Hypercalcaemia in cats

Hypercalcaemic cats are most likely to present with non-specific signs of anorexia and lethargy, although PU/PD, gastrointestinal (GI), urinary and neurological signs are also reported. Accurate assessment of calcium status in cats ideally requires ionised calcium levels to be measured. History is often more valuable than clinical examination in suggesting an underlying cause that can be further evaluated with routine assessment of kidney function, imaging and measurement of parathyroid hormone (PTH), parathyroid-related peptide (PTHrP) and vitamin D levels. Despite extensive investigation, a significant proportion of cats have idiopathic hypercalcaemia.

This article briefly reviews the basic physiology and pathophysiology of calcium metabolism before focussing on the clinical approach to the hypercalcaemic cat. This is followed by a discussion of the various recognised causes of hypercalcaemia in the cat and their treatment.

Keywords: Cat, calcium, hypercalcaemia, idiopathic, hyperparathyroidism, chronic kidney disease

Introduction

With increasing availability of ionised calcium, hypercalcaemic cats are not uncommonly encountered in primary care practice.

Calcium is the most abundant mineral in the body, constituting 2% of total body weight. As well as its role in bone, adequate calcium levels are vital for the normal function of neuromuscular tissue, cellular signalling and coagulation.

Serum calcium exists in 3 forms (approximate proportions in cats between parentheses): ionised (52%), protein-bound (40%) and complexed (8%).

Serum ionised calcium, the biologically active component, is held within tight boundaries by a complex regulatory system and has a narrow reference interval (1.20–1.32mmol/L). The major regulators of calcium metabolism are parathyroid hormone (PTH), vitamin D metabolites and calcitonin (Figure 1). It is PTH that is involved in minute to minute, fine regulation of ionised calcium levels.

Calcitonin, synthesized in the C-cells of the thyroid gland in response to hypercalcaemia or a calcium-rich meal, inhibits bone resorption, but its overall effect on normal calcium homeostasis is minimal.

Serum calcium levels are therefore affected by:

- Dietary intake
- Hormonal environment – parathyroid hormone (PTH), parathyroid related peptide (PTHrP), calcitonin and vitamin D3
- Renal excretion

Actions of PTH and PTHrP

Both PTH and PTHrP have actions to increase serum calcium levels.

- **PTH**
  - Increases blood calcium in two phases. A rapid phase that starts within minutes to hours of the PTH release, associated with calcium release from the bone fluid pool. This is followed by a slower phase in which osteoclasts are indirectly stimulated to resorb bone. PTH also increases calcium by:
    - Enhancing calcium (and magnesium) reabsorption from the renal distal tubules
    - Enhancing intestinal absorption of calcium by increasing activated vitamin D production
  - Under normal circumstances, increasing blood calcium exerts feedback inhibition on PTH production.

- **PTHrP**
  - This is an evolutionarily much older hormone and can be found in many vertebrates including cats, and it is involved in foetal calcium metabolism. In adults it has a paracrine function in skin, mammary glands, endocrine organs, muscle, lymphoid tissue, kidney, bone and brain. Under certain circumstances, abnormal amounts of PTHrP are produced and it exerts an endocrine function causing hypercalcaemia. PTHrP may be increased by:
    - Malignancy
    - Granulomatous disease
    - Lungworm

**Vitamin D**

Vitamin D exists in 2 forms, vitamin D3 (cholecalciferol) in animals and vitamin
D2 (ergocalciferol) in plants. Both forms appear equipotent. Activation is by hydroxylation in the liver and then kidneys to dihydroxyvitamin D which is the most biologically active. Many other metabolites of vitamin D exist with little or no activity (e.g. 24,25 and 25,26 dihydroxyvitamin D). Active vitamin D3 has a complex interplay with PTH, the gut and to some extent the kidneys as a secondary regulator of calcium (Fig. 2).

Calcitonin
Plasma baseline levels of calcitonin in normal cats are very low with a heterogeneous response to increased plasma calcium (Pineda et al 2013). Hypocalcitoninism as a cause of hypercalcaemia in cats is not reported.

Clinical presentation of cats with hypercalcaemia
Unlike dogs where PU/PD is strongly associated with hypercalcaemia, hypercalcaemic cats are more likely to present with non-specific signs of anorexia and lethargy followed by gastrointestinal (GI) signs. PU/PD, vomiting, urinary and neurological signs are also reported in some cases. Bradycardia associated with hypercalcaemia appears to be very uncommon in cats. Cats with idiopathic hypercalcaemia may be asymptomatic. In a retrospective study of 71 cats (Savary et al, 2000) total serum calcium was highest in cats with neoplasia (20% of cases - ⅓rd lymphoma; ⅓rd squamous cell carcinoma; ⅓rd other). Approximately 40% of cases were chronic renal disease (CKD) cats of which ⅓rd had urolithiasis. Approximately 10% of cases had endocrine disease (half hyperparathyroidism) and 15% were ‘idiopathic’.

Sudden rises in calcium can be associated with rapidly growing tumours producing PTHrP or vitamin D intoxication that can occur secondary to the ingestion of mouse poisons, psoriasis creams or eating jasmine. In chronic cases, crises associated with renal calcification or urolith leading to AKI can occur. High circulating calcium levels have been shown experimentally to cause stimulation and destruction of pancreatic acinar cells resulting in pancreatitis (Frick et al 1992) that could contribute to the clinical presentation.

Measurement of calcium
Calcium is primarily bound to albumin, therefore changes in albumin level can significantly affect total calcium ([Ca2+]).

![Figure 1 – Diagram illustrating major mechanisms in calcium homeostasis in the cat](image1)

![Figure 2 – Production, conversion and effects of vitamin D](image2)

**Learning Outcomes**
- To develop a robust logical approach to the investigation of the hypercalcaemic cat.
- To obtain samples for laboratory assessment in an appropriate way so that results are reliable and interpretable.
- To accurately interpret laboratory results in hypercalcaemic cats.
- To be able to develop a management plan depending on the cause of the hypercalcaemia and modify the plan according to the patient response.