ENDOCRINE CHALLENGES: HYPERCALCEMIA **ENDOCRINOLOGY**

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Introduction

Hypercalcemia is a complex disorder and requires a logical diagnostic approach. The associated morbidity is variable, and depends upon the underlying cause and the rate at which serum calcium levels increase. Severe or rapidly progressive hypercalcemia requires emergent therapy as renal damage is likely.

Calcium Homeostasis

There are three forms of circulating calcium: *bound* to serum proteins (approximately 40%), *complexed* with various anions such as citrate and phosphate (approximately 8%), and *ionized* (iCa; approximately 52%). The latter is the biologically active form and the term hypercalcemia should only be used when this fraction is elevated. The calcium value reported on a standard serum biochemical profile reflects the total calcium (tCa) value (i.e., bound, complexed and ionized); this is a useful indication of calcium homeostasis but is influenced by serum protein concentrations and acid-base status. Formulas designed to "correct" for serum protein concentrations have not been validated in cats and are of questionable use in dogs.

Over 99 percent of the body's calcium is stored in bone, less than 0.1 percent in the extracellular fluid. However, iCa must be tightly regulated as it impacts numerous metabolic functions. Under normal circumstances, calcium intake and loss are carefully balanced, and about 90 percent of ingested calcium is excreted through the gastrointestinal (GI) tract. If necessary, the GI tract can excrete > 100 percent of intake, as calcium is added to secretory fluids. The kidneys make small adjustments to calcium homeostasis; active renal secretion does not occur, so a balance exists between glomerular filtration and tubular uptake. Usually, 99 percent of filtered iCa is reabsorbed, primarily by the proximal tubules, where it essentially mirrors the handling of sodium. Hormonal factors impact reabsorption in the later sections of the nephron, but 24-hour urinary calcium excretion is principally determined by serum concentrations. Parathyroid hormone, calcitonin, and vitamin D are the major hormonal regulators of calcium uptake, excretion, and storage in bone.

Parathyroid Hormone (PTH). The essential role of PTH is to increase serum calcium concentration. This is achieved primarily through stimulation of osteoclast activity and release of calcium from bone. Bone reabsorption falls dramatically in the absence of PTH. PTH also increases renal reabsorption of calcium in the loop of Henle and distal tubules, whilst promoting the excretion of phosphorus. There is a feedback loop between PTH and 1,25-hydroxycholecalciferol (calcitriol) in which PTH promotes the renal hydroxylation of 25-hydroxycholecalciferol, and calcitriol deficiency triggers the release of PTH, independent of serum calcium concentrations. The release of PTH is stimulated by both decreased iCa and increased serum phosphate levels.

Calcitonin. This hormone is released from the C-cells in the thyroid glands in response to increased iCa. It decreases serum calcium concentrations through inhibition of osteoclast activity and increased renal excretion of calcium. However, calcitonin has limited biological potency and maximal secretion cannot counterbalance a potent hypercalcemic drive.

Vitamin D. This chemical promotes the intestinal uptake of calcium and phosphorus; absorption of ingested calcium is highly dependent on adequate amounts of this vitamin. Dogs and cats obtain vitamin D from food as cholecalciferol. This form has little biological activity and must undergo hydroxylation, first in the liver and then in the kidney. Hepatic hydroxylation is influenced by serum concentrations of its product, but the second hydroxylation step is limited by renal α 1 hydroxylase activity. This is stimulated by PTH but inhibited by hyperphosphatemia and (to a modest extent) by hypercalcemia. At physiological concentrations, 1,25-hydroxycholecalciferol promotes bone calcification; excessive amounts cause bone reabsorption.

Numerous other factors also influence calcium homeostasis, including hepatic, renal and GI function, adrenocortical hormones (cortisol and aldosterone), thyroid hormone, and serum sodium, phosphate, and magnesium concentrations. Bone contains exchangeable calcium for immediate buffering, along with providing vast storage capabilities. The interplay between these hormones, organs, and ions is complex, and our understanding of the full intricacies of calcium homeostasis is still incomplete.

Causes of Hypercalcemia
Although many disorders may incidentally cause hypercalcemia, such as hypoadrenocorticism, osteosarcoma, and fungal infection, patients with these diseases do not present because of hypercalcemia and identifying the underlying cause is relatively straightforward. The hypercalcemia rarely requires specific intervention in these patients and is not expected to be severe. In contrast, an animal in which hypercalcemia is the number one problem can be a challenge, and establishing a diagnosis will require a logical approach.

In dogs, the most common causes of hypercalcemia are malignancy (esp. anal sac apocrine gland adenocarcinoma; lymphoma), toxicity (vitamin D analogues), granulomatous diseases (histoplasmosis, blastomycosis, tuberculosis, schistosomiasis), and primary hyperparathyroidism. For cats, neoplasia (esp. squamous cell carcinoma, mammary gland carcinoma, lymphoma), primary hyperparathyroidism, idiopathic, and renal disease are the most likely causes. Idiopathic hypercalcemia and renal disease are rarely associated with severe increases in iCa.

Signs of Hypercalcemia
In dogs, hypercalcemia causes polyuria and a compensatory polydipsia (pu/pd, due to compromise in the attachment of antidiuretic hormone to its receptors in the collecting ducts. This can be severe, and hyposthenuria is often noted. In cats, pu/pd is relatively uncommon, although concurrent renal disease may impair urine concentrating abilities. Gastrointestinal disturbances, such as anorexia and constipation, are often noted. Generalized bone pain may be evident in dogs with severe hypercalcemia. Urolithiasis is commonly associated with chronic hypercalcemia in both species, and may cause dysuria, hematuria, or urinary tract obstruction.

Moderate to severe hypercalcemia accompanied by normal/increased serum phosphorus (PO_4) concentrations will result in nephrocalcinosis and renal injury. A rapid rise in iCa (independent of PO_4 levels) is also likely to cause tubular injury. Signs related to acute kidney injury may be noted in some animals with hypercalcemia.

Diagnostic Approach
As tCa can be impacted by sample handling and processing, always verify hypercalcemia by repeating the tCa or (ideally) measuring iCa before starting a workup. The urgency of this process is determined by various factors, including the severity of the hypercalcemia (mild: tCa < 13 mmol/L; moderate: tCa 13–15 mmol/L; severe: tCa > 15 mmol/L), the calcium x phosphorus product (< or > 70), and the presence or absence of azotemia.

In a patient with mild to moderate hypercalcemia, Ca x PO_4 < 70 and a normal serum creatinine, there is little urgency and no indication for emergency treatment. This is in contrast to those with tCa > 15 mmol/L, Ca x PO_4 > 70 and azotemia. This animal needs immediate medical therapy while diagnostics are performed.

The physical examination may identify evidence of neoplasia. Particular attention should be paid to the anal sacs (dogs), mammary chain (cats), lymph nodes (both), toes (dogs), and oral cavity (cats). Suspicious lesions should be investigated as appropriate. A fundic examination may indicate systemic fungal (e.g., histoplasmosis) or neoplastic disease (lymphoma).

Serum phosphorus concentrations can help narrow down the differential list, as some conditions are associated with decreased PO_4 levels (neoplasia, primary hyperparathyroidism), while others are associated with increased concentrations (granulomatous disease, toxicities, renal disease) (see Table 1). I use serum PO_4 status to reorganize my differential list and prioritize further testing. However, calcium-related renal compromise will result in decreased PO_4 excretion and can confuse matters. If PO_4 levels are low, I will perform thoracic radiographs and abdominal ultrasonography, to look for neoplastic lesions. If these tests are unremarkable, I will submit blood for measurement of PTH and PTH-related protein (PTH-rp).

PTH levels must be interpreted in light of concurrent iCa concentrations. If the parathyroid glands are behaving appropriately, a hypercalcemic animal will have very low levels of this hormone. In contrast, “normal” PTH levels in a hypercalcemic patient indicate primary hyperparathyroidism, and in fact, many dogs and cats with this disease have PTH measurements within the reference range. Other hallmarks of primary hyperparathyroidism are low serum PO_4 levels, a slowly progressive hypercalcemia, and relatively modest systemic signs (except for marked pu/pd in dogs). Ultrasonography of the neck may identify the affected gland(s) prior to surgical extirpation although a skilled operator and a high frequency probe are necessary as these tumors are often small.

PTH-rp is a hormone released by various tumors, and is a common mechanism for hypercalcemia of malignancy. Although identification of PTH-rp strongly suggests an underlying neoplastic cause, this hormone has been associated with non-neoplastic disorders, in particular canine schistosomiasis (due to *Heterobilharzia americana*). It is also important to remember that an undetectable PTH-rp does not rule out an underlying neoplastic disease. If the PTH-rp is positive, I would test for *Heterobilharzia* (PCR through Texas A&M GI Lab) if the dog has been to an endemic area. If this test is negative, I would aspirate peripheral lymph nodes, spleen, and bone marrow, looking for evidence of malignancy.

If the PO_4 is increased, I would consider vitamin D related toxicosis. Sources would include diets, supplements, topical medications (used for human psoriasis), and rodenticides. Identifying an origin can be difficult, as some products are not detected on standard vitamin D tests.

In cats, many patients with mild to moderate hypercalcemia are eventually classified as idiopathic. This is frustrating, as an extensive and expensive workup is needed before this diagnosis can be made. In addition, there is little consensus or good evidence-based options for managing these cats.

Table 1 Biochemical Parameters Associated with Total Hypercalcemia

Disorder	iCa	Creat.	PO_4	PTH	PTH-rp	*Vit D
Granulomatous disease[$]	↑	N, ↑	↑	↓	U	N
Osteolytic disease	↑	N	↑	↓	U	N
1^o Hyperparathyroidism	↑	N	↓	High N, ↑	U	N
Drug-related	↑	N	Variable	↓	U	N
Addison's disease	↑	↑	↑	N, ↓	U	N
Renal failure	Variable	↑	↑	↑	U	N, ↓
Nutritional	↑	N	Variable	Variable	U	N
Neoplasia (non-osteolytic)	↑	N, ↑	N, ↑, ↓	↓	↑, U	N
Idiopathic	↑	N	N	Low N	U	N
Vitamin D toxicity	↑	↑	↑	↓	U	↑

* 25-hydroxycholecalciferol
[$] *Heterobilharzia* has been associated with detectable PTH-rp.
U = undetectable; N = within reference range; ↑ = increased; ↓ = decreased
Note: These parameters are generalizations; individual cases may not fit these patterns.

Management of the Emergent Hypercalcemic Patient
Patients with tCa > 15, Ca x PO_4 > 70 or moderate hypercalcemia with azotemia merit immediate intervention. The mainstay of therapy is saline diuresis (0.9% NaCl); sodium loading the proximal tubules decreases calcium reabsorption and promotes calciuresis. Any existing fluid deficits should be addressed within 12 hours, unless concurrent cardiac disease limits fluid tolerance. After replacement of losses, diuresis (2–3x maintenance volumes) should be provided. When patients are effectively hydrated, calcium loss can be potentiated with furosemide. This can be given as a bolus (2 mg/kg IV q6 hrs) or continuous rate infusion (0.5 mg/kg/hr). Fresh water should be available at all times.

As most of the body's calcium lies in bone, limiting osteolysis is a key part of patient management. Osteoclasts can be inhibited using bisphosphonates. The bisphosphonates share a similar chemical structure and are all ingested by osteoclasts. Consequently, very high concentrations can be achieved in bone and will persist for long periods. The nitrogen-containing agents (e.g., alendronate and pamidronate) block an enzyme called farenesyl diphosphate synthase, which is required for effective contact between osteoclasts and bone. They also bind to calcium phosphate and directly block dissolution crystals. In patients with severe or rapidly progressive hypercalcemia, pamidronate is

the best choice, and can be given IV (1.3–2 mg/kg) over several hours, along with fluid therapy. The drug is nephrotoxic, and renal injury can occur after a single dose. It should be used cautiously in animals with creatinine > 3 mg/dl, but the benefits may well outweigh the risks in these patients and I have used it effectively in severely azotemic dogs. The effect is rapid, with serum calcium levels expected to drop within 24 hours and the effect lasts about 3 weeks.

Alendronate can be given orally, but has very limited bioavailability (< 1%) and is not a good choice in an emergent patient. It has been used with variable success to manage idiopathic hypercalcemia in cats, but administration is difficult and it is associated with a substantial risk of esophageal injury in people. Long-term use has been linked to orthopedic issues in cats.

Salmon calcitonin is often listed as a treatment for emergent hypercalcemia (4–10 nMRC units/kg SQ daily), but may be cost prohibitive and are rarely used in veterinary patients.

Glucocorticoids can nonspecifically mitigate hypercalcemia through decreased gastrointestinal uptake and increased calciuresis. These effects are due in part to counteraction of the effects of vitamin D. However, they should not be given until a diagnosis is established, particularly if lymphoma is a possibility.

Long-Term Management of Hypercalcemia
Establishing a diagnosis is essential, as this will direct long-term treatment options for these patients. In animals with hypoadrenocorticism, paraneoplastic hypercalcemia, vitamin D toxicity, and schistosomiasis, appropriate definitive therapy should return the iCa to the reference range. Residual renal injury, however, may impact calcium homeostasis.

For patients with primary hyperparathyroidism, removal or ablation of the affected gland(s) is usually very successful, although postoperative hypercalcemia can be problematic. If an owner declines definitive therapy, a calcimimetics (such as cinacalcet/Sensipar®) may be helpful. These drugs essentially resensitize the parathyroid-secreting cells and inhibit release of PTH. However, there are few reports of their use in dogs and cost is an issue.

For cats with idiopathic hypercalcemia, management strategies may include dietary modification (alkalinizing, anti-stone, or high fiber), along with glucocorticoids and oral bisphosphonates. There is still substantial controversy regarding the underlying cause and optimal management of these patients. If hypercalcemia is mild, aggressive intervention may not be necessary.

Recommended Reading
Bergman PJ. Paraneoplastic hypercalcemia. *Topics in Companion Animal Medicine* 2012:27;156–158.

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