Identifying feline hypercalcaemia

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Calcium is very tightly regulated within the body. As 99% of calcium is stored in bones, this acts as a reservoir enabling the release of calcium when the extracellular fluid calcium levels decrease\(^1\).

Parathyroid hormone (PTH), vitamin D and calcitonin are actively involved in the regulation of serum calcium concentrations.

PTH largely controls the minute-to-minute regulation of calcium and is secreted by the chief cells of the parathyroid glands. It has a short half-life of three to five minutes\(^2\).

PTH is secreted in response to decreased serum concentrations of calcium and raises these by encouraging increased calcium absorption from the bone, and increased calcitriol formation and decreased calcium excretion by the kidneys.

Calcitriol also encourages increased serum calcium concentrations by rising the internal absorption of calcium, decreasing renal calcium excretion and enhancing the ability of PTH to cause bone reabsorption.

Calcium exists in three forms within the serum: ionised, protein bound and complexed\(^2\). Investigations are only required if ionised calcium is persistently high.

Heparinised whole blood is used for assessment of calcium via in-house machines. Ethylenediaminetetraacetic acid (EDTA) plasma cannot be used, as a falsely low calcium concentration will be obtained due to chelation of the calcium by EDTA.

Ionised calcium concentrations need to be assessed at physiological pH, as an acidic pH will increase the ionised calcium concentration. The sample should be processed anaerobically because this will result in artificially decreased ionised calcium due to the resultant increase in pH.

Causes of feline hypercalcaemia
Figure 1. An ultrasound image of a large urolith in the bladder. Image: Andrew Parry/Willows Veterinary Centre and Referral Centre.

Figure 2. A radiograph of ureteroliths. Image: Sally Birch/Willows Veterinary Centre and Referral Centre.

There are many causes for hypercalcaemia in cats. Non-pathological causes, which do not require further investigation, include:
• young animals due to normal physiological growth
• lab error
• spurious due to lipaemia or haemolysis

Transient increases in calcium can be seen with:

• haemoconcentration
• hyperproteinaemia

Persistent and pathological causes of hypercalcaemia (using HARDIONS acronym):

• H: hyperparathyroidism (primary or secondary)
• A: hypervitaminosis A and Addison’s disease
• R: renal disease
• D: hypervitaminosis D; for example, rodenticide toxicity and psoriasis cream, or diet
• I: idiopathic hypercalcaemia and infectious, such as granulomatous disease, due to mycobacteriosis
• O: osteolytic disease
• N: neoplasia associated; lymphoma, squamous cell carcinoma and multiple myeloma
• S: spurious and supplements, such as calcium containing phosphate binders

Clinical signs of hypercalcaemia include:

• Polyuria/polydipsia due to inhibition of antidiuretic hormone (ADH) or secondary renal damage.
• Gastrointestinal signs (vomiting and constipation) due to decreased gastrointestinal smooth muscle contractility.
• Urinary signs (dysuria, stranguria and haematuria) due to the formation of uroliths with or without secondary urinary tract infection (Figures 1 and 2).
• Depression, muscle twitching and seizures due to a direct effect on the CNS.

Investigations of hypercalcaemia:

• Repeat the measurement to ensure it is persistent and the ionised component is increased.
• Check thoroughly through the history to see if there is possible exposure to vitamin A, excessive calcium or products containing vitamin D; for example, rodenticide.
• Do a full physical examination. Primary hyperparathyroidism is very rare in cats, but most cats will have palpably enlarged parathyroid glands.
• Perform full haematology and serum biochemistry to assess for malignancy and systemic disease.
• Imaging, ideally with thoracic radiographs and abdominal ultrasound, to assess for granulomatous disease, skeletal lesions or underlying neoplasia.
• Measure PTH, parathyroid hormone-related protein (PTHrP) with or without vitamin D metabolites. Sample handling is important for PTH/PTHrP, so always check with the lab prior to submitting. PTHrP is a hormone that mimics the action of PTH and is secreted by some malignant neoplasm. High PTHrP concentration is, therefore, an indication of malignancy.

Idiopathic hypercalcaemia

In cats, the most common cause of a persistent ionised hypercalcaemia is idiopathic hypercalcaemia. This is a diagnosis of exclusion. The hypercalcaemia may be detected during routine screening. In one study, 46% showed no clinical signs.¹

Idiopathic hypercalcaemia is seen in cats of all ages, varying from 6 months to 20 years of age.² Certain breeds are over-represented, including Persians, Himalayans and domestic long haired cats,³ although there is no gender predisposition.

As it is a diagnosis of exclusion, other causes of hypercalcaemia need to be ruled out by performing the aforementioned investigations. Hormonal testing in these cases usually reveals a low normal PTH concentration, with PTHrP below the limit of detection.

Although some cats with idiopathic hypercalcaemia may be asymptomatic, treatment is advised as chronic hypercalcaemia can cause a wide variety of problems, such as uroliths, gastrointestinal signs and renal dysfunction.

Usually, the first step is to consider transitioning to a high fibre diet, as this should decrease the gastrointestinal absorption of calcium. Urinary diets to prevent calcium oxalate urolithiasis can also be considered as they contain a reduced amount of calcium and result in a neutral urinary pH that decreases the risk of calcium oxalate urolith formation.

If dietary therapy alone does not work, the next step is to consider treatment with glucocorticoids, such as prednisolone. Glucocorticoids will decrease intestinal absorption of calcium, renal tubular reabsorption of calcium and decrease skeletal mobilisation of calcium. The starting dose of oral prednisolone is 5mg PO q24hr per cat and can be increased as required to attain normocalcaemia.

If steroid therapy is ineffective or contraindicated, for example, the patient concurrently has diabetes mellitus, then bisphosphonates can be considered. These work by reducing the activity and number of osteoclasts and, therefore, decreasing calcium mobilisation from the bone.

Pamidronate can be administered intravenously, or oral medication with alendronate once a week can be considered. Ionised calcium should be remeasured prior to each dosing. Bisphosphonates can cause nephrotoxicity, so cats with pre-existing renal disease, or who are dehydrated, should not be treated with these agents.
In addition, alendronate can lead to oesophagitis and, therefore, it should be given with at least 10ml of water. A recent study of 12 cats has shown alendronate at a dose of 5mg/cat to 20mg/cat (median dose of 10mg/cat q1w) orally q1w was well tolerated and resulted in decreased ionised calcium concentrations over a six month period⁶.

Malignancy-associated hypercalcaemia is seen in approximately a third of feline hypercalcaemia cases, compared to two-thirds of canine cases⁶. In cats, this is most commonly noted in associated lymphoma or squamous cell carcinoma, although it has been seen with other neoplastic conditions; for example, multiple myeloma.

Cats with neoplasia have been found to have a higher serum calcium concentration than cats with renal failure or urolithiasis, however, there is significant overlap noted⁷.

Certain neoplasms secrete PTHrP and, therefore, result in hypercalcaemia.

Neoplasia can also result in hypercalcaemia by mechanisms independent of PTHrP. If a tumour invades the bone, such as squamous cell carcinoma or multiple myeloma, then osteolysis occurs, which can release calcium and result in hypercalcaemia.

Unlike idiopathic hypercalcaemia, where cats are generally still well, cats with underlying neoplasia are often systemically ill. Hormonal testing in these cases will reveal a low PTH and, possibly, a high PTHrP. Malignancy-associated hypercalcaemia can occur independent of PTHrP and a low PTHrP does not rule out underlying neoplasia.

Treatment of the underlying neoplasia usually results in normalisation of the calcium concentration. For severe elevations of calcium, additional supportive therapy – for example, fluid therapy with or without bisphosphonates – may be required. The fluid therapy is 0.9% saline, as it contains no calcium and will promote renal calcium excretion.

Prednisolone should not be used prior to thorough investigations as this may mask an underlying neoplasia, hampering effective diagnostics.

**Renal disease**

Total calcium may be elevated in chronic kidney disease; however, the ionised calcium is usually low or normal and only rarely elevated. The severity of hypercalcaemia has been shown to correlate with the severity of renal disease⁸.

As hypercalcaemia can result in renal disease, it poses a dilemma when a patient presents with both. In general, hypercalcaemia in patients with chronic kidney disease is usually mild. In renal disease, production of calcitriol is reduced, which results in secondary hyperparathyroidism.
In animals with chronic renal failure and hypercalcaemia, low-dose calcitriol has been used as a treatment to reduce PTH synthesis and secretion. This has been shown to decrease ionised calcium concentration in dogs\textsuperscript{2}; however, the same effect has not been noted in feline patients\textsuperscript{9}.

Calcium-containing phosphate binders and aluminium-based phosphate binders have not been shown to result in feline hypercalcaemia, although it is a possibility\textsuperscript{2}.

**Hypervitaminosis D**

Granulomatous inflammation can result in hypercalcaemia, as macrophages can synthesise calcitriol. In the UK, this can be seen with mycobacterial disease, toxoplasmosis, cryptococcosis and feline infectious peritonitis (FIP)\textsuperscript{10,11}.

Vitamin D toxicity is uncommonly noted in cats, but has been seen in diets with excessive vitamin D concentration or following ingestion of products containing vitamin D, such as rodenticides\textsuperscript{12}.

In cases of hypercalcaemia due to hypervitaminosis D, PTH concentrations are expected to be low due to negative feedback and increased vitamin D metabolites.

**Primary hyperparathyroidism**

Primary hyperparathyroidism has been very rarely reported in feline medicine. It may be possible to palpate the enlarged parathyroid gland on physical examination (approximately 57% of cases)\textsuperscript{13}.

PTH is high or high normal in cats with this condition. In a hypercalcaemic cat, PTH secretion should be suppressed, so a PTH in the higher end of the reference range is abnormal and consistent with this condition. Surgical therapy is the treatment of choice.

As the hypercalcaemia will have resulted in atrophy of the remaining parathyroid glands, a postoperative hypoparathyroidism can occur and the patient must be closely monitored for hypocalcaemia and treated appropriately with calcium supplementation and calcitriol, which is tapered over time.

- Some drugs mentioned in this article are used under the cascade.

**References**