Abstract

Hypercalcemia (an elevated level of calcium in the blood) in dogs is a relatively uncommon electrolyte abnormality that can affect multiple body systems. The most common pathologic causes of hypercalcemia are malignancy and hyperparathyroidism. Comprehensive diagnostics must be carried out to reach a concrete diagnosis, which will allow for appropriate treatment options to be pursued. Treatment of the underlying cause is necessary to obtain resolution of the hypercalcemia. While waiting on diagnostic results, supportive treatments can be provided to lower calcium levels until a long-term solution can be found. Treatment options include fluid diuresis, steroids, bisphosphonates, and other pharmacologic compounds. Surgery and/or chemotherapy may be necessary if a neoplastic process is discovered. By combining diagnostic results and appropriate treatment modalities, resolution of hypercalcemia can be obtained in most cases.
INTERNAL MEDICINE

Hypercalcemia in Dogs: Emergent Care, Diagnostics, and Treatments

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Hypercalcemia is a relatively uncommon electrolyte abnormality from a disease process or external influence leading to excess calcium in the body. The most common pathologic cause of hypercalcemia in dogs is neoplasia; 60% of dogs with hypercalcemia are diagnosed with cancer. Abnormal calcium levels can lead to severe disturbances in normal body functions as calcium is a key component in neuromuscular transmission, enzyme function, clotting, vasodilation, vasoconstriction, and bone production and stability.

There are 2 primary ways to measure calcium: total and ionized. Total reflects all calcium within the body, while ionized reflects the biologically active calcium levels. When only total calcium levels are used, hypercalcemia can be overestimated while hypocalcemia can be underestimated. When calcium levels in a patient are being evaluated,

### Take-Home Points

- Calcium homeostasis is of vital importance to maintain normal physiologic function of many body systems.
- HARDIONS is an acronym for remembering the most common causes of hypercalcemia.
- The most common pathologic cause of hypercalcemia is malignancy, with lymphoma and apocrine gland anal sac adenocarcinoma being the most common culprits.
- The extent of initial treatment is largely based on the severity of clinical signs and often includes fluid diuresis, diuretics, and steroids.
- Without treating the underlying cause, resolution of hypercalcemia cannot occur.
- Comprehensive and complete diagnostics are key to diagnosing the underlying cause of hypercalcemia.
- The hypercalcemia of malignancy panel is an important diagnostic tool in differentiating hypercalcemia of malignancy and hyperparathyroidism.
ionized calcium is the more accurate value used to initially diagnose and monitor hypercalcemia.

NORMAL CALCIUM REGULATION
Calcium regulation is maintained by 3 main substances within the body: calcitriol, parathyroid hormone (PTH), and calcitonin (FIGURE 1).

The body acquires much of its calcium from vitamin D obtained by ultraviolet light exposure or by consuming foods or supplements containing vitamin D. Once vitamin D has entered the body, it is converted in the liver to 1,25-dihydroxyvitamin D. This precursor (an inactive substance that is converted to an active substance) is then processed by the kidney and converted into calcitriol. Calcitriol is released into the bloodstream and helps to increase intestinal calcium absorption and supports both bone and kidney calcium reabsorption.

Calcium levels in the body are further regulated by the parathyroid gland. The parathyroid gland produces PTH, whose primary role is maintaining a homeostatic calcium level. PTH increases plasma calcium levels via 3 mechanisms: utilizing bone stores of calcium via resorption, increasing renal tubule calcium reabsorption, and increasing the synthesis of calcitriol in the kidneys.

The parathyroid gland will adjust its PTH production, with PTH and calcitriol inhibiting further secretion of PTH. When excess calcium levels are detected by the parathyroid gland, calcitonin production is increased in the thyroid gland, which inhibits osteoclast activity and bone resorption, thereby helping to stabilize calcium levels in normal dogs.

However, in dogs with a disease process in which this cycle is affected or circumvented (such as cancer), excess calcium production continues regardless of the normal negative feedback loop in the calcium cycle.

CAUSES OF HYPERCALCEMIA
HARDIONS is an effective mnemonic device to remember common causes of hypercalcemia:

![Diagram of Calcium Regulation](Thyroid glands: N Vinod Narasingam/shutterstock.com; Bone: Alexander P/shutterstock.com)
Other uncommon causes of hypercalcemia include excess intestinal phosphate binders, excessive calcium supplementation, hypervitaminosis A, milk-alkali syndrome, thiazide diuretics, acromegaly, thyrotoxicosis, postrenal transplantation, and aluminum exposure.

Hypercalcemia of Malignancy
In dogs, HM is most often associated with T-cell lymphoma and anal gland adenocarcinoma. HM can also occur with multiple myeloma, parathyroid tumors (often benign), thymoma, melanoma, mammary tumors, and others. HM is most commonly caused by release of PTH-related peptide (PTHrP) from tumor cells into circulation, referred to as HHM. Other growth factors and cytokines released from cancer cells can further contribute to and synergize the role of PTHrP in HM. PTHrP can function just as PTH does in the calcium cycle by increasing osteoclast activity, resulting in bone resorption, and increasing renal tubule calcium reabsorption. HM can also occur more directly due to osteolysis from bone tumors, releasing excess calcium into circulation.1,3

Hyperparathyroidism
Primary hyperparathyroidism is another potential cause of hypercalcemia, although its incidence is less than that of malignant causes. Hyperparathyroidism results in the parathyroid glands producing and secreting too much PTH, leading to excessive calcium recruitment by the bones, kidneys, and intestines. This overzealous production of PTH is caused by a nodule or nodules within the parathyroid glands. These nodules are statistically benign, although malignant nodules are possible.1

Primary hyperparathyroidism most commonly occurs in older dogs around 7 years of age. Sex and breed predilection are not statistically relevant, with the exception of the keeshond, which has a hereditary form of the disease.4

Clinical signs of hyperparathyroidism coincide with general hypercalcemia signs but are often less severe or nonexistent at the time of diagnosis. Evidence of primary hyperparathyroidism is often an incidental finding on routine lab work in older dogs.

Hypoadrenocorticism
Approximately one-third of dogs diagnosed with hypoadrenocorticism are found to have mild hypercalcemia. Multiple factors may influence this finding, including increased calcium citrate, hemoconcentration, increased renal resorption of calcium, and increased affinity of serum proteins for calcium. When the hypoadrenocorticism is treated and stable, the hypercalcemia resolves quickly.

Renal Disease/Failure
Hypercalcemia can be an attributing cause or sign of renal failure. The association of hypercalcemia and renal failure almost always accompanies a primary comorbidity, such as neoplasia, primary hyperparathyroidism, or vitamin D toxicity. Severe hypercalcemia can contribute to acute renal failure. Mild to moderate hypercalcemia may be a result of chronic renal failure.1

Toxicity
Hypercalcemia secondary to toxicity can occur from ingestion of calcium or vitamin D supplements, cholecalciferol (vitamin D₃)-containing rodenticides, calcitriol, glycoside-containing plants, and intestinal phosphate binders. Treatments specific to the toxin can be instituted in addition to supportive treatments for hypercalcemia.

Idiopathic
Unlike cats, in which idiopathic hypercalcemia is a common diagnosis when hypercalcemia is discovered, idiopathic hypercalcemia is very rare in dogs.
PRESENTING CLINICAL SIGNS OF HYPERCALCEMIA IN DOGS

Calcium is involved in many of the daily body processes. When calcium is not properly regulated, it can cause a variety of clinical signs:

- Vomiting
- Diarrhea
- Polyuria
- Polydipsia
- Anorexia
- Muscle weakness
- Twitching (muscle tremors)
- Seizures and cardiac arrhythmias (severe hypercalcemia)

Commonly affected organs are the gastrointestinal system, heart, kidneys, musculoskeletal system, and central nervous system.

DIAGNOSTICS FOR HYPERCALCEMIA

To investigate the source of hypercalcemia, a set of base diagnostics should be performed. A complete blood cell count, comprehensive biochemical profile, and urinalysis should be run to evaluate for any other lab work abnormalities, such as azotemia, that could give an indication of the root cause (TABLE 1).\(^1\) Given their close connection to calcium levels, phosphorous levels are an important part of lab work interpretation as well.

Thoracic radiography and full abdominal ultrasonography should be performed to evaluate for any evidence of neoplasia. If any evidence of neoplasia is discovered, additional diagnostics such as ultrasound-guided fine-needle aspiration or biopsy should be performed.

Aberrant calcium lab values can occur due to a nonfasted sample, the physiologic growth of young animals, or lab error and for spurious reasons due to lipemia or detergent contamination of the sample, hemoconcentration, hyperproteinemia, hypoadrenocorticism, and exposure to drastically cold temperatures during transport.

The common diagnostics above are all appropriate when testing for primary hyperparathyroidism. An additional test—an HM panel—can help differentiate between a malignant cause and primary hyperparathyroidism. The HM panel tests PTH, ionized calcium, and PTHrP. An elevated PTH in conjunction with hypercalcemia is indicative of hyperparathyroidism. A low PTH and positive PTHrP concentration is indicative of malignancy as PTHrP is not produced in measurable quantities in adult dogs, although a negative PTHrP can still occur with malignancy.

When hyperparathyroidism is suspected, an ultrasound of the thyroid and parathyroid glands is appropriate to evaluate for any evidence of nodules or masses. As previously mentioned, presence of a nodule is common with primary hyperparathyroidism; these nodules are most often benign.\(^1\)

### TABLE 1 Laboratory Abnormalities Commonly Associated With Causes of Hypercalcemia\(^a\)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>TOTAL CALCIUM</th>
<th>IONIZED CALCIUM</th>
<th>PTH</th>
<th>1,25-DIHYDROXYVITAMIN D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>High</td>
<td>High</td>
<td>Normal to high</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypercalcemia of malignancy</td>
<td>High</td>
<td>High</td>
<td>Low to low-normal</td>
<td>Low to normal</td>
</tr>
<tr>
<td>Hypoadrenocorticism</td>
<td>Low, normal, or high</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Low, normal, or high</td>
<td>Normal to low</td>
<td>Normal to high</td>
<td>Low to normal</td>
</tr>
<tr>
<td>Hypervitaminosis D</td>
<td>High</td>
<td>High</td>
<td>Low to low-normal</td>
<td>Low to normal; high with vitamin D(_2) or D(_3) toxicity</td>
</tr>
<tr>
<td>Granulomatous disease</td>
<td>High</td>
<td>High</td>
<td>Low to low-normal</td>
<td>Low to normal</td>
</tr>
</tbody>
</table>


PTH = parathyroid hormone; PTHrP = parathyroid hormone–related peptide
TREATMENT OF HYPERCALCEMIA

Treatment can depend on the severity of clinical signs. The most effective treatment for hypercalcemia is addressing or removing the underlying cause. For example, in the case of HM, the tumor should be removed or treated with chemotherapy to alleviate the hypercalcemia. Without these treatments, the hypercalcemia will persist unchecked. If the underlying cause cannot be directly treated, such as tumors that are not surgical, supportive treatments to combat the hypercalcemia should be pursued.

If neoplasia has been diagnosed as a probable cause of hypercalcemia and surgery is an option, such as in the case of apocrine gland anal sac adenocarcinoma, surgical removal of the tumor is the gold standard treatment that will thus lower high calcium levels.

If primary hyperparathyroidism has been diagnosed, surgery or ethanol ablation of the parathyroid nodule(s) should be pursued. Surgery is the preferred treatment; however, in patients that are not good surgical candidates or when the client is not willing to pursue surgery, ablation can be an alternative treatment option. The efficacy of ethanol ablation can vary depending on the size of the nodule and skill/experience of the clinician performing the procedure but has been estimated at approximately 72%.6–8 Complications that can occur include bark changes, coughing, dysphagia, hypersalivation, and laryngeal paralysis (if the laryngeal nerve is affected). When treatment is successful, resolution of hypercalcemia can occur within 3 days of the procedure.

Emergent Care

Emergent care for hypercalcemia may be necessary in patients with total calcium levels >18 mg/dL and/or ionized calcium levels >1.6 mmol/L in conjunction with severe clinical signs. Supportive treatment to manage calcium levels will need to be started while the root cause is diagnosed and treated.

First-Line Treatments

Fluid diuresis with 0.9% sodium chloride (NaCl) can increase renal calcium loss. A fluid rate of 100 to 125 mL/kg/day should improve glomerular filtration rate and sodium excretion, thereby decreasing calcium reabsorption. All crystalloids containing calcium should be avoided.

Diuretics can further increase renal calcium loss in conjunction with fluid diuresis. Loop diuretics should be used over thiazide diuretics, which are contraindicated in hypercalcemia because they decrease renal excretion of calcium. Furosemide at 2 to 4 mg/kg or higher q8h to q12h will increase renal calcium excretion.

Glucocorticoids can be very beneficial in the treatment of hypercalcemia when it is related to neoplasia. Their use before a diagnosis of neoplasia can potentially inhibit obtaining a concrete diagnosis, especially in patients with probable lymphoma. Glucocorticoids have lymphocytic properties, which can change the architecture of the lymph nodes, making cytologic or histopathologic diagnosis difficult. Falsely low PTHrP concentrations can also occur secondary to steroid administration, which can inhibit differentiating between HM and primary hyperparathyroidism.

Other agents that may be useful when first-line treatments are suboptimal include bisphosphonates, mitramycin, calcitonin, or calcimimetics.

Bisphosphonates

Bisphosphonates are a group of drugs used in both human and veterinary medicine to treat osteoporosis and bone cancer and to mediate hypercalcemia. Bisphosphonates work by inhibiting osteoclast activity in the bones by attaching to the osteoclast and disrupting intracellular enzyme functions essential to bone resorption. Bone resorption is the process of breaking down bone, which leads to the release of calcium into the bloodstream. By interrupting this

<table>
<thead>
<tr>
<th>PHOSPHOROUS</th>
<th>PTHrP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to low</td>
<td>Negative</td>
</tr>
<tr>
<td>Normal to low</td>
<td>Positive (sometimes)</td>
</tr>
<tr>
<td>Normal to high</td>
<td>Negative</td>
</tr>
<tr>
<td>High</td>
<td>Negative</td>
</tr>
<tr>
<td>Normal to high</td>
<td>Negative</td>
</tr>
<tr>
<td>Normal to high</td>
<td>Negative</td>
</tr>
</tbody>
</table>
process, we can decrease excess calcium release while also providing improved bone structure/stability and pain control in patients with bone neoplasia.

Bisphosphonates can be administered intravenously or orally. Bioavailability of oral bisphosphonates in dogs is poor in contrast to IV administration, but it can be a more attractive option for long-term treatment of hypercalcemia in some cases. IV administration will not result in osteoclast inhibition for 24 to 48 hours postinfusion; therefore, bisphosphonates are not an initial treatment of choice in cases of acute hypercalcemia with severe clinical signs.

Bisphosphonates must be used cautiously or avoided entirely in patients with renal disease as they can cause nephrotoxicity. An additional side effect is mandibular osteonecrosis. Generalized skeletal pain for a few days after infusion is a common complaint from humans receiving bisphosphonates; therefore, it is reasonable to surmise that dogs may experience similar effects. In the author’s experience, some clients do report lethargy and stiffness in their dogs for 2 to 3 days postinfusion.

Pamidronate was previously the most commonly used intravenous bisphosphonate for many years, but zoledronate has taken over due to its drastically increased antiresorption properties and effectiveness, along with a shorter administration time. Zoledronate is dosed at 0.1 to 0.2 mg/kg (not to exceed 4 mg/dog), diluted in 0.9% NaCl over 15 minutes. A shorter or longer administration time can increase the risk of nephrotoxicity; therefore, it is vital to calculate the administration rate to provide the full dose in exactly 15 minutes.

**Calcitonin**
Calcitonin, a hormone produced by the thyroid gland, is an effective agent for decreasing calcium levels rapidly. Calcitonin inhibits osteoclast activity in bone and renal reabsorption of calcium and phosphate, thereby lowering calcium levels. These effects occur quickly but are short-lived due to resistance building up over 12 to 24 hours. Calcitonin is best used for reducing calcium levels quickly in patients with severe hypercalcemia and severe clinical signs. Close monitoring of ionized calcium levels is necessary as hypocalcemia can occur. Other important values to monitor include phosphorous, blood urea nitrogen, creatinine, hydration status, and urine cast formation.

Calcitonin is an expensive medication and availability can be inconsistent. Although calcitonin can decrease calcium levels rapidly, it is not a sustainable decrease due to development of resistance; therefore, use of calcitonin in veterinary medicine is limited and uncommon.

**Calcimimetics**
Calcimimetics are a newer class of drugs that reduce the secretion of PTH and can suppress circulating PTH. Calcimimetics increase the sensitivity of calcium-sensing receptors within the parathyroid gland, leading to a decrease in PTH and total calcium levels. This can be an effective treatment option for primary hyperparathyroidism and to reduce calcium levels in renal failure patients.

**Mithramycin**
Mithramycin, an antibiotic with antineoplastic properties and calcium-lowering activity, can be used as an emergent treatment choice to attempt to lower calcium levels quickly. Mithramycin has great potential for hepatotoxicity, bone marrow toxicity, and renal toxicity based on its dosing; therefore, it should be used judiciously and only after serum biochemical values have been evaluated. The calcium-lowering activity of mithramycin is short-lived, making it useful for quickly lowering calcium levels, but not for maintaining normal calcium values over the long term.

**SUMMARY**
Calcium homeostasis in the body is of paramount importance given the significant effects aberrations can cause. Hypercalcemia in dogs can be caused by a variety of disease processes influencing its severity and treatment options, including HM, primary hyperparathyroidism, hypoadrenocorticism, renal failure, and toxicity. Use the acronym HARDIONS to remember the common causes. Careful consideration of diagnostic results in conjunction with severity of clinical signs can guide short- and long-term treatment options. It is important to always remember that treatment of the underlying disease process causing hypercalcemia must be instituted to achieve resolution of clinical signs.
References


Brooke Quesnell
Brooke has been a certified veterinary technician for more than 13 years and a veterinary technician specialist in oncology for more than 5 years. She currently works as the clinical education specialist for WestVet Emergency and Specialty Center (parent corporation, MedVet). Brooke is passionate about educating fellow veterinary nurses and clinical team members, with a special interest in oncology and specialized procedures such as electrochemotherapy and compassionate client care. She regularly presents continuing education courses on local and national levels for various companies and conferences, contributes to textbooks relating to oncology, and writes articles for veterinary journals.

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