

Hypocalcemia

Updates in diagnosis and management for primary care

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Abstract

Objective To provide family physicians with an evidence-based approach to the diagnosis and management of hypocalcemia.

Quality of evidence MEDLINE and EMBASE articles from 2000 to 2010 were searched, with a focus on the diagnosis and management of hypocalcemia. Levels of evidence (I to III) were cited where appropriate, with most studies providing level II or III evidence. References of pertinent papers were also searched for relevant articles.

Main message Chronic hypocalcemia is commonly due to inadequate levels of parathyroid hormone or vitamin D, or due to resistance to these hormones. Treatment focuses on oral calcium and vitamin D supplements, as well as magnesium if deficiency is present. Treatment can be further intensified with thiazide diuretics, phosphate binders, and a low-salt and low-phosphorus diet when treating hypocalcemia secondary to hypoparathyroidism. Acute and life-threatening calcium deficit requires treatment with intravenous calcium. The current treatment recommendations are largely based on expert clinical opinion and published case reports, as adequately controlled clinical trial data are not currently available. Complications of current therapies for hypoparathyroidism include hypercalciuria, nephrocalcinosis, renal impairment, and soft tissue calcification. Current therapy is limited by serum calcium fluctuations. Although these complications are well recognized, the effects of therapy on overall well-being, mood, cognition, and quality of life, as well as the risk of complications, have not been adequately studied.

Conclusion Family physicians play a crucial role in educating patients about the long-term management and complications of hypocalcemia. Currently, management is suboptimal and marked by fluctuations in serum calcium and a lack of approved parathyroid hormone replacement therapy for hypoparathyroidism.

Hypocalcemia is a common biochemical abnormality that can range in severity from being asymptomatic in mild cases to presenting as an acute life-threatening crisis.¹ Serum calcium levels are regulated within a narrow range (2.1 to 2.6 mmol/L) by 3 main calcium-regulating hormones—parathyroid hormone (PTH), vitamin D, and calcitonin—through their specific effects on the bowel, kidneys, and skeleton.^{1,2} Approximately half of the total serum calcium is bound to protein, and the remaining free ionized calcium is physiologically active.² Serum calcium levels must be corrected for the albumin level before confirming the diagnosis of hypercalcemia or hypocalcemia.¹

Hypocalcemia (corrected serum total calcium level <2.12 mmol/L) is most commonly a consequence of vitamin D inadequacy or hypoparathyroidism, or a resistance to these hormones^{1,3} (**Box 1**^{1,2,4,5}). Hypocalcemia has also been associated with many drugs, including bisphosphonates, cisplatin, antiepileptics, aminoglycosides, diuretics, and proton pump inhibitors (level III evidence); as well, there are other causes.³

KEY POINTS Family physicians play a key role in managing hypocalcemia and hypoparathyroidism, one of the main causes of hypocalcemia. Conventional therapy for hypocalcemia is currently suboptimal. Treatment for hypoparathyroidism is hampered by the lack of an approved parathyroid hormone replacement therapy. This article reviews the literature regarding the causes of hypocalcemia, including vitamin D deficiency and congenital and acquired causes of hypoparathyroidism, as well as key issues in management, such as intravenous administration of calcium for acute hypocalcemia, and vitamin D and calcium supplementation for chronic hypocalcemia.



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Quality of evidence

We searched MEDLINE and EMBASE for articles published between 2000 and 2010 with a focus on the diagnosis and management of hypocalcemia. Most peer-reviewed studies offered level II and level III evidence. References of pertinent papers were also searched for relevant articles.

Main message

Low vitamin D levels. The presence of 1,25-dihydroxyvitamin D enhances intestinal absorption of calcium and phosphorus, and promotes bone remodeling.^{4,6} Vitamin D inadequacy (25-hydroxyvitamin D [25(OH)D] level <75 nmol/L) remains common in children and adults.^{1,2,4,7,8} Inadequate vitamin D levels lead to a reduction in gastrointestinal calcium absorption of up to 50%, resulting in only 10% to 15% of dietary intestinal calcium being absorbed.⁴

Vitamin D inadequacy is also caused by reduced skin synthesis (owing to limited sun exposure, skin

pigmentation, or skin thinning with age). Decreased absorption, increased catabolism, impaired hepatic or renal hydroxylation to form 1,25-dihydroxyvitamin D, or acquired and genetic disorders of vitamin D metabolism and responsiveness also lead to low vitamin D levels.^{1,2,4,7} Vitamin D requirements increase during and after pregnancy, and low maternal vitamin D levels are associated with hypocalcemia in breastfed infants.⁹

Hypocalcemia can develop in individuals with inadequate 25(OH)D levels following initiation of bisphosphonate therapy and should be excluded before starting intravenous bisphosphonate therapy, particularly in individuals with osteoblastic metastases (level III¹⁰⁻¹³ and level I¹⁴ evidence). Serum 25(OH)D and 1,25-dihydroxyvitamin D levels should be measured in individuals with hypocalcemia (level III evidence).²

Reduced or inappropriately normal PTH. Low PTH levels result in excessive urinary calcium losses, decreased bone remodeling, and reduced intestinal calcium absorption.^{1,15} Rarely, PTH resistance in the form of pseudohypoparathyroidism can produce a similar physiologic profile and should be considered in the presence of an elevated serum PTH level.¹

Hypoparathyroidism is most commonly seen following inadvertent removal of or damage to the parathyroid glands or their vascular supply during a total thyroidectomy. This occurs in 0.5% to 6% of total thyroidectomies.¹⁶ Persistent hypocalcemia 6 months after surgery confirms the diagnosis of hypoparathyroidism in the presence of low or inappropriately normal PTH levels.

Autoimmune hypoparathyroidism can present alone or as part of a polyglandular endocrinopathy.^{1,2,16,17} Genetic mutations involving the development of the parathyroid glands, and synthesis or secretion of PTH can also cause hypoparathyroidism. Genetic mutations can also result in resistance to PTH at the proximal renal tubule, causing excessive renal calcium losses and hypocalcemia.^{2,16,17} Activating mutations of the calcium-sensing receptor are among the most common causes of congenital hypoparathyroidism. These mutations are marked by the presence of considerable hypercalciuria, typically increased by administration of vitamin D metabolites.^{2,16-23}

Other congenital abnormalities. Abnormalities in the embryonic development of the parathyroid glands can result in DiGeorge syndrome, which can be associated with cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia. Other genetic abnormalities can also cause hypoparathyroidism or pseudoparathyroidism.

Uncommon causes of hypoparathyroidism include heavy metal infiltration of the parathyroid glands with iron, as seen in hemochromatosis, or thalassemia.

Box 1. Causes of hypocalcemia

The causes of hypocalcemia include the following:

- Vitamin D inadequacy or vitamin D resistance
- Hypoparathyroidism following surgery
- Hypoparathyroidism owing to autoimmune disease or genetic causes
- Renal disease or end-stage liver disease causing vitamin D inadequacy
- Pseudohypoparathyroidism or pseudopseudohypoparathyroidism
- Metastatic or heavy metal (copper, iron) infiltration of the parathyroid gland
- Hypomagnesemia or hypermagnesemia
- Sclerotic metastases
- Hungry bone syndrome postparathyroidectomy
- Infusion of phosphate or citrated blood transfusions
- Critical illness
- Drugs (eg, high-dose intravenous bisphosphonates)
- Fanconi syndrome
- Past radiation of parathyroid glands

Data from Cooper and Gittoes,¹ Murphy and Williams,² Holick,⁴ and Bilezikian.⁵

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

Copper deposition as seen in Wilson disease is also an uncommon cause, as is metastatic infiltration of the parathyroid glands. Magnesium deficiency or excess can impair PTH secretion and also result in hypoparathyroidism.¹⁰

Clinical presentation and evaluation. Acute hypocalcemia can result in severe symptoms requiring hospitalization, whereas patients who gradually develop hypocalcemia are more likely to be asymptomatic.¹ Symptoms of hypocalcemia most commonly include paresthesia, muscle spasms, cramps, tetany, circum-oral numbness, and seizures.^{1,2,16} Hypocalcemia can also present with laryngospasm, neuromuscular irritability, cognitive impairment, personality disturbances, prolonged QT intervals, electrocardiographic changes that mimic myocardial infarction, or heart failure.^{2,16}

It is essential to ask about family history of hypocalcemia as this can indicate a genetic cause for the hypoparathyroidism. Previous head or neck surgery needs to be confirmed. Growth or mental retardation, congenital anomalies, or hearing loss also suggest the presence of a genetic abnormality.¹⁶ On physical examination, look for neck scarring, as patients might not recall remote neck surgery. Chvostek and Trousseau signs can be elicited in patients with hypocalcemia. Chvostek sign is the twitching of the upper lip with tapping on the cheek 2 cm anterior to the earlobe, below the zygomatic process overlying the facial nerve.²⁴ Trousseau sign (a more reliable sign present in 94% of hypocalcemic individuals and only 1% to 4% of healthy people) is the presence of carpopedal spasm observed following application of an inflated blood pressure cuff over systolic pressure for 3 minutes in hypocalcemic patients.^{24,25}

Diagnostic laboratory investigations: Initial laboratory investigations are outlined in **Box 2**.^{1,2,16} Hypoparathyroid patients will have hypocalcemia, low or inappropriately normal PTH levels, hyperphosphatemia, hypercalciuria, and low 1,25-dihydroxyvitamin D₃ levels.¹⁶ Measuring ionized calcium is highly recommended in critically ill patients, as variation in serum pH affects calcium binding to albumin (level II evidence).²⁶⁻²⁸

Acute management of hypocalcemia. Intravenous calcium is given if serum calcium levels fall below 1.9 mmol/L, or ionized calcium levels are less than 1 mmol/L, or if patients are symptomatic (level III evidence).^{1,2,29} Intravenous calcium gluconate administered with a central venous catheter is preferable to avoid extravasation and irritation of the surrounding tissue, which is most often seen with calcium chloride administration.^{1,2,16,30,31} Intravenous calcium is given as 1 or 2 10-mL ampoules of 10% calcium gluconate diluted in 50 to 100 mL 5% dextrose, infused over 5 to 10 minutes

(level III evidence).^{1,2} To avoid precipitation of calcium salts, phosphate and bicarbonate should not be infused with the calcium (level III evidence).³⁰ Patients should also receive oral calcium supplements and calcitriol (0.25 to 1 µg/day) as needed (level III evidence).¹ Magnesium deficiency or alkalosis should be corrected if present.^{2,16,18} Acutely, magnesium supplementation therapy will not elevate serum PTH or calcium, as peripheral PTH resistance can last for several days.³⁰

Rapid correction of hypocalcemia can contribute to cardiac arrhythmia.^{1,3} Cardiac monitoring during intravenous calcium supplementation is necessary, particularly in patients taking digoxin therapy (level III evidence).^{1,16,18}

Long-term management of chronic hypocalcemia. Oral calcium and vitamin D and its metabolites are essential in management, in addition to correction of hypomagnesemia.² Calcium carbonate and calcium citrate have the greatest proportion of elemental calcium (40% and 28%, respectively) and are easily absorbed; they are considered the supplements of choice.^{6,16,32} Calcium supplement dosages are 1 to 2 g of elemental calcium 3 times daily (level III evidence).¹⁶ Elemental calcium supplements can be started at 500 to 1000 mg 3 times daily and titrated upward (level III evidence).¹⁶ Asymptomatic electrocardiography changes usually normalize with calcium and calcitriol supplementation (level II evidence).³³

Hypercalciuria is a complication of vitamin D therapy, particularly for patients with hypoparathyroidism, as the absence of PTH enhances urinary calcium

Box 2. Basic investigations to establish a specific diagnosis, along with more specialized tests that might be required in specific cases (level III evidence)

Basic investigations

- Serum calcium (corrected for albumin)
- Phosphate
- Magnesium
- Electrolytes
- Creatinine
- Alkaline phosphatase
- Parathyroid hormone
- 25-hydroxyvitamin D
- Serum pH
- Complete blood count

Further investigations

- Ionized calcium
- 24-hour urinary phosphate, calcium, magnesium, and creatinine
- 1,25-dihydroxyvitamin D
- Renal ultrasonography to assess for nephrolithiasis
- DNA sequencing to exclude genetic mutations
- Biochemistry in first-degree family members

Data from Cooper and Gittoes,¹ Murphy and Williams,² Shoback.¹⁶

losses.² If hypocalcemia is due to malabsorption of vitamin D, physicians should treat the underlying cause (eg, implementing a gluten-free diet for patients with celiac disease).³⁴ Magnesium supplementation corrects hypomagnesemia-related hypocalcemia.³

Vitamin D inadequacy: Vitamin D inadequacy requires correction with either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3). Ergocalciferol can be given in doses of 50 000 IU weekly or twice a week with assessment of levels 3 months later, titrating up until a normal 25(OH)D level is reached (level III,^{1,4,8} level II,^{35,36} and level I³⁷ evidence). Alternatively, 300 000 IU of ergocalciferol can be administered intramuscularly, with the first 2 injections spaced 3 months apart, followed by regular injections every 6 months (level III evidence).^{1,2}

Cholecalciferol is more potent than ergocalciferol.^{4,6,16,38,39} Administering 100 000 IU of vitamin D3 once every 3 months is also effective in maintaining adequate 25(OH)D levels (level I evidence).⁴⁰ Further study is needed to evaluate the use of tanning beds in correcting vitamin D inadequacy (level III evidence).^{4,41}

Hypoparathyroidism: The treatment of hypoparathyroidism requires careful evaluation of the patient and consideration of the treatment options other than calcium supplementation. The primary goals of management with calcium and vitamin D supplementation include symptom control, maintaining serum calcium in the low-normal range (2.00 to 2.12 mmol/L), maintaining serum phosphorus within a normal range, and maintaining a calcium-phosphate product below 4.4 mmol²/L² (55 mg²/dL²) without developing hypercalciuria, nephrocalcinosis, or precipitation of calcium-phosphate salts in soft tissues (level III evidence).^{2,16,18,42}

Vitamin D analogues, particularly calcitriol or alfacalcidol, can be used.² Usual starting doses are 0.5 µg of calcitriol or 1 µg of alfacalcidol daily.¹ Upward titration with increases in the doses every 4 to 7 days is advised until a low-normal serum calcium level is achieved (level III evidence).¹ Calcitriol is preferable as it is relatively more potent, and has a rapid onset and offset of action attributable to its short half-life.^{2,6,16} Vitamin D treatment in patients with gain-of-function mutations of the calcium-sensing receptors results in further hypercalciuria, nephrocalcinosis, and renal impairment; thus, asymptomatic patients can simply be followed.²

Thiazide diuretics decrease urinary calcium excretion by increasing distal renal tubular calcium reabsorption.^{2,16,43} Combining diuretics with a low-salt, low-phosphate diet and phosphate binders is beneficial (level III evidence).⁶

Serum calcium, phosphorus, and creatinine should be measured weekly to monthly during initial dose adjustments, with quarterly or twice-yearly measurements once the therapy protocol has stabilized (level III evidence).^{1,6,16}

Unfortunately, patients with hypoparathyroidism have poor quality of life as measured on standard scales, which illustrates the limitations of therapy (level II evidence).⁴⁴

Replacement therapy with PTH is a viable option, as it corrects hypercalciuria and potentially reduces the risk of nephrocalcinosis, nephrolithiasis, and renal insufficiency. It can also reduce the wide fluctuation in serum calcium as well as the need to administer very large doses of calcium and vitamin D metabolites. Also, PTH 1-34 reduces urinary calcium excretion (level II evidence),⁴⁵⁻⁴⁹ possibly allowing reductions in the dose of calcium and vitamin D; PTH 1-84 has also been studied and might become a valuable addition to current treatment options (level II evidence).⁵⁰ Hypoparathyroidism is the only remaining hormonal insufficiency that is currently not being treated with direct replacement of the deficient hormone.⁵¹ At this time, PTH supplementation has not been approved by Health Canada for the treatment of hypoparathyroidism.²

Conclusion

Family physicians play a key role in the management of hypocalcemia and hypoparathyroidism. Management requires identification of the cause of hypocalcemia, followed by calcium and vitamin D metabolite supplementation. Treatment can be further enhanced by introducing thiazide diuretics and other options, which are effective in treating hypocalcemia and preventing symptoms. Unfortunately, current evidence is largely based on clinical experience rather than controlled comparison trials. Conventional therapy for hypoparathyroidism is currently suboptimal and is associated with wide fluctuations in serum calcium, as well as the risks of hypercalciuria, renal impairment, and hypercalcemia. Following evaluation and determination of the cause of hypocalcemia, physicians should treat aggressively and closely monitor patients. 

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Contributors

Mr Fong and **Dr Khan** contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Competing interests

None declared

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