Primary Hyperparathyroidism

Cynthia R. Ward, VMD, PhD, DACVIM (Small Animal Internal Medicine)
Associate Professor of Medicine
Department of Small Animal Medicine and Surgery
College of Veterinary Medicine
University of Georgia

Primary hyperparathyroidism is uncommon in dogs and rare in cats. It is most often caused by parathyroid gland hyperplasia or adenoma; only rarely is carcinoma present. Diagnosis of this disease has become much easier with the development of immunoassays that accurately detect canine and feline parathyroid hormone (PTH). In addition, the routine measurement of ionized calcium has made it easier to detect hypercalcemia and has given a basis on which to evaluate whether paired PTH levels are appropriate. More accurate ultrasonographic techniques have been instrumental in detecting parathyroid tumors or enlarged parathyroid glands before surgery. Surgical removal of the hyperplastic parathyroid gland or parathyroid adenoma is still considered the best treatment for this disease.

Diagnostic Criteria

Historical Information

Gender Predisposition
- None.

Age Predisposition
- Dogs: Mean age, 9 to 11 years; range, 4.5 to 17 years.
- Cats: Mean age, 13 years; range, 8 to 20 years.

Breed Predisposition
- Keeshond dogs.
- Siamese cats may be overrepresented.

Owner Observations

Dogs
- None (hypercalcemia detected on routine blood work).
- Polyuria/polydipsia.
- Weakness.
- Lethargy.
- Inappetence.
- Weight loss/muscle wasting.
- Vomiting.
- Shivering/tremors.
- Dysuria/hematuria.
- Collapse.
- Seizures.

Cats
- None.
- Anorexia.
- Lethargy.
- Vomiting.
- Weight loss.
- Polyuria/polydipsia.
- Constipation.
- Dysuria.
- Muscle fasciculation.

Other Historical Considerations/Predispositions
- Congenital disease has been noted in two German shepherd puppies.
- Concurrent hyperparathyroidism and hyperthyroidism were reported in a kitten.
- Most owners do not notice clinical signs.
- Some animals have had a history of calcium-containing uroliths.
- Disease onset is insidious.

Physical Examination Findings

- No abnormalities are detected in most cases.
- Muscle wasting.
- Weakness.
- Obesity or thin body condition.
- Shivering/tremors.
- Palpable cervical masses (cats).

Laboratory Findings

- Elevated total calcium.
- Elevated ionized calcium.
- Normal or elevated immunoreactive PTH level.
- Low or low-normal serum phosphorus levels; rarely elevated.
- Urine specific gravity of less than 1.024; rarely, above 1.030.
- Urine sediment: Hematuria, pyuria, bacteriuria, calcium-containing crystalluria.
- Urine culture positive for bacterial growth.
- Elevated blood urea nitrogen and creatinine.
- Elevated serum alkaline phosphatase.
- Elevated cholesterol.
• PTH-related protein levels are undetectable.

**Other Diagnostic Findings**

• Thoracic radiography: Usually normal.
• Abdominal radiography: Radiodense urinary calculi may be present.
• Ultrasonography:
  — Neck: Single or multiple parathyroid gland masses; parathyroid gland cyst.
  — Abdomen: Uroliths (renal, ureteral, and/or urethral).
• Radionuclide scans are not helpful.

**Summary of Diagnostic Criteria**

• Demonstration of total and/or ionized hypercalcemia paired with normal or elevated PTH levels, which is an inappropriate response to hypercalcemia.
• Parathyroid mass(es) or enlarged parathyroid gland found on ultrasonographic evaluation of the neck.
• Low or low-normal serum phosphorus levels.
• Exclusion of other, more common causes of hypercalcemia.

**Diagnostic Differentials**

• Malignancy is the most common cause of hypercalcemia.
  — **Humeral hypercalcemia of malignancy**: Lymphoma; anal sac adenocarcinoma; carcinoma of mammary glands, lungs, pancreas, nasal cavity, thyroid, skin (sporadic); thymoma (rare).
  • Diagnosed by biopsy or fine-needle aspiration of enlarged lymph nodes or masses detected during physical examination or imaging studies.
  • Serum PTH-related protein may be elevated
  — **Hematologic malignancy** (local osteolysis of bone marrow): Lymphoma, multiple myeloma, lymphocytic leukemia (rare), myeloproliferative disease (rare).
  • Diagnosed by complete blood count analysis and cytologic evaluation of bone marrow aspirates.
• Renal failure: Ruled out by normal blood urea nitrogen and creatinine levels or normalizaton of these levels following volume expansion.

• Hypoadrenocorticism: Ruled out by a normal corticotropin stimulation test.
• Hypervitaminosis D: For example, associated with vitamin D supplements, rodenticide toxicity (cholecalciferol), antipsoriasis creams (calcipotriol, calcipotriene), plants (calcitriol glycosides).
  — Ruled out by history and measurement of serum vitamin D levels, although the latter will not detect calcipotriol or calcipotriene.
• Granulomatous disease: Ruled out by a combination of biochemical data, imaging studies, cytology of infectious masses or fluids, or fungal titers.
• Skeletal lesions (malignant and nonmalignant): Rare; ruled out by physical examination and radiographic findings.
• Idiopathic hypercalcemia of cats: Diagnosis of exclusion.

**TREATMENT RECOMMENDATIONS**

**Initial Treatment**

The goal of initial therapy is to lower serum calcium levels while obtaining a diagnosis. Treatment should be instituted when total calcium values exceed 17 mg/dl or ionized calcium is greater than 1.7 nmol/L. NOTE: Clinically compromised animals with any degree of hypercalcemia should be treated immediately.

• **Crystalloid therapy:**
  — 0.9% NaCl: 100–125 ml/kg/day; dose should be increased in volume-depleted animals.
  — Promotes calciuresis.
  — Should be used with caution in patients with cardiac failure, hypertension, or hypoproteinemia.
• **Furosemide:**
  — 2–4 mg/kg IV, SC, or PO bid–tid.
  — Patient must be sufficiently volume expanded.
  — Rapid response.
• **Calcitonin:**
  — 4–6 IU/kg SC bid–tid.
  — Patients may become refractory after 2 to 3 days.
• **Glucocorticoids:**
  — Prednisone: 1 mg/kg PO, SC, or IV bid.
  — Dexamethasone: 0.1 mg/kg IV.
  — Rapid onset.

• Acute or chronic renal failure may be a serious consequence of hyperparathyroidism; this is supported by one study but not another.

STANDARDS of CARE: EMERGENCY AND CRITICAL CARE MEDICINE
— Promotes calciuresis.
— Must not be used until diagnostics are completed; may inhibit definitive diagnosis of hypercalcemia.

**Bisphosphonates:** NOTE: Most of these doses have been extrapolated from the human literature and are not derived from veterinary clinical studies.

— Pamidronate (cats, dogs): 1–2 mg/kg IV in 150 ml saline over 2 hours. May be repeated in 1–3 weeks.
  • Dehydration should be corrected first.
  • Should not be used in animals with renal disease.
  • Before pamidronate is administered, patients should be diuresed with an IV saline infusion for 2 to 4 hours to counteract potential nephrotoxicity.
  • Rapid action.
— Etidronate (dogs): 5–20 mg/kg PO sid–bid before a meal; may be poorly absorbed.
— Alendronate (cats, dogs): 0.5–1 mg/kg PO sid before a meal; better oral absorption than with etidronate.

**Standard Treatment**

• Surgical removal of parathyroid mass or hyperplastic parathyroid gland.

• Subtotal parathyroidectomy: Removal of three of the parathyroid glands if no discrete mass or hyperplastic parathyroid can be found.

**Alternative Treatment**

**Sodium EDTA:**

— 50 mg/kg/hr as an infusion over 2 hours.
— Used as a last resort for patients in hypercalcemic crisis when no other therapies have worked; forms a complex with calcium, which is then excreted.
— Side effects include nephrotoxicity.
— Should not be used in patients with renal failure.

• **Percutaneous ultrasonographic-guided ethanol injection.**
  — Ethanol is injected into parathyroid mass or hyperplastic parathyroid under ultrasonographic guidance.
  — Requires anesthesia.
  — Results are variable.
  — Offers no real advantage over surgery.

• **Percutaneous ultrasonographic-guided heat ablation.**
  — Thermal necrosis of parathyroid mass under ultrasonographic guidance.
  — Requires anesthesia.
  — Results are variable, and the proper needle must be used to penetrate the capsule of the parathyroid gland.
  — Offers no real advantage over surgery.

**Supportive Treatment**

Supportive treatment focuses on correcting postsurgical hypocalcemia; the risk of hypocalcemia is greater in patients with preoperative total serum calcium levels in excess of 14 mg/dl.

• **Calcitriol:** 23–30 ng/kg/day PO divided bid. Administration should start 24 hours before surgery and continue until the patient is discharged. At that time, the dose can be reduced to 15 ng/kg/day PO divided until serum calcium normalizes.

• **Calcium supplementation:** Should begin 24 hours before surgery and continue until the patient is discharged or until serum calcium normalizes.
  — Calcium carbonate: 100 mg/kg/day divided PO.
  — Calcium gluconate: 0.5–1 ml/kg of a 10% solution IV slowly up to tid or 10–15 mg/kg/hr constant-rate infusion. Electrocardiogram and respiratory rate should be closely monitored; administration should be discontinued if there are changes in either of these parameters.

• Serum total and/or ionized calcium should be monitored closely and kept in the slightly low or low-normal range as long as clinical signs are not evident.

**Patient Monitoring**

• Normal parathyroid tissue atrophies in response to unregulated PTH secretion; PTH levels decrease precipitously after treatment.
• Dangerous hypocalcemia can occur 1 to 20 days after surgery but usually occurs in the first 7 days. Close monitoring for clinical signs of hypocalcemia (see box, above) and serum total or ionized calcium levels is needed for 1 to 7 days after treatment.
• Patients should be hospitalized; if a patient is released to its owners, it should be checked daily at the hospital.

**Clinical Signs of Acute Hypocalcemia**

• Muscle tremors/twitching
• Facial rubbing
• Panting
• Ataxia/stiff gait
• Behavior changes; restlessness
• Focal or generalized seizures

— Serum total and/or ionized calcium should be monitored closely and kept in the slightly low or low-normal range as long as clinical signs are not evident.
STANDARDS OF CARE: EMERGENCY AND CRITICAL CARE MEDICINE

Home Management

• If the patient is not hospitalized, owners must observe their pet closely for signs of hypocalcemia for 1 to 7 days after treatment and take their pet to the hospital for daily monitoring of serum ionized calcium; level should be kept in the low-normal reference range.
• Withdrawal of supplemental calcitriol can begin 7 days after treatment if serum total or ionized calcium level has normalized. Serum ionized calcium should be checked before each downward adjustment; if the level is below the reference range, the dose of calcitriol should be increased to the previous level.
  — 7.5 ng/kg sid for 2 weeks.
  — 7.5 ng/kg every other day for 2 weeks.
  — 7.5 ng/kg q3d for 2 weeks.
  — 7.5 ng/kg once/week for 2–4 weeks; then discontinue.
• Calcium supplementation can be withdrawn slowly after calcitriol is discontinued and serum calcium is within the reference range:
  — 50 mg/kg sid for 2 weeks.
  — 50 mg/kg every other day for 2 weeks; then discontinue.
• Animals should be fed a complete diet.
• Animals should be closely monitored for urinary tract infection.

Milestones/Recovery Time Frames

• Most acute hypocalcemic crises occur within 1 week after treatment.
• Rarely, hypocalcemia can occur up to several weeks after treatment.

Treatment Contraindications

• Glucocorticoids should not be used to treat hypercalcemia unless all diagnostic work has been completed.
• Furosemide should not be used until dehydration is corrected.
• High doses of vitamin D and calcium supplementation should be avoided; to avoid tissue mineralization, only enough vitamin D and calcium should be used to keep the serum ionized calcium within the low-normal range.
• Phosphate supplements should be avoided.

PROGNOSIS

• Excellent with appropriate treatment and monitoring.
• Hyperplasia will return in some animals, so ongoing monitoring for recurrence of hypercalcemia is required.
• Approximately 40% of hyperparathyroid animals become hypocalcemic after treatment.

Favorable Criteria

• Visualization of a parathyroid mass on imaging studies.
• Complete removal of a discrete parathyroid mass.

Unfavorable Criteria

• Patients with serum total calcium levels above 14 mg/dl are more likely to become hypocalcemic after treatment.
• Renal failure at the time of diagnosis.
• Urolithiasis and urinary tract infections are common sequelae.
• Adenocarcinoma.

RECOMMENDED READING