CALCIUM HOMEOSTASIS: UNDERSTANDING THE HYPERCALCEMIC CAT

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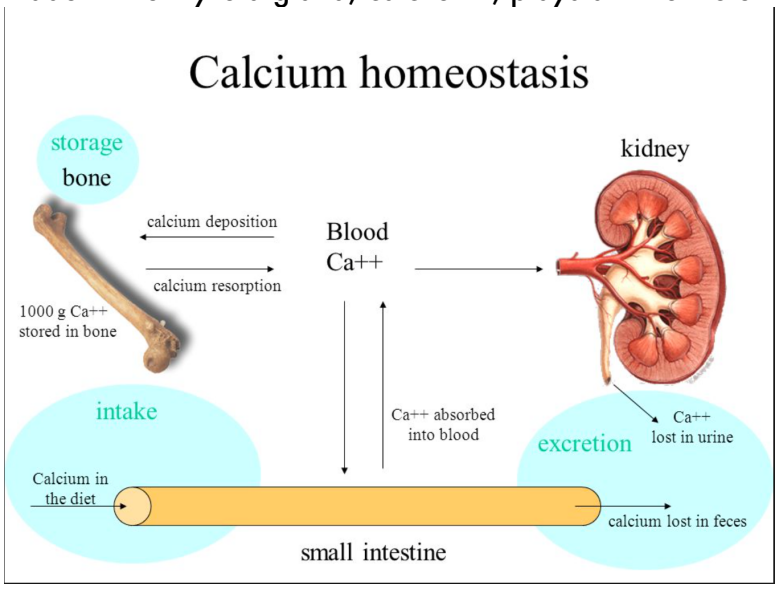
Calcium Homeostasis

Calcium plays multiple roles in the body including skeletal support, muscle contraction, transmission of nerve impulses and blood clotting. It is an important ion in some cellular trans-membrane channels. Calcium is available in three forms in the body: ionized or free calcium, protein bound calcium and complexed calcium. Ionized calcium is the only physiologically active form and makes up 50-60% of extracellular fluid (ECF) calcium. Protein bound calcium makes up 10% of the ECF calcium, while calcium complexed to phosphate, bicarbonate, or lactate makes up 30-40% of the ECF calcium. The majority of total body calcium is stored in the bones (99%). Regulation of calcium is a complex process.

When there is a need for ECF calcium, it can be increased by absorption from the gastrointestinal (GI) tract, release from bone and/or reabsorption by the kidneys. Calcium is excreted via the GI tract (90%) and the kidneys (10%). When necessary, the kidneys are capable of resorbing 99% of calcium filtered into the urine.

The need for more or less ECF calcium is mediated by parathyroid hormone (PTH) and calcitriol. At times that ionized calcium levels are low, the chief cells of the parathyroid gland are stimulated to release PTH. Within the kidneys, PTH acts to stimulate the conversion of vitamin D to calcitriol.

In situations where ECF calcium is in excess, a negative feedback loop reduces PTH production and subsequently calcitriol production. Elevated phosphorus also has a negative impact on this loop, decreasing PTH production. An additional hormone made in the thyroid gland, calcitonin, plays a minor role in decreasing ECF calcium.



Clinical signs

Evidence of hypercalcemia in a cat may be non-specific and may be related to the disease associated with the hypercalcemia. Signs of high calcium may include weakness, depression and mental dullness as the excitability of muscular and nervous tissue becomes depressed. Cats may have GI tract signs including anorexia, vomiting and constipation as a result of reduced contractility of smooth muscle in the GI tract. Central nervous system effects may include muscle twitching, shivering or seizures. Cardiac arrhythmias may occur. The cat may experience renal disease as a result of nephroliths or lower urinary tract disease signs as a result of urolithiasis. Polyuria and polydipsia can be observed, particularly in cases where renal disease has occurred as a result of hypercalcemia (and nephrolithiasis) or in cases of renal secondary hyperparathyroidism.

Testing

Routine blood screening should include measurements of total calcium (tCa++) in the minimum database. In cases where an elevation in tCa++ is observed, confirmation of this elevation should be confirmed approximately 2 weeks later. Persistent elevations in tCa++ need to be followed up with further testing, even in the situation where renal secondary hyperparathyroidism is strongly suspected. Further tests recommended include ionized calcium (iCa++) and PTH. In some cases, the clinician may also wish to request measurement of PTH related proteins (PTHrp) and Vitamin D metabolites. Cats should be fasted more than 12 hours prior to additional testing. A serum sample should be collected and handled in an anaerobic manner, with chilling of the sample instituted immediately after collection. Centrifugation in a refrigerated or chilled centrifuge is recommended. The lab should receive the chilled sample within 6 hours of collection if possible. If chilling is not possible, the sample should be received and analyzed within 2 hours.

Differential Diagnoses

Differential diagnoses of hypercalcemia in cats is most easily remembered by the two mnemonics SHIRT and GOSHDARNIT. The mnemonic SHIRT represents the most common causes of hypercalcemia in cats including Spurious, Hyperparathyroidism, Idiopathic, Renal disease and Tumours. For a more exhaustive list, GOSHDARNIT is helpful:

- Granulomatous disease
- Osteolysis
- Spurious (lab error)
- Hyperparathyroidsim, house plant ingestion, hyperthyroidism
- D toxicosis, Dehydration
- Addisons, Aluminum toxicity
- Renal disease
- Neoplasia, Nutrition
- Idiopathic
- Temperature (hyperthermia)

Diagnosis

Once an elevation in ECF calcium has been confirmed by iCa++ testing, the clinician will need to review the case, as well as the relevant data in order to shorten the list of differentials and recommend either further testing or therapeutics.

	tCa++	iCa++	PTH	PTHrp	25-OH Vit D	1,25(OH) Vit D
Neoplasia	H	Often very HIGH	0 to L to LN	N or high	N	varies
Renal 2° Hyperparathyroid	H	N or H	H	N	N or L	N or L
Idiopathic	H	H	N or L	N	N	varies

Patients with hypercalcemia parameters that suggest idiopathic or neoplastic disease will require further diagnostic testing. As noted in the table, there is sufficient overlap in the patterns observed with neoplasia and idiopathic hypercalcemia to require further clarification. In order to rule out neoplasia, the patient should be assessed via imaging for evidence of tumours. This should include a full abdominal ultrasound screening as well as 3-4 radiographic views of the thorax.

Patients with known renal disease confirmed to have renal secondary hyperparathyroidism will need to be assessed and treated for their renal disease. This includes complete IRIS staging (International Renal Interest Society) with assessment for comorbidities such as hypertension, proteinuria, renal or lower urinary tract infection. Treatment with calcitriol is an option provided the patient phosphorus levels are low normal. There is popularity in the use of calcitriol in all renal patients, which still requires further testing and publication of further evidence based medicine. At this time, the author uses calcitriol only in cases of renal secondary hyperparathyroidism. If this patient is hyperphosphatemic, or the levels are above an acceptable minimum for calcitriol use, phosphate binders should be employed to reduce the phosphorus levels. Calcitriol may be started once the phosphorus levels can be reduced and maintained at or below the accepted level. Ionized calcium and phosphorus levels should be monitored regularly.

The presence of nephroliths and/or uroliths will also need to be addressed. Patients with uroliths will require surgical removal of the stones, while patients with nephroliths may benefit from analgesia, medical and dietary management.

Treatment Options for Chronic Hypercalcemia

Patients with acute hypercalcemia are not addressed in this lecture. The following treatment options are not necessarily applicable to acute situations.

1. Identify and treat underlying cause
2. Dietary therapy: a consultation with a reputable veterinary diet company such as Royal Canin can be very beneficial in these cases. A diet change from dry to all canned may be sufficient. The use of high fibre diets, renal diets and calcium oxalate preventing/therapeutic diets may be recommended. These diets should be recommended on a case by case basis.
3. Subcutaneous fluids. This has not been assessed as a modality for treatment of hypercalcemia in cats. It is not likely to be harmful and may benefit cats with renal disease
4. Low dose diuretics. These have not been assessed in chronic hypercalcemia in cats. They increase the risk of dehydration and may negatively impact kidney health. This is not currently recommended by the author
5. Glucocorticoids. These may be effective but should not be used until all diagnostic testing is complete and the cat has a confirmed negative urinary culture. These drugs can decrease the efficacy of chemotherapy, increase the risk of diabetes mellitus and increase the risk of calcium in the urine. The latter will increase the risk of nephrolithiasis and urolithiasis.
6. Bisphophonates. These are not reported well in the literature but some anecdotal evidence has been shared and accumulated.

Reference

Little, Susan. ©2012. The Cat. Clinical Medicine and Management. Elsevier Saunders. St. Louis, Missouri