Frequently-Asked Questions: Calcium Disorders

Does a negative PTHrP result rule out malignancy?

Unfortunately, a normal (or negative) concentration of parathyroid hormone related protein (PTHrP) does not rule out the presence of malignancy. PTHrP is only one of a number of factors that tumors may secrete that can result in an elevated calcium concentration (e.g. interleukins, tumor necrosis factor, etc.). Thus even if the PTHrP concentration is within normal limits, malignancy may still be present. A positive PTHrP concentration is indicative of malignancy, since PTHrP is not normally secreted in an appreciable quantity in adult animals.

What are the causes of hypercalcemia?

There are many causes of hypercalcemia in dogs and cats:

Nonpathologic
- Nonfasting (minimal increase)
- Physiologic growth of young
- Laboratory error
- Spurious
  - Lipemia
  - Detergent contamination of sample or tube

Transient or Inconsequential
- Hemoconcentration
- Hyperproteinemia
- Hypoadrenocorticism
- Severe environmental hypothermia (very rare)

Pathologic or Consequential—Persistent
- Parathyroid Dependent
  - Primary Hyperparathyroidism
    - Adenoma (common)
    - Adenocarcinoma (rare)
    - Hyperplasia (uncommon)
- Parathyroid Independent
  - Malignancy-associated (most common cause in dogs)
  - Humoral hypercalcemia of malignancy
    - Lymphoma (common)
    - Anal sac apocrine gland adenocarcinoma (common)
    - Carcinoma (sporadic): lung, pancreas, skin, nasal cavity, thyroid, mammary gland, adrenal medulla
    - Thymoma (rare)
- Hematologic malignancies (bone marrow osteolysis – local osteolytic hypercalcemia)
  - Lymphoma
  - Multiple myeloma
  - Myeloproliferative disease (rare)
  - Leukemia (rare)
- Metastatic or primary bone neoplasia (very uncommon)
Idiopathic Hypercalcemia (most common association in cats)
Chronic renal failure (with and without ionized hypercalcemia)
Hypervitaminosis D
   Iatrogenic
   Plants (calcitriol glycosides)
   Rodenticide (cholecalciferol)
   Antipsoriasis Creams (calcipotriol or calcipotriene)
Granulomatous disease
   Blastomycosis
   Dermatitis
   Panniculitis
   Injection reaction
Acute renal failure (diuretic phase)
Skeletal lesions (nonmalignant) (uncommon)
   Osteomyelitis (bacterial or mycotic)
   Hypertrophic osteodystrophy
   Disuse osteoporosis (immobilization)
Excessive calcium-containing intestinal phosphate binders
Excessive calcium supplementation (calcium carbonate)
Hypervitaminosis A
Raisin/Grape Toxicity
Hypercalcemic conditions in human medicine
   Milk-alkali syndrome (rare in dogs)
   Thiazide diuretics
   Acromegaly
   Thyrotoxicosis (rare in cats)
   Postrenal transplantation
   Aluminum exposure (intestinal phosphate binders in dogs and cats?)


What are the causes of hypocalcemia?

Hypocalcemia is less common than hypercalcemia in dogs and cats, and there are a number of potential causes.

**Common**
- Hypoalbuminemia
- Chronic renal failure
- Puerperal tetany (eclampsia)
- Acute renal failure
- Acute pancreatitis
- Undefined cause (mild hypocalcemia)

**Occasional**
- Soft tissue trauma or rhabdomyolysis
- Hypoparathyroidism
  - Primary
    - Idiopathic or spontaneous
    - Postoperative bilateral thyroidectomy
  - After sudden reversal of chronic hypercalcemia
Secondary to magnesium depletion or excess
Ethylene glycol intoxication
Phosphate enema
After NaHCO$_3$ administration

**Uncommon**
- Laboratory error
- Improper sample anticoagulant (EDTA)
- Infarction of parathyroid gland adenoma
- Rapid intravenous infusion of phosphates
- Acute calcium-free intravenous infusion (dilutional)
- Intestinal malabsorption or severe starvation
- Hypovitaminosis D
- Blood transfusion (citrated anticoagulant)
- Hypomagnesemia
- Nutritional secondary hyperparathyroidism
- Tumor lysis syndrome

**Human**
- Pseudohypoparathyroidism
- Drug-induced
- Hypercalcitonism
- Osteoblastic bone neoplasia (prostate cancer)


**Why should I measure ionized calcium and parathyroid hormone in cases of chronic renal failure?**

In chronic renal failure serum total calcium may be within the reference range. However, this does not ensure that alterations in calcium metabolism are not present. Commonly in renal failure due to loss of functional renal tissue, calcitriol is inadequately produced. Calcitriol is important in the regulation of ionized calcium concentration. This deficient calcitriol production allows the serum ionized calcium concentration to fall, which stimulates the production of parathyroid hormone (PTH). PTH will try to raise ionized calcium back into the normal reference range by activating osteoclasts with resorption of bone. To maintain the ionized calcium concentration, PTH continues to elevate, causing secondary hyperparathyroidism. PTH itself is a uremic toxin, and some of the signs of chronic renal failure can be attributed to excess PTH. If secondary hyperparathyroidism is noted, then treatment can be initiated to decrease the PTH concentration (typically with calcitriol therapy).

**How can the serum total calcium be increased, yet the serum ionized calcium is normal?**

This most commonly occurs in patients with chronic renal failure. Serum total calcium is composed of three fractions: ionized, complexed, and protein-bound. Alterations in any one of the fractions can impact total calcium concentration. An increase in the complexed fraction of calcium has been documented in chronic renal failure patients which results in an elevated total calcium, with a normal serum ionized calcium. Hypercalcemia should not be treated in these cases, since ionized calcium is normal (and may be low).
What is idiopathic hypercalcemia in cats?

Within the past 10 years, idiopathic hypercalcemia as a diagnostic consideration for cats with hypercalcemia has been recognized. Its frequency of diagnosis continues to increase, and it is now appears to be the most common cause of ionized hypercalcemia in cats in the USA. Serum calcium is often increased for months to more than one year, often without obvious clinical signs. Hypercalcemia is often a fortuitous discovery from blood samples taken for other reasons (pre-anesthesia, geriatric screening, vomiting episode that often has resolved).

In a recent report of clinical signs seen in 427 cases of feline idiopathic hypercalcemia, 46% had no clinical signs, 18% had mild weight loss with no other clinical signs, 6% had inflammatory bowel disease, 5% were chronically constipated, 4% were vomiting and 1% were anorectic. Uroliths or renoliths were observed in 15%, and calcium oxalate stones were specifically noted in 10% of cases. Cats ranged in age from 0.5 to 20 years old (mean 9.8 ± 4.6 yr), and long-haired cats were over represented, accounting for 27% of the cases (compared to an overall submission rate of 14% from long-haired cats). Males and females were equally represented. Ionized serum calcium concentration was increased in all cats, mean PTH concentration was in the lower half of the reference range and PTHrP was negative. Ionized magnesium analysis was normal. Mean concentration of 25-hydroxyvitamin D was normal in most cases.

An increase in dietary fiber has been reported to decrease serum calcium in affected cats in some reports. Challenge with prednisolone therapy results in long-term decreases in iCa and tCa in some cats. There is concern that this treatment could increase hypercalciuria, which could subsequently enhance genesis of urinary calculi. However, the declining filtered load of calcium decreases as serum iCa declines, which offsets the enhanced formation of calculi. When dietary modification and challenge treatment with prednisolone have been unsuccessful in resolving hypercalcemia, bisphosphonate treatment should be considered. The cause(s) of idiopathic hypercalcemia in cats remains elusive. It is conceivable that hypercalcemia develops only in a genetically susceptible population of cats.

References:

Do dogs get idiopathic hypercalcemia?

A specific syndrome of idiopathic hypercalcemia has not been recognized in dogs. In almost all cases of hypercalcemia in dogs, an underlying cause can be identified.

I have a patient with an increased total calcium concentration. What tests should I choose?

This depends on what diseases might be suspected. Parathyroid hormone and ionized calcium concentrations are best evaluated together, so these should be requested in all cases (Basic Parathyroid Profile). If malignancy is a possibility, then the parathyroid hormone related protein (PTHrP) concentration should also be requested. PTHrP analysis is included in the Malignancy profile. If there is a history of cholecalciferol rodenticide ingestion, houseplant ingestion, nutritional inadequacy, or if there
is an elevated serum phosphorus concentration, then measurement of 25-hydroxyvitamin D should also be considered. Measurement of 25-hydroxyvitamin D is included in the Vitamin D Profile.

I’ve measured serum total calcium. Why should I measure serum ionized calcium?

Serum total calcium is made up of three parts: ionized, complexed, and protein-bound. Ionized calcium is the biologically active fraction. Serum total calcium concentrations do not always correlate to the ionized calcium concentration, especially in disease states. In a review of over 1500 dogs, when total calcium was used to predict iCa status, diagnostic discordance was 27%. When total calcium was adjusted to total protein, diagnostic discordance increased to 37%. When total calcium was adjusted to albumin, the diagnostic discordance with iCa measurement was 38%. In a subpopulation of dogs with chronic renal failure, tCa, adjusted tCa to TP, and adjusted tCa to albumin resulted in diagnostic discordance of 36%, 53%, and 54% respectively in the prediction of iCa. Hypercalcemia is overestimated, and hypocalcemia is underestimated when tCa or adjusted tCa is used to predict iCa. A reason that these formulas perform poorly is that the adjustment formulas were based solely on the protein-bound fraction of calcium, ignoring the complexed calcium fraction. Complexed calcium is not a constant, especially in CRF patients, where the complexed fraction can range from 6 to 39% of tCa. In a retrospective review of over 400 feline cases, using tCa to predict iCa resulted in a diagnosis discordance of approximately 25%. Total calcium or adjusted tCa are unacceptable predictors of iCa status due to the high levels of diagnostic discordance, especially in CRF patients. Changes in the magnitude of serum protein concentration, individual protein binding capacity and affinity, changes in serum pH, and alterations in complexed calcium all interact to change the ionized calcium concentration, independent of the total calcium concentration. Serum ionized calcium must be measured to accurately assess calcium status.

What tumors are most often associated with hypercalcemia?

The tumors most often associated with hypercalcemia in dogs are lymphoma and anal sac adenocarcinoma. Often the lymphoma is in the cranial mediastinal region, or it can be in the gastrointestinal tract or bone marrow. Other tumors causing hypercalcemia include thymoma, carcinomas (bronchogenic, pancreatic, skin, etc.) and multiple myeloma. In cats, lymphoma and squamous cell carcinomas are the most common causes of hypercalcemia. Other tumors causing hypercalcemia in cats include osteosarcoma, fibrosarcoma, bronchogenic carcinoma and multiple myeloma.

I heard that ionized calcium should be measured anaerobically. Why do you measure it aerobically?

Ionized calcium can be accurately measured even after the sample has been exposed to air, as long as some technical issues have been addressed. Exposure to air increases the pH of serum, which causes proteins to bind to calcium, resulting in low ionized calcium concentrations. This protein-binding/pH interaction behaves in a linear fashion, and thus a correction formula can be developed to adjust the measured ionized calcium of a sample at a known pH to the ionized calcium concentration at a standard pH (7.4). This is routinely done in human medicine. In our laboratory, we have developed formulas to correct the ionized calcium concentration to a pH of 7.4, and these formulas have been verified by comparison to samples handled without exposure to air.
Will the 25-hydroxyvitamin D concentration be elevated in suspected cases of Dovonex ingestion?

No. Dovonex is an anti-psoriasis cream that contains calcipotriene which is a calcitriol analogue. This compound does not cross-react with the assay for 25-hydroxyvitamin D, so the concentration of 25-hydroxyvitamin D may be normal in cases of suspected Dovonex ingestion.

Can PTHrP be measured in serum or do I really need to submit plasma?

Plasma is preferred for PTHrP measurement. In a study that did here at MSU, we looked at PTHrP concentrations in paired plasma and serum samples. PTHrP was negative in about 50% of the serum samples when the plasma sample showed an elevated concentration of PTHrP. Thus, false negative results are obtained with serum, most likely due to the degradation of PTHrP.

What sample do I need to send for ionized calcium measurement?

Ionized calcium concentration should be measured in serum. EDTA will chelate calcium, and an ionized calcium concentration is often undetectable in an EDTA plasma sample. For small species (such as birds or some reptiles), ionized calcium concentration can be measured in heparinized plasma, but care must be taken to standardize the collection procedure since the type of heparin and amount of heparin can impact the ionized calcium result.