage to the parathyroid glands. Postsurgical hypoparathyroidism can occur after thyroid, parathyroid, or radical neck surgery for head and neck cancer. Thus, a history of head and neck surgery or the presence of a neck scar suggests postsurgical hypoparathyroidism.

Autoimmune hypoparathyroidism can occur as an isolated abnormality and is also a common feature of polyglandular autoimmune syndrome type I, which is a familial disorder. The presence of chronic mucocutaneous candidiasis and adrenal insufficiency suggests a polyglandular syndrome.

There are several drugs that also may cause hypocalcemia.

Other causes of hypocalcemia that may be apparent from the history, physical examination, and routine laboratory data include acute or chronic kidney disease, acute pancreatitis, rhabdomyolysis, and marked increases in tissue breakdown with the release of phosphate from cells, as occurs in the tumor lysis syndrome.

The physical examination may reveal findings of latent tetany, such as Chvostek's and Trousseau's signs, which are strongly suggestive of hypocalcemia.
Laboratory evaluation — Among the tests that may be helpful in defining the etiology of hypocalcemia, measurement of serum intact parathyroid hormone (PTH) is the most valuable and should be performed in all patients with hypocalcemia.

Other measurements that may be helpful include serum magnesium, creatinine, phosphate, the vitamin D metabolites calcidiol (25-hydroxyvitamin D [25(OH)D]) and calcitriol (1,25-dihydroxyvitamin D, the active vitamin D hormone), alkaline phosphatase, amylase, and urinary calcium and magnesium excretion. These tests should be performed selectively based upon the patient's history and physical examination.

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<td><strong>PTH</strong></td>
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* In individuals with concurrent nutritional deficiency.
Serum PTH concentrations — Serum intact parathyroid hormone (PTH) measurements provide critical information in patients with hypocalcemia but can be interpreted correctly only when serum calcium is measured simultaneously. Hypocalcemia is the most potent stimulus of PTH secretion; as a result, a low or even normal serum PTH concentration in a patient with hypocalcemia is strong evidence of hypoparathyroidism.

The serum PTH concentration varies with the cause of the hypocalcemia.

- Serum PTH is reduced or inappropriately normal in patients with hypoparathyroidism.
- Serum PTH is elevated in patients with acute or chronic kidney disease, vitamin D deficiency, and pseudohypoparathyroidism.
- Serum PTH is typically normal or low in patients with hypomagnesemia or autosomal dominant hypocalcemia, a rare disorder characterized by an activating mutation in the calcium-sensing receptor gene.

Magnesium — Hypomagnesemia (serum magnesium concentration below 0.8 mEq/L [1 mg/dL or 0.4 mmol/L]) causes hypocalcemia by inducing PTH resistance or deficiency.

Serum magnesium should be measured in any patient with hypocalcemia in whom the cause is not obvious. Hypocalcemia should resolve within minutes or hours after restoration of normal serum magnesium concentrations if hypomagnesemia was the cause of the hypocalcemia.

A few patients with magnesium-responsive hypocalcemia have normal serum magnesium concentrations. These patients are presumed to have tissue magnesium deficiency. Thus, magnesium supplementation may be indicated in patients with unexplained hypocalcemia who are at risk for hypomagnesemia, such as patients with chronic malabsorption or alcoholism.

Phosphate — Phosphate levels may be elevated, low, or normal depending upon the etiology of hypocalcemia.

- Elevated — Persistent hypocalcemia and hyperphosphatemia is, in the absence of kidney disease or increased tissue breakdown, virtually diagnostic of either hypoparathyroidism (PTH deficiency) or pseudohypoparathyroidism (PTH resistance). The elevated serum phosphate concentration in patients with either disorder is due to loss of the stimulatory effect of PTH on urinary phosphate excretion and is therefore associated with an inappropriately low fractional excretion of phosphate.
- Low — The presence of a low serum phosphate concentration indicates either excess PTH secretion, which in the context of hypocalcemia means secondary hyperparathyroidism (and some abnormality in vitamin D intake or metabolism), or low dietary phosphate intake, which is uncommon.
- Normal — Normal serum phosphate in the setting of hypocalcemia may be consistent with hypomagnesemia or mild vitamin D deficiency.

Vitamin D metabolites — Vitamin D deficiency increases PTH secretion by causing hypocalcemia (due to the reduction in intestinal calcium absorption) and, to a lesser degree, by removing the normal inhibitory effect of calcitriol on PTH production. Vitamin D deficiency also diminishes intestinal phosphate absorption. Excess PTH enhances phosphate excretion and lowers the serum phosphate.
Measurement of serum 25(OH)D (calcidiol) provides more information about vitamin D deficiency than does measurement of serum 1,25-dihydroxyvitamin D (calcitriol) because the hypocalcemia-induced increase in PTH secretion stimulates renal 1,25-dihydroxyvitamin D production (in patients without underlying renal insufficiency). Thus, in individuals with vitamin D deficiency, serum 25(OH)D is low whereas 1,25-dihydroxyvitamin D is typically normal or high. In contrast, patients with hypoparathyroidism may have normal serum 25(OH)D and low 1,25-dihydroxyvitamin D concentrations.

The various causes of vitamin D deficiency usually can be distinguished by the history and other clinical findings (deficient dietary intake, inadequate sunlight exposure, malabsorption, phenytoin therapy) and by measurement of 25(OH)D (calcidiol). A more in-depth discussion of the individual disorders can be found elsewhere.

Patterns of vitamin D metabolites and phosphate — The following patterns in vitamin D metabolites and serum phosphate may be seen in patients with hypocalcemia and secondary increases in PTH and point to different underlying causes of hypocalcemia.

- A low serum 25(OH)D concentration in a patient with hypocalcemia and hypophosphatemia usually indicates that vitamin D intake or absorption (usually coupled with decreased production in skin) is low. Other possibilities include phenytoin therapy, hepatobiliary disease, or the nephrotic syndrome (in which vitamin D-binding protein is lost in the urine).
- The combination of normal or low serum 25(OH)D concentration and low serum 1,25-dihydroxyvitamin D concentration, with high-normal or elevated serum phosphate, indicates the presence of chronic kidney disease (easily diagnosed from the serum creatinine concentration). Chronic kidney disease is the only condition in which hypocalcemia and secondary hyperparathyroidism are not associated with low or low-normal serum phosphate (as a result of the inability of the diseased kidney to respond to the high PTH).
- The combination of normal or low serum 25(OH)D concentration, low serum 1,25-dihydroxyvitamin D concentration, and low serum phosphate suggests the presence of vitamin D-dependent rickets, type 1 (renal 1-alpha-hydroxylase deficiency), also called pseudo-vitamin D deficient rickets.
- Hereditary vitamin D-resistant rickets (also called vitamin D-dependent rickets, type 2) presents in early childhood and is associated with a defect in the vitamin D receptor. It should be suspected in hypocalcemic patients if serum phosphate is low and serum 1,25-dihydroxyvitamin D concentrations are high.

Other — Other tests that may be helpful in determining the cause of hypocalcemia include serum alkaline phosphatase, serum amylase, and 24-hour urinary excretion of calcium and magnesium:

- An elevated alkaline phosphatase is common in osteomalacia (as a result of severe vitamin D deficiency and secondary hyperparathyroidism) and can occur with osteoblastic bone metastases, which can cause hypocalcemia due to rapid deposition of calcium in bone metastases.
- Serum amylase is elevated in acute pancreatitis but only slightly in chronic pancreatitis.
- Low urinary calcium occurs in patients with untreated hypoparathyroidism or vitamin D deficiency.
Assessment of urinary magnesium may be helpful in individuals with hypomagnesemia. In this setting, an elevated value is consistent with renal losses.

SUMMARY AND RECOMMENDATIONS

- The first step in the evaluation of a patient with hypocalcemia is to verify with repeat measurement (total serum calcium corrected for albumin or ionized calcium) that there is a true decrease in the serum calcium concentration. If available, previous values for serum calcium should also be reviewed.
- If the patient has a low albumin-corrected serum calcium or ionized calcium concentration, further evaluation to identify the cause is indicated.
- Hypocalcemia has many causes. The etiology of hypocalcemia may be apparent from history and physical examination.
- Among the tests that may be helpful in distinguishing the etiology of hypocalcemia, measurement of serum intact parathyroid hormone (PTH) is the most valuable.
- Other measurements that may be helpful include serum magnesium, creatinine, phosphate, vitamin D metabolites (primarily 25-hydroxyvitamin D [25(OH)D]), and alkaline phosphatase.

![Algorithm for requesting investigations to elucidate the cause of hypocalcaemia](image-url)

**Fig 5** | Algorithm for requesting investigations to elucidate the cause of hypocalcaemia