

# Managing Calcium Disorders

Adesola Odunayo, DVM, MS, DACVECC

University of Tennessee



You have asked...  
What role does calcium play in my patients' health?

## The expert says...

Calcium is required for many cellular day-to-day functions: coagulation, vascular smooth muscle tone, skeletal muscle contraction, hormone secretion, and cell growth and division. Most calcium is stored in the skeleton, and less than 1% is readily available for its biologic function. Calcium exists in 3 forms in the body: ionized (iCa), protein-bound, or complexed to other ions (ie, phosphate, bicarbonate, sulfate, citrate, lactate); iCa is the most important fraction. Total calcium (tCa) measurement is more widely available, although it can be affected by serum albumin concentrations and does not reliably predict iCa.<sup>1,2</sup> iCa should be evaluated directly with any patient with calcium disturbances, as the correction formulas developed for normalizing calcium concentrations in hypoalbuminemic patients are inaccurate and unreliable for predicting this fraction.<sup>3</sup> Normal homeostatic mechanisms maintain serum calcium concentration within a narrow range; disruption results in hypocalcemia or hypercalcemia.

## Calcium Homeostasis

Parathyroid hormone (PTH), calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>), and calcitonin are the main regulators of calcium homeostasis. The GI tract, kidneys, and bone are the major organs affected by calcium regulatory hormones; action of the hormones causes increased reabsorption or redistribution of calcium. PTH, secreted by the chief cells of the parathyroid gland, exerts its action on the bone and kidneys and increases calcitriol production. This can ultimately lead to increased bone, renal, and intestinal reabsorption. Hypocalcemia can cause a significant increase in PTH concentration and increased calcitriol secretion; conversely, the opposite effects can occur with hypercalcemia. Calcitonin is produced in the thyroid in response to increased serum calcium concentration and acts on the bone to inhibit osteoclastic bone resorption activity.

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iCa = ionized calcium, PTH = parathyroid hormone, tCa = total calcium

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## Hypercalcemia

Hypercalcemia is an important electrolyte abnormality that may be either primary or secondary. While laboratory reference ranges can vary, hypercalcemia is defined by a tCa greater than 12 mg/dL (iCa concentration >1.5 mmol/L) in dogs or a tCa greater than 11 mg/dL (iCa concentration >1.4 mmol/L) in cats. Young animals show a slightly elevated calcium concentration as compared with adults.<sup>4</sup>

Hypercalcemia can affect all organs, but signs are generally seen in the neuromuscular, GI, renal, and cardiac systems, including polyuria/polydipsia, lethargy, vomiting and anorexia, and cardiac arrhythmia (typically seen with tCa >18 mg/dL). Severity of signs usually depends on magnitude, rate, and duration of hypercalcemia. Mild-to-moderate signs are usually seen when tCa concentrations approach 12 to 14 mg/dL; levels above 18 mg/dL are often life threatening.

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Mineralization of soft tissue (particularly heart and kidneys) is a significant complication of hypercalcemia. Mineralization generally depends on serum phosphorus concentration, and risk for mineralization can increase when the calcium–phosphorus product is greater than 60. Hypercalcemia can lead to renal dysfunction (potentially reversible) but may also potentiate the development of chronic renal insufficiency.

### Diagnosis

Any patient diagnosed with increased tCa should undergo iCa concentration testing (preferably via a fasted sample) to confirm hypercalcemia (Table). Once diagnosis has been confirmed, the chemistry and electrolyte panels should be closely evaluated for indications of hypoadrenocorticism or renal disease. Serum phosphorus concentrations are usually normal to low with primary hyperparathyroidism and hypercalcemia of malignancy. Renal failure, vitamin-D toxicity, hypoadrenocorticism, and

**Table** Differentials for Hypercalcemia

<i>Causes</i>	<i>Differentials</i>
<b>Nonpathologic</b>	Laboratory error Nonfasting (minimal changes) Puppies <sup>4</sup> Spurious (eg, lipema, contamination of sample or tube)
<b>Pathologic</b>	Acute renal failure Chronic renal failure Excessive calcium supplementation Granulomatous disease Hypercalcemia of malignancy Anal sac apocrine gland adenocarcinoma Lymphoma Mammary gland adenocarcinoma Multiple myeloma Hypervitaminosis D Cholecalciferol-containing rodenticide poisoning Antipsoriasis cream ingestion Plant (calcitriol glycosides) ingestion Idiopathic hypercalcemia (common in cats) Primary hyperparathyroidism Skeletal lesions (eg, hypertropic osteodystrophy, osteomyelitis)
<b>Transient</b>	Hemoconcentration Hyperproteinemia Hypoadrenocorticism Severe environmental hypothermia (rare)

Modified from **Disorders of Calcium: Hypercalcemia and Hypocalcemia**. Schenck PA, Chew DJ, Nagode LA, Rosol T. In DiBartola SP (ed). *Fluid, Electrolyte and Acid-Base Disorders in Small Animal Practice*, 3rd ed—St. Louis, Elsevier: 2006, pp 122-209.

nutritional secondary hyperparathyroidism can cause normal-to-elevated serum phosphorus concentrations.

A thorough physical examination should be repeated, including rectal and fundic examinations, to evaluate for lymphadenopathy, fungal granuloma, or mammary masses. Fine-needle aspiration, with or without obtaining biopsy specimens, should be considered for all appreciated masses. Thoracic radiography and abdominal imaging, including ultrasonography, should also be part of the diagnostic plan. If the primary cause is not obvious, bone marrow aspiration ( $\pm$  biopsy) and splenic and liver aspirations should be considered. Evaluation of iCa, PTH, and parathyroid hormone-related protein (PTHrP) levels from the same blood sample can help differentiate primary hyperparathyroidism from hypercalcemia of malignancy. Increased iCa, detectable PTHrP, and low PTH concentrations suggest hypercalcemia of malignancy.

### Treatment

Definitive hypercalcemia therapy should focus on resolving its underlying cause. Therapy should be considered after repeated documentation of elevated serum iCa. Targeted therapy should likewise be considered if signs are present, the patient is azotemic, tCa concentration is greater than 16 mg/dL, or the calcium-phosphorus product is greater than 60.

The cornerstone of therapy is restoring normal hydration status and diuresis (see **Therapeutic Options for Hypercalcemia in Dogs & Cats**). The fluid of choice for hypercalcemic animals is 0.9% sodium chloride IV because it can result in enhanced calciuresis. Diuretics may be considered (eg, furosemide), although only after fluid deficits have been restored. Glucocorticoids can contribute to significant reduction in iCa concentration in patients with lymphoma, multiple myeloma, hypoadrenocorticism, apocrine gland adenocarcinoma, and hypervitaminosis D; however, they should only be given after definitive diagnosis has been established to prevent masking underlying disease.

Salmon calcitonin can be used in patients with severe hypercalcemia or without definitive diagnosis, in which corticosteroids will be contraindicated. Calcitonin reduces the activity and formation of osteoclasts and can rapidly reduce serum calcium concentration, but it can be expensive, is short-lived, and is unpredictable in terms of the magnitude of its effect. Bisphosphonates can decrease osteoclast activity and function, although full clinical efficacy may not be noted until after a few days; there is also a risk for nephrotoxicity. Hemodialysis or peritoneal dialysis may be considered in patients resistant to conventional drug therapy.

## Hypocalcemia

While laboratory reference ranges for both dogs and cats may vary, hypocalcemia is defined by a serum tCa concentration of less than 9 mg/dL or a serum iCa of less than 1.2 mmol/L (see **Conditions Associated with Hypocalcemia**, next page). Signs associated with hypocalcemia include behavioral changes, focal muscle twitching, stiff gait, tetany, seizures, intense facial rubbing, and pyrexia; however, some patients may be subclinical.

### Diagnosis

Low tCa concentrations should be confirmed and iCa concentration measured before treatment is initiated. Treatment should be initiated immediately, however, if the patient shows moderate-to-severe signs suggestive of hypocalcemia. A complete physical examination and history should be conducted and recorded, including CBC, serum chemistry panel, urinalysis, abdominal ultrasonography and thoracic radiography, along with history of pregnancy and recent whelping. Serum iCa and PTH concentrations can help make a diagnosis of primary hypoparathyroidism, for which PTH concentrations should be inappropriately low or undetectable.

### Therapeutic Options for Hypercalcemia in Dogs & Cats

- Fluid therapy with 0.9% NaCl IV (70–120 mL/kg/hr; lower end of range for cats) to restore hydration and promote diuresis. Dehydration should be corrected over 8–24 hours based on observed percentage of fluid deficit.
- Furosemide at 1–4 mg/kg IV, IM, or PO q8–12h; consider also CRI at 0.7–1 mg/kg/hr
- Glucocorticoids (prednisone 0.5–2 mg/kg, dexamethasone 0.1–0.4 mg/kg IV or PO) after definitive diagnosis
- Salmon calcitonin at 4 U/kg IV or PO, then 4–8 U/kg SC q12h
- Bisphosphonates (eg, pamidronate, zoledronate, etidronate) IV or PO

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## Treatment

Treatment for hypocalcemia should focus on correcting the underlying cause. Supplemental calcium therapy or active vitamin D should be initiated if the patient is clinical or has a tCa concentration of less than 7.5 mg/dL. Therapy should also be considered in any patient undergoing parathyroidectomy, as hypocalcemia may develop from chronic suppression of the remaining parathyroid glands. Because there is a lag until effects are seen, active vitamin-D metabolites should be provided for these patients before surgery.

For patients presenting with signs of tetany or seizures, IV calcium should be administered as soon as possible. Calcium gluconate 10% (0.5–1.5 mL/kg) is preferred over calcium chloride because the former is not as caustic when extravasated. IV calcium salts should be administered slowly (ie, 10–20 min infusion), with close heart rate monitoring via auscultation or electrocardiogram. Bradycardia may indicate cardiotoxicity from rapid calcium infusion.

After tetany signs have resolved, long-term management should be planned; a single bolus injection of elemental calcium lasts only 1 to 12 hours postadministration. Vitamin-D metabolites should be given as soon as possible, as it may take a few days before their effects are seen. Oral vitamin D is the primary mode of therapy for chronic hypocalcemia. Patients with easily reversed hypocalcemia (eg, a bitch with postparturient hypocalcemia) do not typically require vitamin-D therapy.

Additional supplementation with parenteral calcium is necessary until vitamin-D metabolites are effective at maintaining serum calcium levels. This can be continued as intermittent IV injections or CRI of calcium gluconate (60–90 mg/kg of elemental calcium per day). Of note, calcium gluconate contains 9.3 mg/mL of elemental calcium. Calcium salts should not be administered SC because of risk for skin necrosis and abscess formation. Oral calcium supplementation should be initiated as soon as the patient can eat and drink and continued until the cause of the hypercalcemia is resolved or oral calcium/vitamin D supplementation is enough to maintain normocalcemia.

iCa = ionized calcium, tCa = total calcium

## Conditions Associated with Hypocalcemia

- Acute pancreatitis
- Acute renal failure
- Chronic renal failure
- Critical illness
- Ethylene glycol intoxication
- Hypoalbuminemia (iCa usually normal)
- Hypoparathyroidism
- Laboratory error
- Postparturient tetany
- Postadministration of sodium bicarbonate
- Phosphate-containing enema
- Sepsis
- Tumor lysis syndrome

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The goal of long-term therapy is to keep serum tCa concentrations between 9 and 10 mg/dL, as long as signs are well controlled. Constant monitoring of tCa or iCa concentrations is important for the first 24 to 72 hours of therapy but is required less frequently once levels have been stabilized. ■ **cb**

See **Aids & Resources**, back page, for references & suggested reading.