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## Hypercalcaemia in cats

### **Abstract**

*Practical relevance:* Calcium is essential for many normal physiological processes within the body. Hypercalcaemia can therefore result in clinical signs such as polyuria and polydipsia, lethargy and weakness due to depressed excitability of muscle and nervous tissue and gastrointestinal (GI) signs due to effects on GI smooth muscle. The most common causes of hypercalcaemia in cats are idiopathic, chronic kidney disease and neoplasia.

*Clinical challenges:* Hypercalcaemia can be a diagnostic challenge and a good understanding of the regulation of calcium homeostasis can aid in interpreting results. Furthermore, the management approach may depend on the underlying cause of hypercalcaemia and also its severity and chronicity.

*Audience:* This review offers a comprehensive discussion of the regulation of calcium homeostasis with a focus on the normal response to hypercalcaemia. It also discusses the diagnostic approach, management and specific aetiologies of hypercalcaemia in cats. This is relevant to all clinicians working with feline patients.

*Evidence base:* The review draws evidence from peer-reviewed publications and also the author's own clinical experience.

### **Calcium function and homeostasis**

Calcium plays a key role in many normal physiological processes. It is important in neuromuscular transmission, enzyme activity, blood coagulation, muscle contraction (including skeletal, smooth and cardiac muscle) and is required for intracellular signalling and normal cellular function. Calcium also regulates vascular smooth muscle tone and hence blood pressure. It is the most abundant component of the skeleton being required for both new bone formation and resorption and in maintaining structural integrity of bones and teeth.

Regulation of calcium is complex. It is generally accepted that parathyroid hormone (PTH) is responsible for the minute-to-minute control of calcium, calcitriol for the day-to-day control and calcitonin having a relatively minor role in its regulation in the adult. The three organ systems responsible for calcium homeostasis include the gastrointestinal (GI) tract, kidneys and bone. PTH increases calcium reabsorption in the distal convoluted tubules of the kidney and decreases phosphate reabsorption from the proximal tubules resulting in reduced calcium and increased phosphate excretion in urine. It is reported that approximately 98-99% of filtered calcium is reabsorbed in the kidneys of normal human patients<sup>1</sup> with the predominant site of reabsorption being the proximal tubules. PTH also stimulates osteoclastic bone resorption and increases the number of osteoclasts on the bone surface to release calcium and phosphate from bone. Calcitriol (1,25 dihydroxycholecalciferol), otherwise known as the active form of vitamin D, increases the absorption of calcium and phosphate

from the GI tract and reabsorption in the renal tubules. Intestinal absorption of calcium is via an active transport process in the duodenum.<sup>2</sup> A calcium pump system transports calcium from the mucosa into blood. Transport of calcium across the enterocyte requires the carrier protein calbindin that is vitamin D dependent. If diet is low in calcium then this pump system becomes more active and if dietary calcium is high, the pump system becomes less active. Passive diffusion of calcium across the enterocyte can also occur at high concentrations of calcium in the jejunum and ilium and to a lesser extent in the colon.<sup>2</sup> However, it has been suggested that calcium absorption is unaffected by calcium intake and that mechanisms other than GI absorption are more important for its homeostasis in the short term in cats and dogs.<sup>3</sup> Calcitonin is a potent calcium lowering hormone and acts predominantly on bone to inhibit osteoclastic bone resorption. The terms reabsorption and resorption may be easily confused. Within this review they are used to describe the process of absorbing a substance again and the process of losing a substance (s) from bone respectively.

Figure 1: Regulation of calcium homeostasis in the body

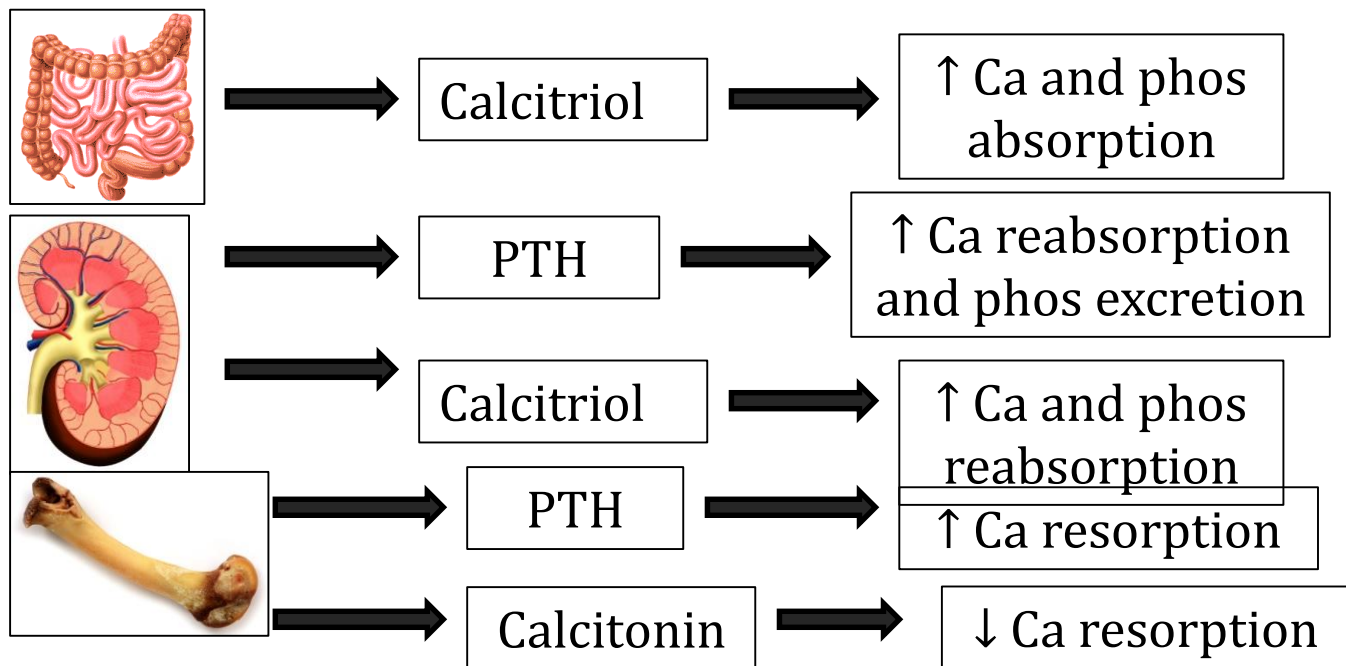
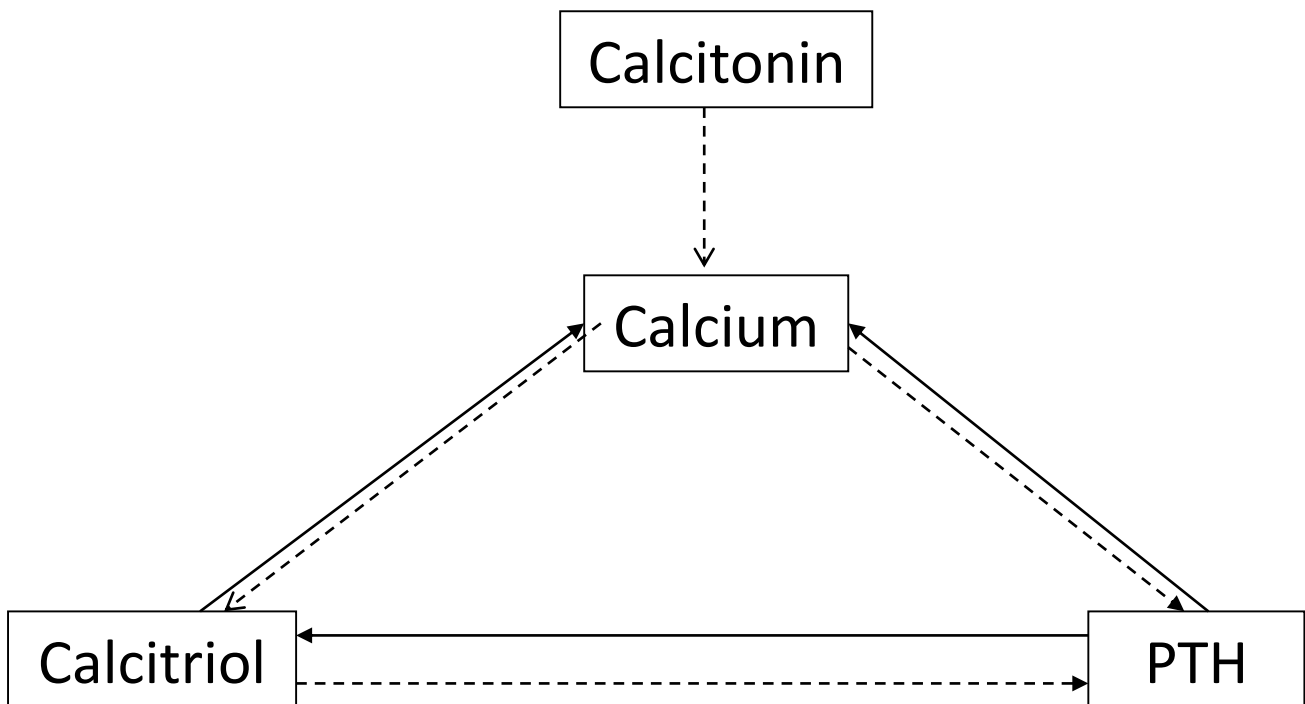


Figure 2: Relationship between calcium and its homeostatic regulators. Bold line indicates a positive (stimulatory) relationship and dashed line indicates a negative (inhibitory) relationship.



PTH is produced from chief cells in the parathyroid gland in response to ionised hypocalcaemia. Its actions to increase renal tubular reabsorption of calcium, increase bone resorption and increase calcitriol production in the kidneys, results in a net effect of increasing ionised calcium concentration. Calcitriol is produced in the kidneys and increases calcium absorption in the GI tract, and reabsorption in the renal tubules and enhances the ability of PTH for bone resorption. Therefore, the net effect is also to increase ionised calcium concentration. Cats have low levels of vitamin D in their skin and it is not synthesised in the skin in response to sunlight as in humans.<sup>4</sup> Therefore, cats are dependent on dietary intake and it is often supplemented in pet foods. It is important to remember that PTH and calcitriol are also influenced by phosphate concentrations. Calcitonin is secreted from C cells in the thyroid gland in response to hypercalcaemia. Calcitonin inhibits osteoclastic activity that decreases bone resorption. It can also increase renal excretion of both calcium and phosphate. GI hormones such as gastrin can stimulate the secretion of calcitonin<sup>2</sup> and this mechanism is considered to help regulate postprandial hypercalcaemia.

### Physiological response to hypercalcaemia

The normal physiological response to hypercalcaemia includes decreased production of PTH from the parathyroid gland, increased production of calcitonin from C cells in the thyroid gland and decreased calcitriol production in

the kidneys due to direct inhibition and also decreased PTH production. This results in:

- 1) Reduced release of calcium and phosphate from bone due to reduced PTH concentrations
- 2) Increased renal excretion of calcium due to decreased PTH and calcitriol concentrations
- 3) Decreased intestinal absorption of calcium due to decreased calcitriol concentration.

The relationship between calcitropic hormones and calcium can be evaluated further by examining the PTH-calcium and calcitonin-calcium curves (see Figures 3 and 4). When examining the calcitonin-calcium curve, it can be seen that there is a group of cats that do not increase their calcitonin concentration in response to hypercalcaemia. This group has been termed 'non-responders'.<sup>5</sup> This recent finding may suggest that certain cats are unable to evoke a normal physiological response in the face of hypercalcaemia to increase calcitonin and hence decrease ionised calcium concentration.

Figure 3: PTH-calcium curve. PTH concentration decreases in response to increasing ionised calcium concentration. I-PTH is intact PTH and W-PTH is whole PTH. Taken from<sup>6</sup>

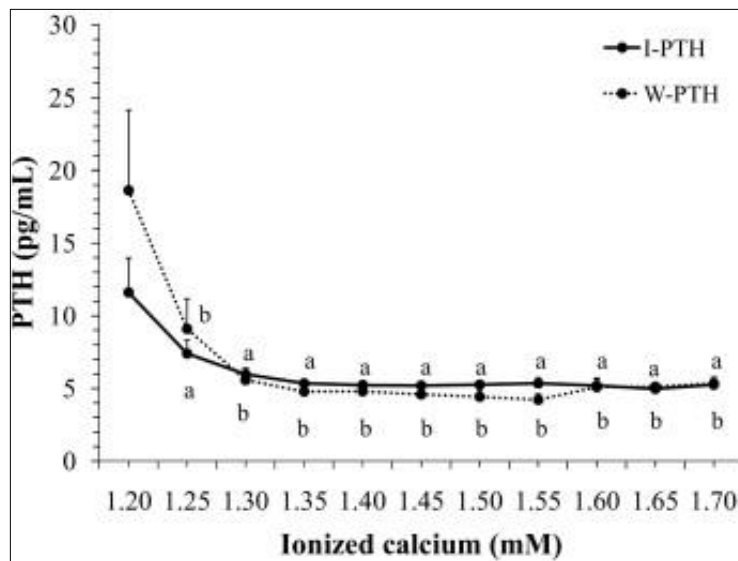
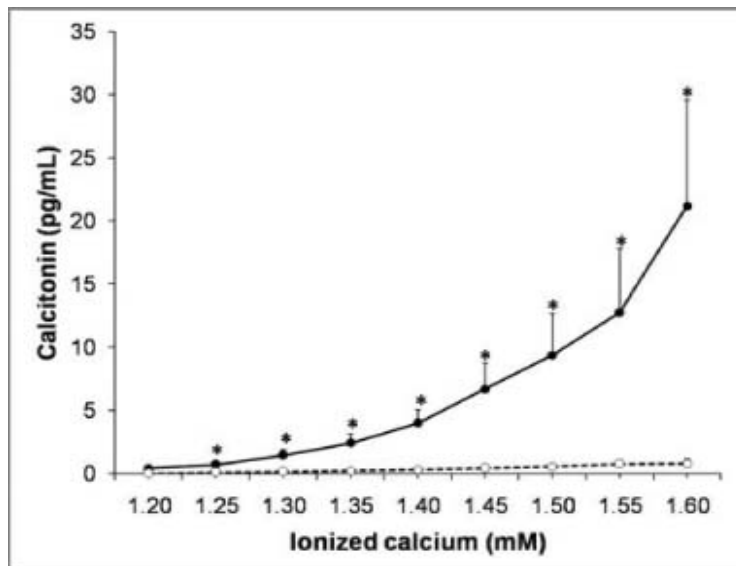


Figure 4: Calcitonin-calcium curve. Bold line represents the group of cats in which calcitonin concentration increases in response to increasing ionised calcium – that is the expected response. The dashed line represents a second group of cats that do not increase their calcitonin concentration in response to hypercalcaemia. Taken from<sup>5</sup>



Identification of hypercalcaemia and implementation of appropriate therapy is important as it may lead to development of soft tissue calcification (especially in cardiac and skeletal muscle, stomach and kidneys). Mineralisation of renal tissue may result in nephron injury or changes in renal blood flow causing a decline in renal function and azotaemia. Hypercalcaemia may promote formation of calcium oxalate uroliths that can lead to urinary tract obstruction. Whether acute hypercalcaemia induces pancreatitis remains controversial. Early studies examining the effects of calcium administration on the pancreas of cats identified necrosis of pancreatic acinar<sup>7, 8</sup> and ductal cells<sup>8</sup> after 12hrs of IV calcium infusion suggesting hypercalcaemia may play a role in pancreatitis.

### Measurement of calcium

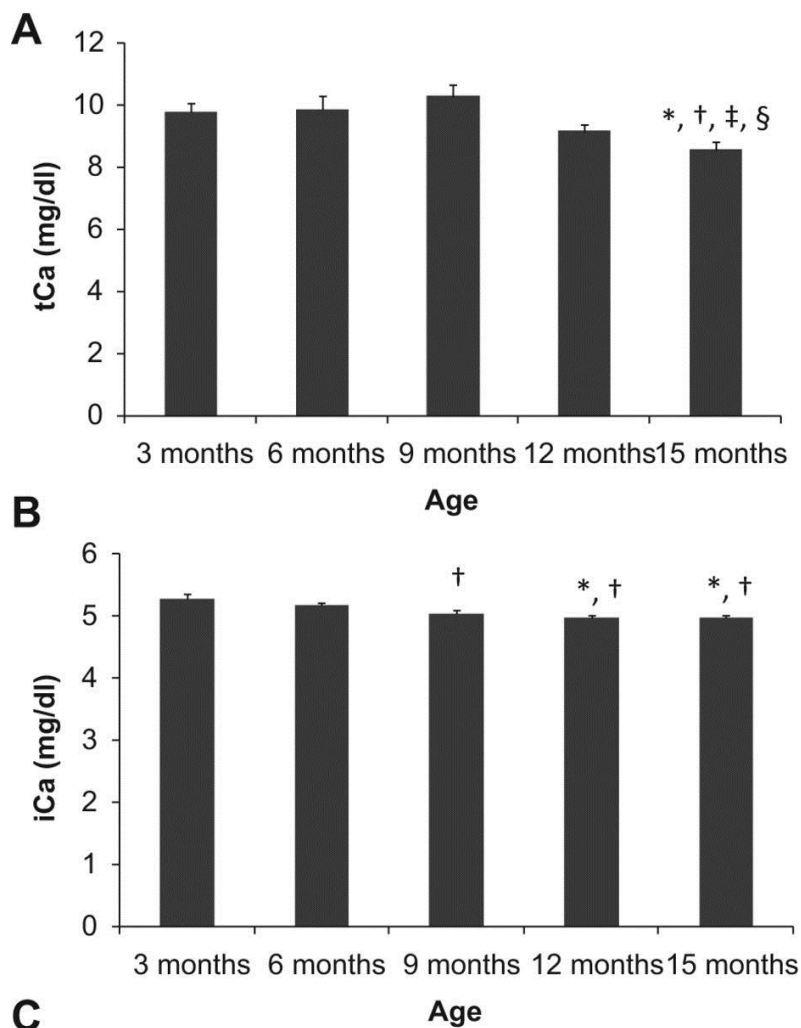
Approximately 99% of total body calcium is stored in bones in the form of hydroxyapatite crystals.<sup>9</sup> These crystals contain calcium, phosphate and water and can act as a reservoir to release calcium when extracellular calcium concentration declines. Calcium can also be found intracellularly and is important in normal cellular function. The smallest pool of calcium in the body is found in the extracellular space. This includes calcium in the blood, interstitium and accessible bone-calcium pool. It is calcium in the extracellular space that is measured in the clinical patient. Extracellular calcium exists in 3 fractions:-

- 1) Ionised calcium. This is the largest fraction considered to be approximately 52% of total calcium in normal cats.<sup>10</sup> It is the biologically active form of calcium.
- 2) Complexed calcium. This is the smallest fraction considered to be approximately 8% of total calcium in normal cats.<sup>10</sup> It can be complexed with anions such as phosphate, lactate or bicarbonate.
- 3) Protein bound calcium. Approximately 40% of total calcium is considered to be protein bound.<sup>10</sup>

It is important when collecting a blood sample for measurement of calcium not to transfer the sample into a tube containing anticoagulant. This is because the anticoagulant will chelate calcium and artificially decrease its concentrations. Results for ionised calcium are also lower in heparinised blood samples

compared to serum samples so cannot be directly compared.<sup>11</sup> The age of the cat will also affect calcium concentration. Plasma calcium has been reported to be higher in young animals along growth phases due to increased bone turnover. In particular kittens will have increased concentrations and both total and ionised calcium concentration can remain increased until 12 months of age (see figure 5).<sup>12</sup>

Figure 5: Total and ionised calcium in growing cats. Taken from<sup>12</sup>



Adjustment formulas to correct total calcium for the albumin or total protein concentration are not recommended. Moreover, it is not possible to accurately predict ionised calcium from total calcium. In one study total calcium was inaccurate in predicting ionised calcium in 40% of cats with the prevalence of hypercalcaemia and normocalcaemia being underestimated and hypocalcaemia being overestimated.<sup>10</sup>

Ionised calcium concentration must be measured to accurately assess the calcium status. Analysis with ion-selective electrodes is required for measuring ionised calcium (See Figure 6). Samples should be collected anaerobically if analysis cannot be performed immediately. Exposure to air will lead to loss of CO<sub>2</sub>, which increases pH and consequently increases calcium binding to protein and results in decreased ionised calcium concentration. The converse of this is

important in acidaemic patients in which hydrogen ions will displace protein bound calcium ions and increase ionised calcium concentration. If in-house analysis of ionised calcium is not possible, samples will need to be transported to a reference laboratory on ice and submission of the sample should be discussed with the laboratory prior to collection.

Figure 6: Ion-selective electrode analysers should be used for the measurement of ionised calcium.



### Clinical signs

The clinical signs (see box 1) of hypercalcaemia in cats can be vague and non-specific, and are often not noticed by owners. Polyuria and polydipsia (PU/PD) resulting from a nephrogenic diabetes insipidus is common and can also be secondary to renal damage. Lethargy and weakness may result from depressed excitability of muscular and nervous tissue. Anorexia, vomiting and constipation may be a consequence of decreased contractility of the smooth muscle in the GI tract. Muscle twitching and potentially development of seizure activity may be seen due to direct effects of hypercalcaemia on the central nervous system. Cardiac arrhythmias can also develop due to direct effects on cardiac tissue.

Box 1: Common clinical signs associated with hypercalcaemia in cats

- Polyuria and polydipsia
- Lethargy/ weakness
- Anorexia
- Vomiting
- Constipation
- Muscle twitching
- Cardiac arrhythmias

### Differential diagnoses

Box 2 lists the differential diagnoses for hypercalcaemia in cats. The most common causes are idiopathic,<sup>13</sup> CKD<sup>14</sup> and neoplasia.<sup>14</sup> Non-pathological causes



that should be considered when interpreting results include non-fasted sampling, hyperlipidaemia, hyperproteinaemia, haemoconcentration, laboratory error and physiological growth in young animals. Hypoadrenocorticism and primary hyperparathyroidism are very rare in cats with one study reporting primary hyperparathyroidism in only 6% and hypoadrenocorticism in only 1% of hypercalcaemic cats.<sup>14</sup> Hyperthyroidism is generally associated with ionised hypocalcaemia; however, cases of hypercalcaemia have been reported.<sup>15</sup> This may be associated with underlying CKD.<sup>16</sup> Excessive calcium supplementation for example calcium containing intestinal phosphate binders may theoretically contribute to hypercalcaemia although this remains unreported in clinical cases.

**Box 2: Differential diagnoses for hypercalcaemia in cats**

- Idiopathic
- CKD/renal failure
- Neoplasia – malignancy associated
- Hypervitaminosis D
- Granulomatous disease
- Primary hyperparathyroidism
- Hypoadrenocorticism

## **Diagnostic approach**

### Blood testing

#### *Biochemistry*

Measurement of ionised calcium should be performed to confirm hypercalcaemia if total calcium is elevated. Hypercalcaemia should also be demonstrated to be persistent. Full biochemistry should be performed ensuring the panel includes assessment of renal function and phosphate concentration. If available, acid-base analysis should also be performed.

#### *PTH*

One useful approach is to assess if the hypercalcaemia is parathyroid dependent (i.e. arising from the parathyroid gland) or parathyroid independent. This is achieved by measuring PTH. The majority of cats will have parathyroid independent hypercalcaemia. Indeed, in one study only 8.4% of hypercalcaemic cats were reported to have parathyroid dependent hypercalcaemia.<sup>17</sup> In normal patients, PTH production from the PTH glands will be suppressed in response to hypercalcaemia. Therefore, if PTH concentration is in the upper 2/3 of the reference interval or is increased, it suggests a parathyroid dependent cause.

Caution should be taken in interpreting results of PTH assays. Appropriate sample handling must be strictly adhered to as PTH is relatively heat labile, which can affect results. Samples must be shipped on ice and the commercial laboratory to which the sample is to be submitted should be contacted to discuss sample transport. Feline PTH is 84% homologous to human PTH.<sup>18</sup> This is important because assays used to measure PTH in cats are human assays. There

are different assays available for measuring PTH. The second-generation (intact) PTH assays measure intact PTH (1-84) and also PTH (7-84) fragment. C-PTH fragments can accumulate in kidney disease, which may result in falsely elevated results. The third-generation whole PTH assays do not measure the fragments. Earlier studies validating PTH measurement in cats utilised intact PTH assays that are no longer commercially available.<sup>19, 20</sup> A recent study in cats validating newer human intact PTH and whole PTH assays found greater whole PTH concentrations compared to intact PTH.<sup>6</sup> This was thought to be related to reduced affinity of the antibody (which was developed for use with human samples) utilised in the assay against feline PTH. Considering the variable results obtained with different assays, it is important to discuss with the laboratory to which the sample is to be submitted, which assay is being used and whether appropriate validation and reference intervals have been established in the laboratory for the assay.

#### *Parathyroid hormone related peptide (PTH-rp)*

PTH-rp can be measured if malignancy is suspected but can be normal and therefore, a normal value does not fully exclude neoplasia.<sup>17</sup>

#### *Vitamin D metabolites*

1,25 dihydroxyvitamin D<sub>3</sub> (calcitriol) and 25 hydroxyvitamin D<sub>3</sub> (calcidiol) can be measured. Calcitriol reflects metabolically active vitamin D and calcidiol reflects cholecalciferol or ergocalciferol ingestion. Calcidiol is the major circulating form of vitamin D. Vitamin D metabolites are identical in all species and therefore, the performance of assays used to measure vitamin D is better than for those used to measure PTH. Samples should be protected from light to inhibit degradation.

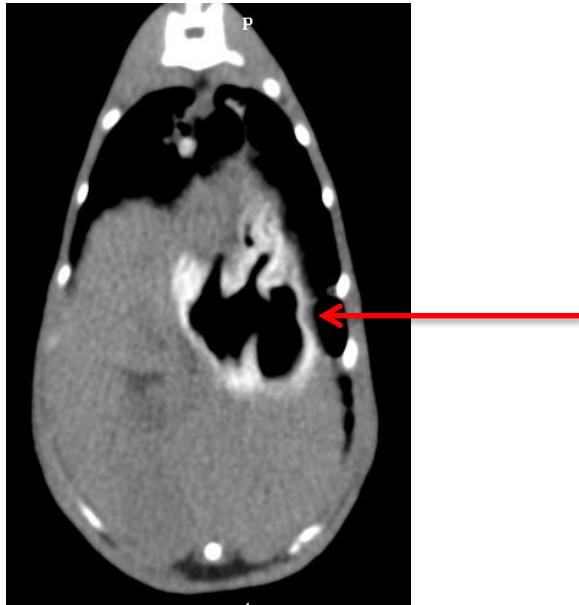
#### Urinalysis

Increased excretion of calcium in the urine of cats that are hypercalcaemic can predispose them to calcium oxalate urolith formation. Uroliths were identified in 15% of hypercalcaemic cats in a retrospective study of which 73% were composed of calcium oxalate.<sup>14</sup>

#### Diagnostic imaging

Thoracic and abdominal imaging can be helpful in screening for neoplasia or granulomatous lesions. Soft tissue calcification can occur when the calcium x phosphate product is >5.6mmol/l. The kidneys and gastric mucosa are the predominant organs to be affected and this may be visualised on radiographs or CT imaging (see figure 7). Radiographs may also identify calcium oxalate nephroliths, ureteroliths or cystoliths. If primary hyperparathyroidism is suspected (which, as discussed above, is rare in cats), cervical ultrasonography can be performed to attempt to visualise a parathyroid mass, although, this requires some expertise.

Figure 7: Transverse CT image of cranial abdomen and caudal thorax. A mineralised gastric wall that was identified in a hypercalcaemic cat is indicated by the red arrow.



### General management

The management approach will depend on not only the severity of the hypercalcaemia but also the time frame of development (i.e. acute versus chronic). Patients with mild hypercalcaemia (ionised calcium  $<0.25\text{mmol/l}$  above the reference interval<sup>21</sup>) which are asymptomatic and have normal calcium x phosphate product may require no immediate treatment whereas patients with a severe acute rise in calcium concentrations may require more aggressive treatment. There is no single treatment that is recommended for managing all causes of hypercalcaemia and therefore the underlying cause should be addressed. Supportive therapy is aimed at enhancing renal excretion of calcium and preventing calcium resorption from bone. Table 1 lists different drugs that can be used for the management of hypercalcaemia and their doses. Specific management for underlying aetiologies is discussed in the specific aetiologies section.

Table 1: Drugs and dosages for use in the management of hypercalcaemic cats

Drug	Class of drug	Dose	Route of administration	Frequency of administration
Furosemide	Diuretic	1-2 mg/kg	IV, SC, PO	BID to TID
Prednisolone	Glucocorticoid	0.5-1 mg/kg	PO	SID to BID
Dexamethasone	Glucocorticoid	0.1-0.2 mg/kg	IV, SC	SID
Pamidronate	Bisphosphonate	1.0-2.0 mg/kg	Slow (approx. 4hrs) infusion in 0.9%NaCl	May be repeated after 7-14 days
Alendronate	Bisphosphonate	5-20 mg/cat	PO	Q 7 days
Calcitonin	Endocrine drug	4-6	SC	BID to TID

		IU/kg		
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### *Promoting calciuresis*

Management can include intravenous fluid therapy (IVFT) and furosemide to promote calciuresis. It is important a cat is well hydrated before initiating furosemide therapy. IVFT can be administered to correct any fluid deficits and the associated volume expansion will aid in diluting circulating calcium concentrations. Isotonic saline (0.9% NaCl) is the recommended fluid of choice as it does not contain calcium. If there is concern regarding a cat's renal or cardiac function, fluid therapy should be approached cautiously as they may be susceptible to fluid volume overload given their small size. Furosemide acts to inhibit calcium reabsorption in the loop of Henle. Thiazide diuretics should not be used as these enhance the reabsorption of calcium in the renal distal tubules.

### *Glucocorticoids*

Glucocorticoids act to reduce bone resorption, decrease intestinal absorption and increase renal excretion of calcium. Their mechanism of action is thought to be through inhibiting prostaglandin E, osteoclastic activating factor and vitamin D production.<sup>22</sup> It is important to avoid steroids if the underlying aetiology remains unclear and further investigations to determine a definitive diagnosis are to be pursued.

### *Bisphosphonates*

Bisphosphonates exert their effect by reducing the number and activity of osteoclasts. There are few reports of the use of these drugs in cats. Pamidronate is available and is administered as an IV infusion. Recently alendronate has been evaluated in a small study of cats with idiopathic hypercalcaemia.<sup>23</sup> Approximately 2/3 of the cats included in the study achieved normocalcaemia during the 6-month study period and adverse effects were not noted. The advantage of alendronate over other bisphosphonates is its oral route of administration rather than via an intravenous infusion. In addition, it requires only once weekly administration. To optimise GI absorption it is best administered after fasting.

### *Calcitonin*

Although calcitonin is one of the normal physiological regulators in decreasing calcium concentration, its effects are short lived requiring multiple daily administration and therefore, it does not lend itself to use in clinical patients. In dogs it has also been associated with side effects such as anorexia and vomiting and development of tolerance to therapy.<sup>24</sup>

### *Dietary change*

Dietary change is perhaps one of the most important aspects of management in cats with idiopathic hypercalcaemia. High fibre diets can be fed which bind intestinal calcium thus reducing its absorption. Wet diets can also be helpful in promoting diuresis and are generally associated with lower calcium content than dry diets. Feeding a renal diet may be successful in some cases as these are formulated to be low in calcium and phosphate concentration and are more

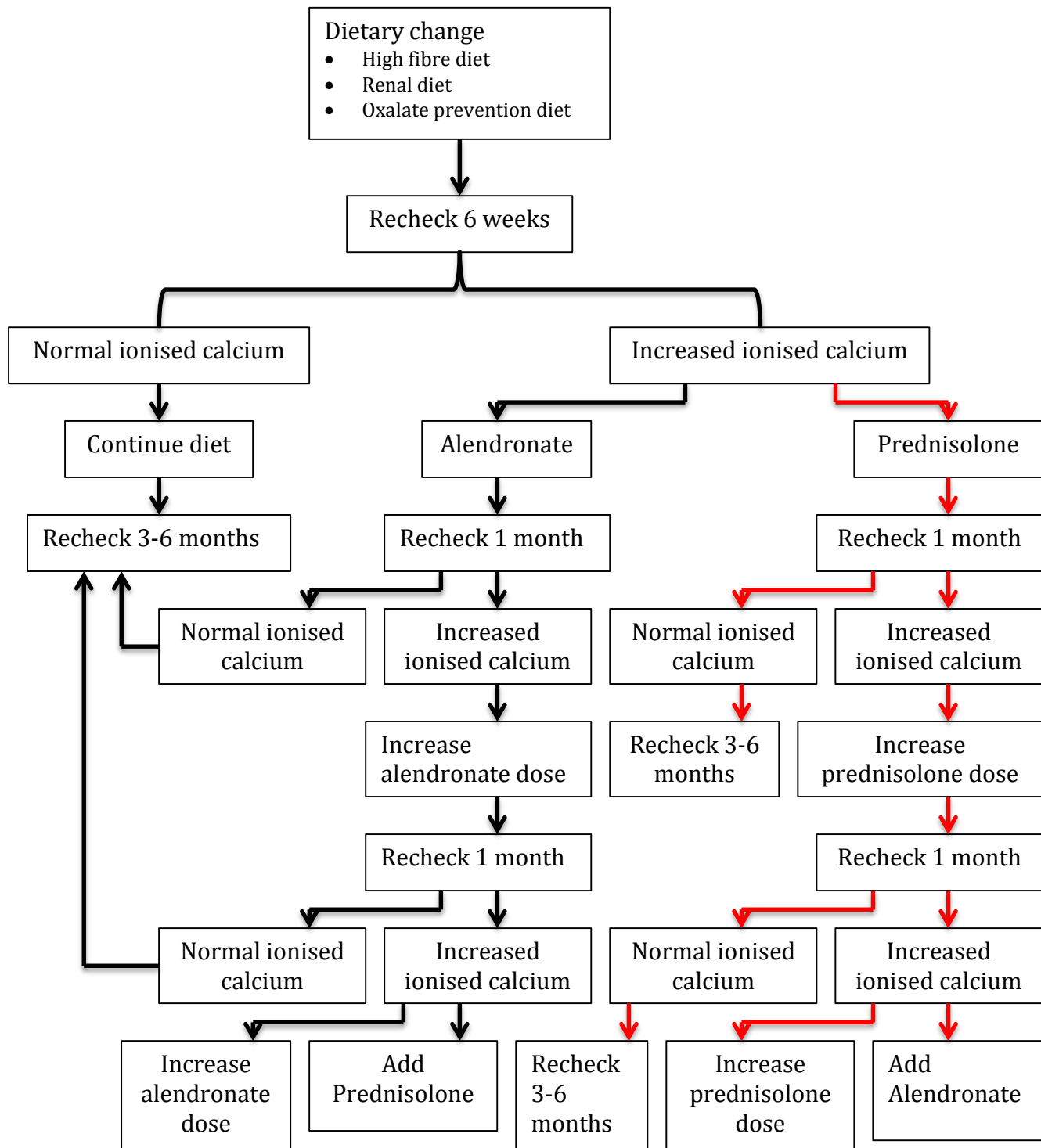
alkalizing than normal maintenance diets. However, hypercalcaemia has been noted in cats fed a renal diet and so this diet should be discontinued if hypercalcaemia worsens. Diets formulated for management of calcium oxalate urolithiasis may also be considered as these diets are restricted in calcium and decrease urinary acidification.

### Specific aetiologies

#### *Idiopathic hypercalcaemia*

Idiopathic hypercalcaemia is considered the most common diagnosis in hypercalcaemic cats and the cause remains unknown. There may be genetic factors or possibly dietary factors. Some studies have reported an association of hypercalcaemia with the feeding of an acidifying diet or use of urinary acidifiers which resolved after dietary change or discontinuation of the urinary acidifying therapy.<sup>25</sup> These diets may result in a chronic metabolic acidosis that increases bone resorption and hence promotes hypercalcaemia and urinary calcium excretion,<sup>26,27</sup> although this remains unproven in healthy cats.<sup>28</sup> Idiopathic hypercalcaemia can be seen in cats of any age and there is no sex predisposition, however, longhaired cats appear to be over represented.<sup>13</sup> Clinical signs are often vague or absent and it may be detected as an incidental finding. In some cases calcium may be increased for months without overt clinical signs. If clinical signs do develop these may include weight loss, diarrhoea, constipation, vomiting or anorexia. In patients with idiopathic hypercalcaemia, the total and ionised calcium are elevated but phosphate, PTH-rp and vitamin D metabolites are normal. PTH may be normal or decreased due to the suppressive effect of hypercalcaemia. The magnitude of hypercalcaemia in affected cases is generally mild to moderate. In one retrospective study, 40% of cases with idiopathic hypercalcaemia were reported to have mild total hypercalcaemia (2.88 – 3.00mmol/l), 55% had moderate total hypercalcaemia (3.00 – 3.50mmol/l) and only 5% reported to have severe total hypercalcaemia (>3.50mmol/l).<sup>13</sup> Dietary change may be successful in many cases and therefore implementing the feeding of a high fibre diet, supplementing with psyllium husks or feeding a wet diet is recommended as an initial first step, particularly in cases with only mild or moderate hypercalcaemia. Feeding a renal diet or diet formulated for management of calcium oxalate urolithiasis can be considered as an alternative as discussed above. Figure 8 presents an algorithm for the approach to managing minimally symptomatic cats with idiopathic hypercalcaemia.

Figure 8: Recommended algorithm for management of minimally symptomatic cats with idiopathic hypercalcaemia. The bold arrows indicate the recommended approach and the red arrows indicate an alternative approach that can be considered. Adapted from<sup>21</sup>



*Chronic kidney disease*

Hypercalcaemia and renal azotaemia can be a difficult diagnostic challenge as hypercalcaemia can cause renal failure or develop as a consequence of renal failure. The prevalence of hypercalcaemia increases with the severity of

azotaemia with one study reporting 8% of cats with early compensated kidney disease to have a total hypercalcaemia, 18% of cats with uraemic kidney disease and 38% with end stage kidney disease.<sup>29</sup> Generally speaking, in cats with early and mid stage CKD, ionised calcium is low and total calcium is normal or increased. This is the result of increased phosphate concentration associated with reduced renal clearance forming complexes with ionised calcium. Indeed, in the study reporting total hypercalcaemia with early compensated, uraemic and end stage kidney disease, only 0%, 9% and 6% of cats had ionised hypercalcaemia for each group respectively.<sup>29</sup> This supports the current understanding that the total hypercalcaemia that may be seen in CKD is generally associated with increased complexed calcium. In late stage CKD tertiary hyperparathyroidism can develop from progression of renal secondary hyperparathyroidism. This is thought to result from an altered set point of the calcium sensing receptor and uncontrolled secretion of PTH from the parathyroid gland. Management of hypercalcaemia in cats with CKD includes reducing phosphate retention through feeding a renal diet that is restricted in protein and phosphate. Intestinal phosphate binders can also be used. However, it important to note that some cats can develop hypercalcaemia when being fed a renal diet, although, the reasons for this remain unclear. Some phosphate binders contain calcium carbonate that may, theoretically speaking, contribute to hypercalcaemia. Some clinicians advocate the use of calcitriol as part of the management of CKD in cats. This is considered to be beneficial due to decreased calcitriol production in the diseased kidney. Calcitriol will also suppress PTH production thus aiding in the management of renal secondary hyperparathyroidism. However, there is a significant risk of development of hypercalcaemia with its use and no proven clinical benefit and therefore, its use is not recommended at this time. It would also be contraindicated in a hypercalcaemic patient.

### *Hyperparathyroidism*

Primary hyperparathyroidism is rare in cats as discussed above. It is associated with increased total and ionised calcium concentration, increased PTH concentration, decreased phosphate concentration and normal or increased calcitriol. If primary hyperparathyroidism is confirmed, the abnormal parathyroid tissue can be surgically resected with close monitoring for development of hypocalcaemia or recurrent laryngeal nerve damage following the surgery. Other alternative management approaches which have been reported in dogs include ultrasound guided radiofrequency heat ablation and ethanol ablation of the parathyroid gland.<sup>30</sup>

Secondary hyperparathyroidism can be classified as nutritional or renal. In nutritional hyperparathyroidism it is low calcium or altered calcium: phosphate ratio in the diet that stimulates production of PTH. Therefore, it is not generally associated with hypercalcaemia. It is something which may be recognised more commonly with the increasing popularity of feeding bone and raw food (BARF) diets with between 20-60% of such diets being unbalanced in calcium, vitamin D and phosphate.<sup>2</sup> Nutritional secondary hyperparathyroidism is often associated with a predominantly meat diet as these are low in calcium but high in phosphate which stimulates PTH production.

Renal secondary hyperparathyroidism results from reduced renal clearance of phosphate in patients with decreased glomerular filtration rate. The increasing blood phosphate forms complexes with calcium resulting in a corresponding decrease in calcium concentration and stimulating PTH production.

Tertiary hyperparathyroidism results from autologous secretion of PTH from the parathyroid gland and can lead to development of hypercalcaemia. It is rarely recognised in cats but can be associated with end stage kidney disease.

#### *Malignancy associated hypercalcaemia*

Hypercalcaemia of malignancy is less common in cats than in dogs. Neoplasia as the underlying cause was found in approximately 2/3 of hypercalcaemic dogs vs. 1/3 of hypercalcaemic cats.<sup>22</sup> Hypercalcaemia can develop through humoral mechanisms or through osteolytic mechanisms. Osteolytic mechanisms can include metastatic spread to bone, haematological abnormalities in the bone marrow or local production of bone resorbing factors. Primary bone neoplasia is rarely associated with hypercalcaemia. In humoral hypercalcaemia of malignancy, production of PTH-rp plays an important role in the pathogenesis; however, cytokines such as interleukin-1 (IL-1) and transforming growth factor -beta (TGF- $\beta$ ) may also play a role.<sup>22</sup> Both PTH-rp and cytokines have similar functions to PTH to stimulate bone resorption. In cats, squamous cell carcinoma and lymphoma would be the two most common neoplasias associated with hypercalcaemia accounting for 2/3 of all neoplasia in one retrospective study.<sup>14</sup> Other neoplasias which have been associated with hypercalcaemia in cats include multiple myeloma<sup>31</sup> bronchocarcinoma<sup>14</sup>, osteosarcoma<sup>14</sup>, and fibrosarcoma.<sup>14</sup> Both total and ionised calcium are increased in patients with malignancy associated hypercalcaemia and therefore, PTH concentration should be normal or low. PTH-rp can be increased but can also be normal.<sup>17</sup> Management involves specific management of the underlying neoplasia. The use of glucocorticoids prior to confirmation of the diagnosis should be avoided, as these drugs will interfere with the ability to make a diagnosis of lymphoma. There are no studies examining whether the survival times of cats with neoplasia associated with hypercalcaemia are worse than those without hypercalcaemia.

#### *Hypervitaminosis D*

Hypervitaminosis D refers to toxicity resulting from calcidiol and calcitriol as well as cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Iatrogenic causes include excessive dietary supplementation or excessive treatment. Certain plants such as Jessamine can contain glycosides of calcitriol and therefore, ingestion can lead to hypercalcaemia. Some rodenticides also contain cholecalciferol. Topical ointments for management of psoriasis can contain vitamin D analogues and possible exposure to such creams should be discussed with the owners. As these ointments contain vitamin D analogues, calcidiol or calcitriol concentrations will not generally be increased if measured. There is typically a parallel increase in calcium and phosphate concentration in patients with hypervitaminosis D. Calcidiol can be normal or increased depending on which form of vitamin D is associated with the intoxication. PTH concentration will be low due to hypercalcaemia and also the suppressive effects of calcitriol. Calcidiol can remain elevated for weeks to months following intoxication due to



lipid storage and slow release. The decline of calcitriol is quicker. The presence of soft tissue calcification may be more suggestive of vitamin D toxicity than other causes of hypercalcaemia as both calcium and phosphate rise in parallel resulting in an increased calcium x phosphate product.

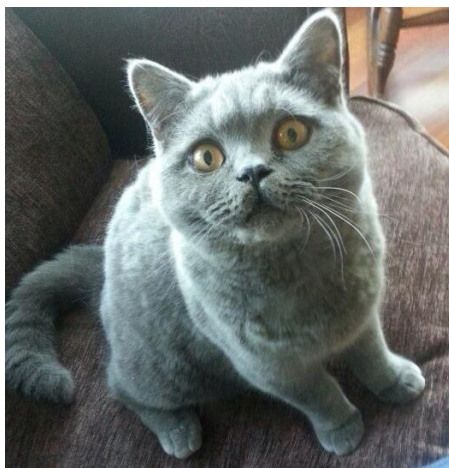
#### *Granulomatous disease*

Granulomatous inflammation is a potential but uncommon cause of hypercalcaemia in cats. Hypercalcaemia can result from granulomatous inflammation because macrophages can synthesise calcitriol from calcidiol without negative feedback regulation. Therefore calcitriol concentrations can be high and calcidiol concentrations normal. Hypercalcaemia has been associated with mycobacteria<sup>32</sup>, feline infectious peritonitis (FIP)<sup>14</sup>, Toxoplasmosis<sup>14</sup>, *Nocardia*<sup>32</sup>, *Cryptococcus*<sup>14</sup> and *Actinomyces* rhinitis<sup>14</sup> in cats. It may be difficult to distinguish between hypercalcaemia associated with granulomatous disease and neoplasia if abnormalities are found on physical examination or imaging. Increased calcitriol concentration may be helpful; however, a definitive diagnosis should be based on cytological or histopathological examination of tissue.

#### *Hypoadrenocorticism*

Hypoadrenocorticism (Addison's) is much less common in cats compared to dogs. The mechanism by which hypercalcaemia develops is poorly understood. It may be associated with increased renal reabsorption of calcium secondary to hypovolaemia, the presence of a metabolic acidosis or due to increased bone resorption. The hypercalcaemia resolves with successful management of hypoadrenocorticism. Standard treatment generally involves the use of fludrocortisone +/- prednisolone.

#### **Case studies**



#### *Case study 1*

Luna and Apollo, 5mth FE and MN BSH presented with a one-week history of lethargy, inappetence and a four-day history of PU/PD. Both kittens lived indoors in the same household and had no access to vitamin D containing rodenticides or psoriasis ointments. Both kittens were fed a variety of complete wet and dry foods and were supplemented with a complementary natural wet food. Physical examination findings were unremarkable. Table 1 presents the biochemical findings at the initial visit. The kittens were non-azotaemic and the only significant finding was a marked total hypercalcaemia. The USG for Apollo was 1.033 and for Luna was 1.012. Calcium oxalate crystalluria was seen on sediment exam in both kittens. Abdominal and thoracic imaging was unremarkable.

Table 1: Biochemical findings at the initial visit.

	<b>Apollo</b>	<b>Luna</b>	Reference interval
Creatinine (µmol/l)	123.0	106.0	133 – 175
Urea (mmol/l)	7.0	6.6	6.5 – 10.5
Phosphorous (mmol/l)	1.34	1.20	0.95 – 1.55
<b>Total calcium (mmol/l)</b>	<b>&gt;4.00</b>	<b>&gt;4.00</b>	<b>2.30 – 2.50</b>
Albumin (g/l)	27.1	28.5	24.0 – 35.0
Globulins (g/l)	41.1	41.2	21.0 – 51.0
Total protein (g/l)	79.9	85.0	77.0 – 91.0
Sodium (mmol/l)	153.0	146.0	145.0 – 157.0
Potassium (mmol/l)	4.7	4.27	3.50 – 5.50
Chloride (mmol/l)	120.0	121.0	100 – 124.0
ALT activity (IU/l)	37.0	33.0	15.0 – 45.0
ALKP activity (IU/l)	48.0	52.0	15.0 – 60.0
Total bilirubin (µmol/l)	0.6	3.5	0.0 – 10.0
Cholesterol (mmol/l)	3.9	3.6	3.0 – 6.9

Ionised calcium, vitamin D metabolites and PTH were measured (see Table 2). The ionised calcium measurement confirmed hypercalcaemia. Both calcitriol and calcidiol were increased in both kittens. PTH was low as would be expected in a patient with hypercalcaemia. PTH-rp was not measured due to the limited suspicion of neoplasia.

Table 2: Ionised calcium, vitamin D metabolites and PTH concentrations

	Apollo	Luna	Reference interval
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Ionised calcium (mmol/l)	1.82	1.83	1.10 - 1.40
Calcitriol (pmol/l)	436	406	192 - 317
Calcidiol (nmol/l)	553	243	126 - 163
PTH (pmol/l)	<0.22	<0.22	0.22 - 1.42

#### Interpretation of results

Both kittens had a total and ionised hypercalcaemia, normal phosphate concentration, increased calcitriol and calcidiol concentrations and low PTH concentration. This excluded parathyroid dependent causes of hypercalcaemia. The primary differential was hypervitaminosis D, although phosphate concentrations were normal. Iatrogenic hypercalcaemia, malignancy associated hypercalcaemia and granulomatous diseases seemed unlikely based on the normal imaging findings and the increased vitamin D metabolite concentrations.

A dietary cause of the hypervitaminosis D was suspected and therefore food analysis was performed (see Table 3). Analysis of one of the diets (a natural complementary cat food) being fed to the kittens revealed excessive levels of both vitamin D3 (cholecalciferol) and D2 (ergocalciferol). The levels were approximately 10 times the nutritional maximum.

Table 3: Dietary analysis of one of the foods being fed to the kittens.

	Original food (wet weight fed)	Dry matter (DM)	Minimum requirement (DM)	Nutritional maximum not associated with harmful effects (DM)
Vitamin D3 (IU/kg)	53500	318325	750 (total Vitamin D3 and D2 combined)	30000 (total Vitamin D3 and D2 combined)
Vitamin D2 (IU/kg)	14500	86275		
Calcium (g/kg)	0.058	0.345	10	-
Phosphate (g/kg)	0.835	4.968	8.4	-
Calcium: phosphorus ratio	0.07:1	0.07:1	1:1	1.5: 1

#### Ongoing management

Both kittens were managed initially with IVFT 0.9% NaCl, furosemide and prednisolone. Diet was changed to a complete commercially available wet kitten

food. Supplementation with psyllium husks was also recommended. IVFT and furosemide was discontinued after 5 days. Normocalcaemia was achieved in 5 days in Luna and 22 days in Apollo. The prednisolone was gradually tapered and discontinued after normocalcaemia was achieved. The kittens both continued to do well and remained normocalcaemic and non-azotaemic for 1-year follow-up.

*Case study 2*

Flossie, 2yr FN DSH presented with a one-month history of weight loss and polydipsia. More recently, she returned home after being missing for five days and was non-ambulatory on her hind limbs. On general physical examination, she was in decreased body condition but was otherwise unremarkable. On neurological examination she was paraparetic. She had bilateral proprioceptive deficits in her hind limbs (paw placement and hopping) and lower motor neurone and cranial nerve function testing was normal. Neurolocalisation was T3 to L3. Initial haematology and biochemistry are presented in Table 4 and 5. The haematology revealed a left shift with increased band neutrophils suggesting inflammation. Biochemistry revealed a total hypercalcaemia and an increase in the muscle markers AST and CK. Urinalysis revealed good urine concentrating ability (1.043). Struvite crystals were noted on sediment examination. Ionised calcium was measured and confirmed the hypercalcaemia (1.77mmol/l). FIV/FeLV testing was negative.

Table 4: Haematology results at initial presentation

		Reference interval
Hb	11.70	8.00 – 15.00 g/dl
Hct	37.3	25.0 – 45.0 %
MCV	53.2	40.0 – 55.0 fl
MCH	16.8	12.5 – 17.0 pg
MCHC	31.5	30.0 – 35.0 g/dl
Platelets	333	200 – 700 x 10 <sup>9</sup> /l
WBC	16.90	4.90 – 19.0 x 10 <sup>9</sup> /l
<b>Band neutrophils</b>	<b>0.85</b>	<b>0.0 0 – 0.30 x 10<sup>9</sup>/l</b>

Segmented neutrophils	10.99	2.40 – 12.50 x 10 <sup>9</sup> /l
Lymphocytes	3.89	1.40 – 6.00 x 10 <sup>9</sup> /l
Monocytes	0.51	0.10 – 0.70 x 10 <sup>9</sup> /l
Eosinophils	0.68	0.10 – 1.60 x 10 <sup>9</sup> /l
Basophils	0.00	0.00 – 0.10 x 10 <sup>9</sup> /l

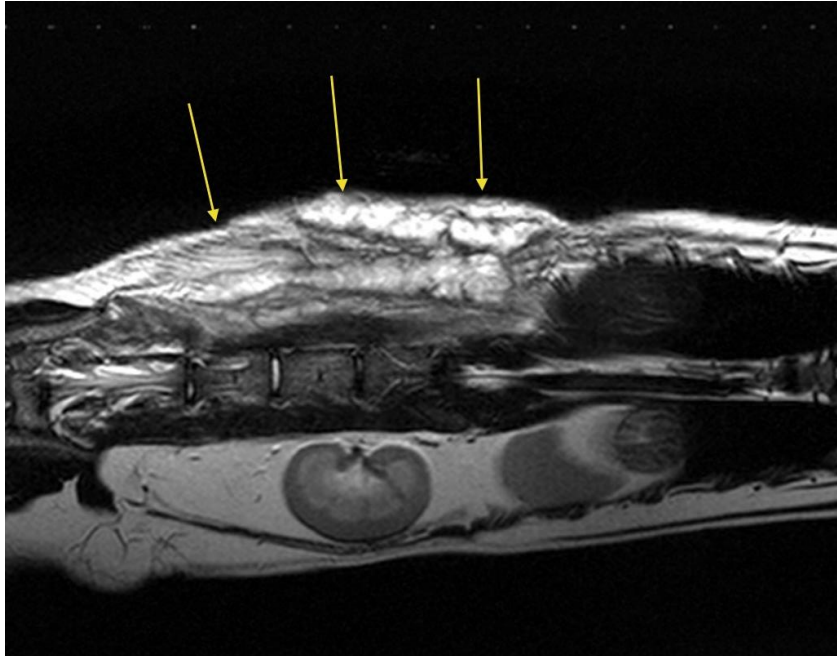
Table 5: Biochemistry results at initial presentation

		Reference interval
Creatinine (µmol/l)	71	133 – 175
Urea (mmol/l)	6.3	6.5 – 10.5
Phosphorous (mmol/l)	1.15	0.95 – 1.55
<b>Total calcium (mmol/l)</b>	<b>3.26</b>	<b>2.30 – 2.50</b>
Albumin (g/l)	27.5	24.0 – 35.0
Globulins (g/l)	43.5	21.0 – 51.0
Total protein (g/l)	71.0	77.0 – 91.0
ALT activity (IU/l)	46.0	15.0 – 45.0
ALKP activity (IU/l)	18.0	15.0 – 60.0
Total bilirubin (µmol/l)	6.8	0.0 – 10.0
Cholesterol (mmol/l)	2.9	3.0 – 6.9
<b>AST (IU/l)</b>	<b>71</b>	<b>0 – 20</b>
<b>CK (IU/l)</b>	<b>3539</b>	<b>50 – 150</b>

On the morning following admittance to the hospital, an approximately 5cm discharging wound appeared over the right lumbar musculature. The area was clipped extensively and there was evidence of local skin necrosis. Cytological examination of fine needle aspirates of the wound was consistent with septic neutrophilic inflammation with moderate numbers of bacteria noted. Ziehl-Neelsen staining was performed and there was no evidence of acid-fast organisms making *Mycobacterium* species unlikely. An MRI of the thoracolumbar spine was performed (see Figure 1). There was an extensive heterogenous lesion extending from T2 to L7 indicated by the arrow on figure 1. The lesion extended

superficially and deep to invade the intervertebral foraminae at T13 to L1 resulting in spinal cord compression. Abdominal ultrasound was unremarkable.

Figure 1: Dorsal MR imaging of the thoracolumbar spine. Arrows indicate the extensive heterogenous lesion that was identified.



A surgical biopsy of the lumbar musculature was obtained and submitted for histopathology. The findings were consistent with pyogranulomatous inflammation. Bacterial culture and sensitivity revealed a moderate growth of mixed anaerobes that was sensitive to metronidazole. Toxoplasma serology and *Mycobacterium* species PCR were negative.

#### Interpretation of results

Prior to the histopathology results, the primary differential was granulomatous disease, however, malignancy associated hypercalcaemia could not be fully excluded. The histopathology confirmed severe extensive paraspinal chronic pyogranulomatous inflammation that was resulting in empyema and hypercalcaemia. The initial cause of this may have been penetrating trauma such as a cat bite or foreign body. The empyema was considered to be the cause of the hind limb paraparesis. The pyogranulomatous inflammation was considered to be causing the hypercalcaemia as a result of calcitriol production by macrophages although calcitriol was not measured.

#### Ongoing management

Flossie was managed with IVFT (0.9% NaCl) and antibiotic therapy and demonstrated a rapid and progressive clinical improvement. The paraparesis fully resolved within 5 days and the hypercalcaemia within 7 days. Given the rapid clinical improvement in response to this therapy, further investigations into hypercalcaemia such as measurement of PTH, PTH-rp and vitamin D metabolites were not pursued. Flossie was continuing to do well at a 6 month recheck.

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