Abstract

Calcium is an important electrolyte and essential element for many cellular processes. This article provides a broad overview of calcium regulation and the development of hypercalcemia, as well as a practical approach to patients presenting with hypercalcemia, including initial stabilization of patients with severe hypercalcemia.
Calcium is a vital electrolyte. It is essential for normal cell function, nerve conduction, muscle contraction (cardiac, skeletal, smooth), hormone secretion, and blood clotting, as well as skeletal support. Ionized calcium (iCa), the biologically active form of calcium, is tightly regulated through the integrated actions of parathyroid hormone (PTH), 1,25-dihydroxyvitamin D₃, and calcitonin.

Hypercalcemia develops when there is increased bone resorption, decreased renal excretion or increased gastrointestinal absorption of calcium, or increased serum binding of calcium to proteins/complexes. The net result is a diverse array of clinical signs that depend on the severity and chronicity of the hypercalcemia. Severely hypercalcemic patients commonly demonstrate polyuria/polydipsia, anorexia, constipation, lethargy, and weakness.

The clinical workup for hypercalcemia initially encompasses a repeat confirmatory calcium measurement, thorough history, and meticulous

Take-Home Points

- In patients with elevated total calcium, the first step in diagnosis is to verify hypercalcemia by measuring ionized calcium.
- Concurrent measurement and evaluation of serum phosphorus may provide further insight into the cause of hypercalcemia.
- If the cause of hypercalcemia remains elusive after a thorough history and physical examination, calcium hormone levels should be measured to ascertain whether the hypercalcemia is parathyroid dependent or independent.
- Clinical signs of hypercalcemia depend on the magnitude, rate of development, and duration of hypercalcemia as well as concurrent electrolyte and acid-base disturbances.
- Overall, the most common causes of hypercalcemia in dogs and cats are nonpathologic and transient conditions.
- Medical therapy for persistent hypercalcemia is dictated by the systemic wellness of the patient, rate of rise of serum calcium concentration, and severity of hypercalcemia.
- No single treatment protocol effectively reduces serum ionized calcium concentrations, and each patient requires an individualized protocol until the cause of hypercalcemia can be determined. Definitive treatment involves treating or removing the underlying cause.
physical examination. If the cause of hypercalcemia remains elusive, calcium hormone levels should be measured to ascertain whether the hypercalcemia is parathyroid dependent or independent. Further diagnostics depend on initial findings and may include thoracic radiography, advanced abdominal imaging, cervical ultrasound, and bone biopsy.

Initial treatment is symptomatic and supportive, aimed at diluting the iCa concentration through volume expansion with intravenous fluids and encouraging calciuresis. Other therapies include calciuretic diuretics (e.g., furosemide), bisphosphonates, and dietary modification. Unfortunately, no single treatment protocol effectively reduces serum iCa concentrations, with each patient requiring an individualized protocol until the cause of hypercalcemia can be determined. Definitive treatment involves treating or removing the underlying cause.

OVERVIEW OF CALCIUM PHYSIOLOGY
Most calcium in the body (99%) is stored in skeletal tissue as hydroxyapatite and is not immediately available. The remaining 1% is found intracellularly (0.9%) and extracellularly (0.1%). Extracellularly, calcium exists in 3 fractions: protein bound (approximately 35% to 40%), complexed (approximately 10%), and unbound (ionized) and biologically active (approximately 50% to 55%).

Blood iCa is maintained within a narrow range by complex, integrated interactions between phosphorus and 3 major hormones: PTH, calcitonin, and 1,25-dihydroxyvitamin D₃ (FIGURE 1). Calcium-sensing receptors in the parathyroid glands, thyroid, and kidney respond to disturbances in blood iCa by altering production of these hormones, which then act on specific cells in the bone, gastrointestinal tract, and kidney to restore calcium homeostasis. Disruptions of these normal homeostatic control mechanisms manifest as hypercalcemia or hypocalcemia.

DEFINITION OF HYPERCALCEMIA
Hypercalcemia is defined as an elevation of serum total calcium (tCa) and/or iCa above the following normal physiological ranges:

- **Adult dogs**: tCa, 9 to 11.5 mg/dL (2.2 to 3.8 mmol/L); iCa, 5 to 6 mg/dL (1.2 to 1.5 mmol/L)

Young dogs and cats have serum iCa concentrations that are 0.1 to 0.4 mg/dL higher than those reported in older animals.

TOTAL VERSUS IONIZED CALCIUM
Historically, measuring tCa has been the most common method of assessing an animal’s plasma or serum calcium level. Total calcium measurements are reported in routine serum biochemistry panels and are
easy to interpret. However, it is iCa, not tCa, that is responsible for deleterious biological effects. Total calcium elevation by itself is not harmful, as several conditions, such as hemolysis, bilirubinemia, and hyperlipidemia, may affect the measured accuracy of tCa, as may patient age, diet, and fasting. Recent studies have investigated the utility of tCa to predict ionized hypercalcemia and concluded that tCa >12 mg/dL in dogs and >11.8 mg/dL in cats is very specific for ionized hypercalcemia. Therefore, moderate to severe elevations in tCa should prompt clinicians to measure iCa. Ionized calcium serves as a better indicator of global physiological calcium status.

Corrected Calcium

The concept of corrected calcium has been proven unhelpful. Initially, this idea was considered because tCa is composed of 3 fractions, and changes in any of those fraction would affect tCa measurement. However, evaluation of formulas that adjusted tCa to correct for total serum protein variability has demonstrated them to be unreliable predictors of iCa, as only about one-third of tCa variability can be accounted for by changes in circulating proteins. The poor performance of these adjustment formulas in predicting iCa is most pronounced in dogs and cats with chronic kidney disease (CKD). In these

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**FIGURE 1.** Normal calcium homeostatic feedback to hypo- or hypercalcemia. Increases in ionized calcium (iCa) above the homeostatic level suppress secretion of parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D₃, which reduces bone resorption of calcium, intestinal calcium absorption, and renal calcium reabsorption to restore iCa to normal. Phosphorus (PO₄³⁻) reabsorption in the kidney is also suppressed by reduced PTH and 1,25-dihydroxyvitamin D₃ secretion. An increase in iCa also prompts calcitonin synthesis by the C cells of the thyroid gland to inhibit osteoclast number and activity as well as decrease renal tubular resorption of phosphorus, with the net effect being to decrease serum calcium and phosphorus.
patients, the diagnostic agreement between measured tCa and predicted iCa is less than 50%, leading to overestimation of hypercalcemia in dogs and underestimation in cats.\textsuperscript{11,13}

Sample Handling and Collection
To ensure accurate measurement of iCa, blood samples must not be hemolyzed, must be handled anaerobically, and must be kept on ice to prevent loss of carbon dioxide, inhibit glycolysis, and maintain pH, as the iCa concentration may be influenced by blood pH (\textit{TABLE 1}), ions, presence of heparin, and time of analysis.\textsuperscript{7,10,13,18} Therefore, when collecting blood for the measurement of iCa, the authors recommend that:

1. Patients be stress free, fasted (approximately 2 hours), and breathing normally.

2. Blood be collected into a red- (preferred) or green-top tube. EDTA, citrate, and oxalate tubes chelate with free calcium, leading to a significant decrease in iCa concentration, and should not be used.

3. Samples that are not being analyzed immediately be allowed to clot and then spun down (immediately or within 30 minutes, if serum is being used) and refrigerated for future analysis.\textsuperscript{10,16}

4. Samples not be frozen. Freezing decreases iCa, which is thought to be related to development of alkalinity within the sample during frozen storage.

### CLINICAL SIGNS OF HYPERCALCEMIA

Clinical signs of hypercalcemia depend on the magnitude, rate of development, and duration of hypercalcemia itself as well as concurrent electrolyte and acid–base disturbances (\textit{TABLE 2}). These signs reflect calcium’s diverse biologic roles and are related to the direct or indirect effects of high calcium concentrations, namely decreased neuromuscular excitability of both smooth and skeletal muscle and interference with antidiuretic hormone binding to renal tubules. Although excessive iCa is toxic to all cells, it has clinically important effects on the central nervous system, gastrointestinal tract, heart, and kidneys. Often, clinical signs are not noted by owners and hypercalcemia is only identified on routine blood tests.

Patients in which hypercalcemia develops gradually may display minimal clinical signs in the early stages. Animals with chronic persistent calcium elevations are

#### TABLE 1 Factors Affecting Ionized Calcium (iCa) Measurement\textsuperscript{14}

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>PHYSIOLOGIC RESPONSE</th>
<th>EFFECT ON iCa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL FACTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Increased lactate leads to decrease in pH and bicarbonate</td>
<td>Increased</td>
</tr>
<tr>
<td>Diet</td>
<td>Calcium complex formation (proteins, phosphates, carbonates) -2 hours after eating</td>
<td>Decreased</td>
</tr>
<tr>
<td>pH</td>
<td>Decreased pH decreases protein binding</td>
<td>Increased</td>
</tr>
<tr>
<td>Acidosis (metabolic and respiratory)</td>
<td>Increased pH promotes binding of calcium to albumin and can reduce the fraction of iCa in the blood</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

#### TABLE 2 Clinical Signs Associated With Hypercalcemia

<table>
<thead>
<tr>
<th>CLINICAL SIGNS</th>
<th>ACUTE HYPERCALCEMIA</th>
<th>CHRONIC HYPERCALCEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Polyuria/polydipsia</td>
<td>Calcium urolithiasis and associated lower urinary tract signs (e.g., stranguria, pollakiuria, hematuria)</td>
</tr>
<tr>
<td></td>
<td>Dehydration and prerenal azotemia</td>
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<td></td>
<td>Acute kidney injury</td>
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<tr>
<td></td>
<td>Urinary incontinence</td>
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<tr>
<td>Gastrointestinal</td>
<td>Anorexia</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Vomiting/nausea</td>
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<tr>
<td></td>
<td>Diarrhea</td>
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<tr>
<td>Neuromuscular</td>
<td>Depression</td>
<td>Muscle wasting</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Stiff gait</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
<td>Seizures/twitching</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Arrhythmia</td>
<td></td>
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<tr>
<td></td>
<td>Bradycardia</td>
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</tr>
</tbody>
</table>
more likely to develop both clinical signs and histopathologic tissue changes (i.e., dystrophic mineralization, especially in the heart and kidneys), regardless of the magnitude of elevation. Most animals with a serum tCa >15 mg/dL show signs of systemic illness, with clinical signs being most severe with rapid development of hypercalcemia. Animals with severe hypercalcemia are likely to develop extensive soft tissue mineralization throughout the body.

CAUSES OF HYPERCALCEMIA

Hypercalcemia may result from 1 or a combination of the following processes:  
- Increased bone resorption of calcium (i.e., osteolysis)
- Decreased renal excretion of calcium  
  - Increased renal tubular reabsorption  
  - Decreased glomerular filtration
- Increased gastrointestinal absorption of calcium (excess vitamin D)
- Increased serum binding of calcium to proteins/complexes

Hypercalcemia may be categorized based on its nature (transient or persistent) and underlying cause (nonpathologic or pathologic) (BOX 1). Several retrospective studies have reported on the prevalence of hypercalcemia in dogs and cats. In these studies, the most common causes of hypercalcemia in dogs and cats were nonpathologic and transient conditions. In dogs, the most common cause of persistent pathologic hypercalcemia was malignancy-associated hypercalcemia. Common neoplasms associated with hypercalcemia included lymphoma, carcinoma, sarcoma, multiple myeloma, leukemia, and thymoma. Other reported causes associated with hypercalcemia in dogs included primary hyperparathyroidism, hypoadrenocorticism, kidney disease (acute and chronic), hypervitaminosis D, and granulomatous disease.

Conditions associated with persistent pathological hypercalcemia in cats varied. One study identified acute kidney injury as the most frequent diagnosis (13% of cases); another identified hypercalcemia of malignancy as the most common cause of hypercalcemia (22.7% of cases). Other reported causes included idiopathic disease and toxicity.

In these studies, the cause of hypercalcemia in up to 7.9% and 39.9% of all cases in dogs and cats, respectively, remained undetermined. It should be noted that these studies were from referral hospitals, and that these numbers may not represent the true distribution of cases presenting in private practice with hypercalcemia.

BOX 1 Common Causes of Hypercalcemia in Dogs and Cats

- **Nonpathologic**
  - Food
  - Age (i.e., young, growing)
  - Laboratory error
  - Spurious

- **Transient**
  - Hemoconcentration
  - Hypoproteinemia
  - Hypoadrenocorticism

- **Pathologic (Persistent)**
  - Parathyroid dependent
    - Primary hyperparathyroidism (adenoma)
  - Parathyroid independent
    - Malignancy associated
      - Humoral hypercalcemia of malignancy
        - Lymphoma
        - Anal sac adenocarcinoma
        - Thymoma
        - Primary or metastatic bone tumors
        - Other (e.g., mammary carcinoma, fibrosarcoma, pancreatic adenocarcinoma)
    - Hematologic (osteolytic hypercalcemia)
      - Multiple myeloma
      - Myeloproliferative disease
      - Leukemia
    - Idiopathic (cats)
    - Kidney disease
      - Acute kidney injury (e.g., urinary tract obstruction, acute-on-chronic kidney disease, raisin toxicosis)
      - Chronic kidney disease
    - Hypervitaminosis D (e.g., cholecalciferol, Cestrum diurnum, antipsoriasis creams, salmon oil [dogs])
    - Granulomatous disease (e.g., fungal infection, parasitic infection, feline infectious peritonitis [cats], dermatitis, lymphadenitis, panniculitis)
    - Skeletal lesions (e.g., hypertrophic osteodystrophy, osteomyelitis)
    - Iatrogenic (e.g., lactulose, hydrochlorothiazide, oversupplementation of intravenous calcium/calcium carbonate)

- **This list is not all-inclusive**
Increased serum total calcium
>12 mg/dL (dogs), >11 mg/dL (cats)

Normal iCa
- Food
- Young growing animal
- Laboratory error
- Spurious

Increased iCa
>1.5 mmol/L (dogs), >1.4 mmol/L (cats)

Recheck iCa

Increased iCa
>1.5 mmol/L (dogs), >1.4 mmol/L (cats)

Repeat careful history, including owner medication(s)/access to toxins, and thorough physical examination

Abnormal results, follow up with appropriate diagnostics based on differential diagnosis
- Complete blood count
- Serum chemistry
- Urinalysis
- Urine culture
- +/- Urine protein:creatinine ratio

Stop medications
- Acute case: decontaminate

Normal physical examination and test results

Measure iCa/PTH/PTHrP/25-hydroxyvitamin D
- iCa
- PTH
- PTHrP

Primary hyperparathyroidism, perform neck ultrasonography

Lung nodules
- Lymphadenopathy
- Intertstitial lung pattern

Perform:
- Lung aspiration
- Lymph node aspiration
- Lymph node biopsy
- Fungal PCR cytology
- Fungal antigen testing (urine/blood)

Hepatomegaly
- Splenomegaly
- Lymphadenopathy
- GI mineralization
- Abdominal mass

Perform:
- Lesion aspiration/biopsy
- Lymph node aspiration
- Fungal PCR cytology
- Fecal PCR (Heterobilharzia)

Abnormal physical examination and test results

Perform imaging:
- Thoracic radiography
- Abdominal ultrasonography
- Whole-body CT (dogs >25 kg [55 lb])
DIAGNOSTIC APPROACH TO HYPERCALCEMIC PATIENTS

When a patient is found to have elevated tCa, the first step is to verify hypercalcemia with a reliable (i.e., external laboratory) measurement of iCa. Once hypercalcemia is confirmed, the authors recommend use of signalment, a meticulous history, and a thorough physical examination to prioritize differential diagnoses (FIGURE 2).

History and Physical Examination

History taking should focus on recent patient/owner travel, current and historic medical problems, current diet, medications (patient and owner), and vitamin/mineral supplementation. Potential exposure to toxins such as rodent poisons (e.g., cholecalciferol), household plants (e.g., lilies, *Cestrum diurnum* [day blooming jessamine]), or psoriasis creams containing vitamin D analogs (e.g., calcipotriol, calcipotriene) should be investigated. Other relevant history should include changes in water intake and whether polyuria has been noted. Changes in appetite, activity, body weight, and the presence/absence of gastrointestinal signs (i.e., vomiting or diarrhea) should also be recorded.

A thorough physical examination should include palpation of peripheral lymph nodes, mammary gland chains, and anal sacs to evaluate for lymphoma, mammary gland cancer, and apocrine anal gland adenocarcinoma, respectively. An orthopedic examination should be performed to assess for lameness and subsequent focal bone pain. A digital vaginal examination should be performed to assess patients for a vaginal tumor. Examination of the neck is typically unhelpful as enlarged parathyroid glands are not routinely detected by palpation.

Initial Diagnostic Tests

Failure to identify an underlying cause from history and physical examination should prompt collection of blood and urine for a complete blood count, serum biochemistry panel, urinalysis, and urine culture. In particular, renal function (e.g., blood urea nitrogen, creatinine), globulins, and serum electrolytes (e.g., phosphorus, sodium, potassium) should be carefully scrutinized. Polyuria with compensatory polydipsia is usually present and manifests as a urine specific gravity <1.030. A concurrent urinary tract infection has been reported in up to 29% of all cases.

Concurrent serum phosphorus evaluation may provide further insight into the cause of hypercalcemia (TABLE 3). Hyperphosphatemia is associated with CKD, cholecalciferol rodenticide toxicosis, psoriasis cream exposure, and hypoadrenocorticism and may be associated with primary osteolytic bone disease or secondary to metastatic bone disease. Low or normal serum phosphate concentrations are consistent with humoral hypercalcemia of malignancy and primary hyperparathyroidism. Hyponatremia or hyperkalemia may be suggestive of hypoadrenocorticism. Hyperglobulinemia may be indicative of multiple myeloma or chronic infection (i.e., granulomatous inflammation).
PTH Measurement
If initial diagnostics do not lead to a diagnosis, serum iCa should be measured in association with calcium-regulating hormones in an attempt to assess the appropriateness of the PTH response to hypercalcemia. This step is to determine whether hypercalcemia is parathyroid dependent (i.e., primary hyperparathyroidism) or parathyroid independent (i.e., normal parathyroid glands suppressing the production of PTH in a normal response to hypercalcemia). Hypercalcemic patients with either a high PTH or a PTH in the upper half to two-thirds of the reference interval (i.e., inappropriate response) are consistent with having parathyroid-dependent disease. In these patients, an autonomous source of PTH (parathyroid adenoma, adenocarcinoma, or hyperplasia) stimulates the increase in iCa.

Most diseases in dogs and cats associated with hypercalcemia are parathyroid independent. In these cases, increases in calcium result in suppression of PTH production to levels in the lower quartile of the reference range (TABLE 3).

Other calcium-regulating hormones of interest include parathyroid hormone–related peptide (PTHrP), a hormone that stimulates bone resorption, and 25-hydroxyvitamin D, a vitamin D metabolite. Excessive PTHrP is associated with humoral hypercalcemia of malignancy; however, PTHrP concentrations are not always increased in cases of neoplasia. Measurement of 25-hydroxyvitamin D is useful in cases of potential cholecalciferol or ergocalciferol ingestion.

Occasionally, PTH values fall above the lower third and below the upper half of the reference interval (i.e., gray zone). These results are considered equivocal and may be associated with early primary hyperparathyroidism or parathyroid-independent disease. Patients falling into this category should have a systemic workup performed, including advanced imaging (computed tomography and/or ultrasonography of the neck, thorax, and abdomen). The authors recommend that when no underlying cause is found in asymptomatic or mildly symptomatic cases, repeat serum iCa be measured 1 to 3 months later in conjunction with calcium-regulating hormones.

Imaging
When primary hyperparathyroidism is suspected, cervical ultrasonography should be performed to assess the size of the parathyroid glands. The normal canine parathyroid gland length is considered to be <2 to 3 mm but varies widely, with lengths up to 7.6 mm being reported. Studies report hyperplastic parathyroid glands as <4 mm in diameter, adenomas as approximately 4 to 6 mm, and carcinomas as approximately 7 to 8 mm. However, there is a significant degree of overlap in ultrasonographic size and pathology between these groups. Also, caution is needed in interpreting the ultrasonographic appearance of parathyroid glands, as multiple structures—most commonly thyroid lobules—can be misinterpreted as parathyroid tissue. Because the ultrasonographic distinction between neoplastic, hyperplastic, and normal parathyroid glands is unclear

<table>
<thead>
<tr>
<th>CAUSE OF HYPERCALCEMIA</th>
<th>tCa</th>
<th>iCa</th>
<th>PHOSPHORUS</th>
<th>PTH</th>
<th>PTHrP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Increased</td>
<td>Increased</td>
<td>Decreased–Normal</td>
<td>Normal–Increased</td>
<td>Normal*b</td>
</tr>
<tr>
<td>Malignancy-associated, humoral hypercalcemia of malignancy</td>
<td>Increased</td>
<td>Increased</td>
<td>Decreased–Normal</td>
<td>Decreased–Normal</td>
<td>Normal–Increased</td>
</tr>
<tr>
<td>Osteolytic</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal–Increased</td>
<td>Decreased–Normal</td>
<td>Normal–Increased</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal–Increased</td>
<td>Increased</td>
<td>Normal*a</td>
</tr>
<tr>
<td>Hypervitaminosis D</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal–Increased</td>
<td>Decreased</td>
<td>Normal*a</td>
</tr>
<tr>
<td>Hypoadrenocorticism</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal–Increased</td>
<td>Decreased–Normal</td>
<td>Normal*a</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>Normal–Increased</td>
<td>Increased</td>
<td>—</td>
<td>Decreased–Normal</td>
<td>Normal–Increased</td>
</tr>
<tr>
<td>Idiopathic (cats)</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal–Increased</td>
<td>Decreased–Normal</td>
<td>Normal*a</td>
</tr>
</tbody>
</table>

*aUndetectable
iCa = ionized calcium; PTH = parathyroid hormone; PTHrP = parathyroid hormone–related peptide; tCa = total calcium.

TABLE 3 Changes in Phosphorus and Calcium Metabolic Hormones in Response to Hypercalcemia
and agreement between ultrasonography and surgery is only moderate (72.3% when considering pathology) to fair (65.9% when considering the number of glands affected), assessment of all parathyroid glands is recommended at the time of surgery to help identify abnormal parathyroid tissue.32

Three-view thoracic radiography (right and left lateral plus ventrodorsal or dorsoventral), computed tomography, and abdominal ultrasonography should be considered when soft tissue masses and calcification, fungal disease, osteolytic, and/or osteoporosis are suspected. Thoracic radiographs should be evaluated for the presence of pulmonary nodules (7 to 9 mm); nodules are best detected in the peripheral lungs if neoplasia is suspected.33,34 Particular attention should also be paid to the sternal, perihilar, and mediastinal regions, as well as all bony structures. Up to 68% of dogs with mediastinal lymphoma are hypercalcemic.35 Discrete osteolytic lesions of bone are suggestive of either multiple myeloma or malignancy-associated hypercalcemia with bone metastasis. Follow-up bone aspiration and biopsies of lytic lesions may be necessary to establish a definitive diagnosis of neoplasia. At minimum, ultrasonographic abdominal examination should be performed in all dogs and cats presenting with hypercalcemia if no obvious cause has been identified. In larger dogs (>25 kg [55 lb]), abdominal computed tomography is preferred to ultrasonography to screen for intra-abdominal disease.36 When imaging the abdomen, the spleen, liver, kidneys, and mesenteric and sublumbar lymph nodes should be assessed and any noticeable abnormalities sampled via fine-needle aspiration or percutaneous biopsy.

### TABLE 4 Treatment Options for Patients With Moderate to Severe Hypercalcemia2,3,23,25,37-42

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>PRESCRIPTION</th>
<th>MECHANISM(S) OF ACTION</th>
<th>TIMING</th>
<th>POTENTIAL ADVERSE EFFECT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous fluids (e.g., 0.9% saline, lactated Ringer’s solution, PlasmaLyte, Normosol R)</td>
<td>80–180 mL/kg/day</td>
<td>• Volume expansion • Increases GFR • Competitive inhibition of iCa reabsorption</td>
<td>Initial</td>
<td>• Pulmonary edema secondary to congestive heart failure • Hypervolemia • Hypertension • Minimal hypernatremia</td>
</tr>
<tr>
<td>Furosemide</td>
<td>1–2 mg/kg q12h IV, SC, or PO 0.66 mg/kg/h (loading) + 0.66 mg/kg/h (CRI)4</td>
<td>• Promotes calciuresis</td>
<td>Once rehydrated</td>
<td>• Dehydration • Hypovolemia</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>4–6 U/kg q8-12h IM or SC</td>
<td>• Inhibits osteoclast formation and activity</td>
<td>Initial</td>
<td>• GI (e.g., anorexia, vomiting) • Effects short lived</td>
</tr>
<tr>
<td>GLUCOCORTICOIDS</td>
<td></td>
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</tr>
<tr>
<td>Dexamethasone</td>
<td>0.1–0.22 mg/kg q12h IV or SC</td>
<td>• Lymphocytolysis • Decreases iCa GI absorption • Calciuresis • Counteracts vitamin D • Decreases iCa bone resorption</td>
<td>Initial? • Long-term management</td>
<td>• Polyphagia • Polyuria • Polydipsia • Alopecia • Muscle wasting • Delayed wound healing • GI ulceration</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1–2.2 mg/kg q12h IV, SC, or PO</td>
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<tr>
<td>BISPHOSPHONATES</td>
<td></td>
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</tr>
<tr>
<td>Pamidronate</td>
<td>1.3–2 mg/kg IVb</td>
<td>• Inhibits osteoclast activity</td>
<td>Long-term management</td>
<td>• Pathologic fractures (cats) • Esophagitis • Extravasation reaction (e.g., soft tissue swelling, ulceration, necrosis) • Electrolyte abnormalities (e.g., hypophosphatemia, hypomagnesemia, hypokalemia)</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>0.1–0.25 mg/kg IVc</td>
<td></td>
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<tr>
<td>Alendronate</td>
<td>Dogs: 0.5–1 mg/kg PO q24h Cats: 5–10 mg/cat PO once per week</td>
<td>• Inhibits dissolution of bone crystal</td>
<td></td>
<td></td>
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</tbody>
</table>

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4Lower doses (<1 mg/kg) have been shown to effectively augment calciuresis.37
5Dilute in 150 mL of 0.9% saline and infuse over 2 hours. Can repeat in 1 to 3 weeks.
6Dilute in 45–100 mL of 0.9% saline and infuse over 30 minutes. Can repeat in 3 to 4 weeks.
CRI = constant rate infusion; GFR = glomerular filtration rate; GI = gastrointestinal; iCa = ionized calcium.
TREATMENT OF HYPERCALCEMIA

Aggressiveness of medical therapy is dictated by the systemic wellness of the patient, rate of rise of serum calcium concentration, and severity of hypercalcemia. Asymptomatic/mildly symptomatic patients or patients with chronic hypercalcemia (12 to 14 mg/dL) do not require immediate treatment. For severely hypercalcemic patients (>14 mg/dL) exhibiting clinical signs and patients that have had an acute rise in serum calcium, initial therapy is aimed at reducing serum calcium concentrations while treating the underlying cause. If a definitive diagnosis is not initially apparent, therapy should be aimed at reducing serum calcium by inhibiting bone resorption, increasing urinary calcium excretion, or decreasing intestinal calcium absorption to ameliorate cardiac, neurologic, and renal toxicity (TABLE 4). Each patient should be managed individually based on severity of clinical signs and magnitude of hypercalcemia (BOX 2).

Symptomatic supportive therapy is directed at correcting dehydration, promoting calciuresis, and inhibiting accelerated bone resorption. Most patients with severe hypercalcemia have marked intravascular volume depletion. In these patients, hypercalcemia is exacerbated due to impaired calciuresis combined with concurrent metabolic acidosis that shifts more calcium to the ionized form. An in-depth review of specific diseases causing hypercalcemia and their treatment is beyond the scope of this article, and medical textbooks should be consulted once an underlying cause for hypercalcemia has been identified.

Fluid Therapy

Transient hypercalcemia is usually corrected with fluid therapy alone, as patients are usually dehydrated and volume contracted. Conditions include hemoconcentration, hyperproteinemia, and hypoadrenocorticism. Intravenous fluid therapy is an essential part of any therapeutic plan, as it expands the extracellular fluid volume and decreases the proximal tubular resorption of calcium. Physiologic saline (0.9% NaCl) is preferred because it is more sodium replete than other fluids, does not contain calcium, and competitively inhibits renal tubular reabsorption of calcium, leading to enhanced calciuresis. Other balanced isotonic crystalloid solutions (e.g., lactated Ringer’s solution, PlasmaLyte, Normosol R) are acceptable as substitutes as they increase renal blood flow and glomerular filtration rate, enhancing both natriuresis and calciuresis. Hypokalemia and hypomagnesemia are anticipated when nonsupplemented fluids are administered at relatively high rates (2 to 3 times maintenance) for more than several hours.

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Infusion IV fluid rates depend on several factors, including severity of hypercalcemia; chronicity of disease; and presence of comorbid conditions, particularly underlying cardiac or renal disease. An acceptable regimen in the absence of comorbidities is replacement fluid therapy over 4 to 6 hours to correct dehydration, provide ongoing fluid requirements, and expand volume at 2 to 3 times maintenance (80 to 180 mL/kg/day, based on 40 to 60 mL/kg/day as the baseline fluid requirement). Continuous subjective and objective evaluations (e.g., respiratory rate and effort, body weight changes) are required to avoid...
overhydration, especially when comorbidities such as cardiac disease are present. Following adequate rehydration, IV fluids should be continued (96 to 144 mL/kg/day) to limit reclamation of calcium from the renal tubules.

**Furosemide**
Following adequate rehydration, patients with persistent or progressively worsening hypercalcemia require adjunctive therapy to promote further renal excretion of calcium. Furosemide, a loop diuretic, promotes renal calcium excretion by inhibiting calcium reabsorption in the thick ascending loop of Henle. Furosemide should not be administered until fluid volume is restored. Administration prior to adequate rehydration will further reduce calcium clearance from the body, leading to exacerbation of hypercalcemia.

**Bisphosphonates**
Bisphosphonates (e.g., alendronate, zoledronate, clodronate) are synthetic pyrophosphate analogues that inhibit osteoclast-mediated bone resorption. They act by disrupting osteoclast intracellular metabolism and promote osteoclast apoptosis. Bisphosphonates have been used to manage a variety of hypercalcemic disorders, including humoral hypercalcemia of malignancy, vitamin D toxicity (cholecalciferol and calcipotriene), primary hyperparathyroidism, feline nocardiosis, and feline idiopathic hypercalcemia; however, they are not considered an initial choice for acute therapy unless prolonged hypercalcemia is expected or excess serum iCa is of bony origin. Parenteral administration is preferred due to poor oral absorption (approximately 5%). Pamidronate has been most commonly used in veterinary medicine and is both safe and effective. Serum calcium begins to decrease in 1 to 2 days; maximal effects are seen at 2 to 4 days and usually last for 2 to 4 weeks.

**Glucocorticoids**
Glucocorticoids lower calcium by inhibiting osteoclast-mediated bone resorption, decreasing intestinal calcium absorption, and promoting renal excretion of calcium. Vitamin D antagonism has also been observed with the use of glucocorticoids. Additionally, glucocorticoids may be directly cytotoxic to steroid-sensitive neoplasms associated with hypercalcemia. Serum calcium usually starts to decline after 1 to 2 days, with peak response requiring 7 to 10 days. Caution is urged when a definitive diagnosis has not been achieved, as glucocorticoids are directly toxic to neoplastic lymphocytes and can exacerbate infectious disease.

Significant beneficial serum iCa reduction has been reported in hypercalcemic animals with certain neoplasms (lymphoma, anal gland adenocarcinoma, multiple myeloma, thymoma), hypoadrenocorticism, hypervitaminosis D, granulomatous disease, and feline idiopathic hypercalcemia.

In general, glucocorticoids have limited use in patients with primary hyperparathyroidism. Nonhematologic malignancies do not respond to glucocorticoids.

**TABLE 5 Alternative Treatment Options in Patients With Hypercalcemia**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>PRESCRIPTION</th>
<th>MECHANISM(S) OF ACTION</th>
<th>INDICATION(S)</th>
<th>ADVERSE EFFECT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium EDTA</td>
<td>25–75 mg/kg/h IV</td>
<td>Chelating agent that binds to iCa in blood</td>
<td>Severe hypercalcemia</td>
<td>Nephrotoxicity, GI (e.g., vomiting, diarrhea, anorexia), CNS depression, Hypocalcemia</td>
</tr>
<tr>
<td>Dialysis* (iCa-free dialysate)</td>
<td>N/A</td>
<td>Extracorporeal renal clearance of iCa</td>
<td>Severe hypercalcemia (acute), Acute kidney injury</td>
<td>Coagulopathy, Hypothermia</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>0.5 mg/kg PO q24h</td>
<td>Decreases PTH secretion</td>
<td>Refractory hypercalcemia</td>
<td>Lethargy, GI (e.g., anorexia, vomiting)</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>1–2 g PO q12h for 2–3 days</td>
<td>Bile acid sequestrant, May increase vitamin D excretion</td>
<td>Cholecalciferol toxicosis</td>
<td>GI (e.g., constipation, nausea)</td>
</tr>
</tbody>
</table>

*Not routinely performed
CNS = central nervous system; GI = gastrointestinal; iCa = ionized calcium; PTH = parathyroid hormone.
Calcitonin
Calcitonin rapidly reduces the biologic activity and synthesis of osteoclasts.\textsuperscript{2-3} It also enhances urinary calcium excretion.\textsuperscript{22} Calcitonin should be considered in severely hypercalcemic patients without a definitive diagnosis; however, it is expensive, and the magnitude of its effect is unpredictable.\textsuperscript{3} Effects are often short-lived (hours) with receptor downregulation resistance often developing within 2 to 4 days.\textsuperscript{22} The effectiveness of calcitonin may be restored 24 to 48 hours after discontinuing therapy.\textsuperscript{3} Simultaneous administration of glucocorticoids may delay development of resistance.\textsuperscript{2} Calcitonin has been used in cholecalciferol toxicity.

Other therapies that have been utilized to reduce the degree of hypercalcemia are listed in Table 5.


A Practical Approach to Hypercalcemia

TOPIC OVERVIEW
Calcium is an important electrolyte and essential element for many cellular processes. This article provides a broad overview of calcium regulation, describes the development of hypercalcemia, and provides a practical approach to patients presenting with hypercalcemia, including initial stabilization of patients with severe hypercalcemia.

LEARNING OBJECTIVES
Upon completion of this article, readers should be able to describe mechanisms of calcium homeostasis, identify causes of hypercalcemia, and provide initial symptomatic and supportive care for severely hypercalcemic patients.

1. What is the most common cause of hypercalcemia in dogs?
   a. Nonpathologic and transient conditions
   b. Pythiosis
   c. Hypercalcemia of malignancy
   d. Hypoadrenocorticism

2. What is the most common cause of hypercalcemia in cats?
   a. Lymphoma
   b. Acute kidney injury
   c. Nonpathologic and transient conditions
   d. Mycobacterial infection

3. A 4-year-old male neutered Maltese presents with a history of lethargy and vomiting. Vaccinations, heartworm prophylaxis, and intestinal deworming are current. The patient is an indoor-only dog and is not currently receiving any medication. Palpation reveals generally enlarged peripheral lymph nodes. A serum biochemistry panel shows total calcium to be 17 mg/dL. How do you confirm that this dog has true hypercalcemia?
   a. No confirmation is necessary.
   b. Collect blood to measure ionized calcium.
   c. Perform thoracic radiography.
   d. Perform abdominal ultrasonography.

4. After confirming true hypercalcemia in the dog in question 3, what is your next diagnostic step?
   a. Perform an adrenocorticotropic hormone stimulation test.
   b. Aspirate a lymph node.
   c. Obtain thoracic radiographs.
   d. Perform a bone marrow biopsy.

5. What initial therapy could you give the patient in question 3?
   a. A nonsteroidal anti-inflammatory drug
   b. Cholestyramine
   c. Prednisone
   d. Intravenous 0.9% NaCl

6. When collecting a blood sample for measurement of ionized calcium, which of the following is recommended?
   a. Instruct owners to feed patients immediately before blood collection.
   b. Exercise the patient directly prior to blood collection.
   c. Collect blood collected in a purple-top tube (EDTA).
   d. Collect blood in a red-top tube.

7. Of the listed conditions, which is the most common reported cause of pathologic hypercalcemia in dogs?
   a. Malignancy
   b. Hypoadrenocorticism
   c. Hypervitaminosis D
   d. Granulomatous disease

8. Of the listed conditions, which is the most common reported cause of pathologic hypercalcemia in cats?
   a. Hypoadrenocorticism
   b. Kidney disease
   c. Diabetes mellitus
   d. Hypervitaminosis D

9. Which of the following processes can cause hypercalcemia?
   a. Decreased bone resorption of calcium (i.e., osteolysis)
   b. Increased renal excretion of calcium
   c. Decreased gastrointestinal absorption of calcium
   d. None of the above