How common is hypercalcemia in cats?
The frequency of the detection of hypercalcemia in cats has dramatically increased in many regions of the world over the past 20 years mostly due to the diagnosis of idiopathic hypercalcemia (IHC).\textsuperscript{1,2} Hypercalcemia is most often initially defined in primary care practice by the finding of increased serum total calcium on routine serum biochemistry. Mild hypercalcemia based on serum total calcium is often overlooked during analysis of serum biochemical profiles, so the frequency of hypercalcemia is likely to be more common than generally recognized. Mild serum total hypercalcemia is frequently attributed to hemoconcentration from dehydration.

Total serum calcium cannot be reliably used to predict the metabolically active ionized calcium fraction in cats.\textsuperscript{8} There was an overall diagnostic discordance of 40\% during evaluation of 434 feline serum samples using total calcium to predict ionized calcium in cats of one study. Ionized hypercalcemia and normocalcemia were underestimated and ionized hypocalcemia was overestimated.

Characterization of hypercalcemia
Once ionized hypercalcemia has been identified, the next step is to determine if the process is PTH-dependent (high PTH from failure to suppress abnormal parathyroid glands) or PTH-independent (PTH is appropriately suppressed as the response of normal parathyroid glands). In a study of 322 cats, ionized hypercalcemia was parathyroid independent in 82\%, equivocal in 10\%, and parathyroid-dependent in 8\% of these cats.\textsuperscript{9} In cats with parathyroid-independent hypercalcemia, malignancy-associated hypercalcemia (MAH) needs to be excluded. MAH most often results from humoral mechanisms as the tumor secretes calcemic substances such as PTHrP into the circulation; local osteolytic hypercalcemia is far less common. When PTHrP is reported to be high, the presence of malignancy is likely. A low or undetectable PTHrP does not exclude malignancy as the cause for hypercalcemia since other cytokines that cause calcemia can be elaborated by the tumor instead of PTHrP on occasion.

If the diagnostic evaluation does not reveal malignancy as the cause for parathyroid-independent hypercalcemia (PTHrP and body cavity imaging), evaluation of circulating vitamin D metabolites may be useful in determining the underlying cause or mechanism for the hypercalcemia. Hypervitaminosis D is classically characterized by increased concentrations of circulating 25(OH)-vitamin D (calcidiol) following excess ergo/cholecaliferol exposure from food\textsuperscript{10,11} or from cholecalciferol-containing rat-bait.\textsuperscript{12,13} Increased circulating calcitriol has been reported in cats with granulomatous disease and hypercalcemia, likely the result of unregulated conversion of calcidiol to calcitriol by activated macrophages.\textsuperscript{14,16}

What are the causes of hypercalcemia in cats?
The frequency for the occurrence of total serum hypercalcemia from biochemical panels from sick or well cats is not known. The only large survey of the causes of hypercalcemia in cats was reported from a veterinary teaching hospital based on the measurement of serum total calcium in 2000.\textsuperscript{17} Ionized hypercalcemia concentration has been sporadically reported in cats with specific diseases, but not in a series of cats with varying causes of hypercalcemia. Idiopathic hypercalcemia, CKD, and neoplasia are the most common and important differential diagnoses to exclude as the cause for parathyroid independent hypercalcemia. Overt hypervitaminosis D, granulomatous disease, and hypoadrenocorticism are other far less common causes of hypercalcemia in cats. Calcium oxalate urolithiasis was reported to be associated with hypercalcemia in cats; however, it is likely that hypercalcemia preceded the formation of stones rather than the urolithiasis acting as a stimulus for the formation of hypercalcemia.\textsuperscript{17,18} IHC was not considered as a diagnostic category in one large study of cats with hypercalcemia,\textsuperscript{17} but in another study the occurrence of IHC in 20 cats was published that same year.\textsuperscript{18} Primary hyperparathyroidism was infrequently diagnosed as the cause of the hypercalcemia at a teaching hospital (4 of 71 cats),\textsuperscript{17} but this diagnosis is far more frequently made by veterinary endocrine referral laboratories.\textsuperscript{19} Based on the number of consultations by veterinary internists and endocrinologists, as well as sample submissions to endocrine laboratories, idiopathic hypercalcemia (IHC) is currently the most-common cause of hypercalcemia in cats in North America and likely so in other parts of the world.\textsuperscript{1,2,5-7}

While MAH is the number one cause of pathological hypercalcemia in the dog,\textsuperscript{19} it occurs far less frequently in the cat. Based on serum total calcium and how the data is parsed, MAH is 3rd in frequency behind IHC and CKD in cats with hypercalcemia.\textsuperscript{17} In dogs, the overwhelming cause of MAH is lymphoma with occasional carcinoma as the diagnosis,\textsuperscript{19} whereas in cats lymphoma and carcinomas each account for about 1/3 of the cases.\textsuperscript{17} Patients with MAH are usually “sick” as it takes a reasonably large tumor burden to synthesize the messengers that result in hypercalcemia.

Signalment and clinical signs of IHC cats
In a report from 427 cats with IHC evaluated at an endocrinology laboratory, the age at diagnosis ranged from 0.5 to 20 years (mean 9.8 ± 4.6 yr). Males and females were equally represented in this study. Long-haired cats were noted to be overrepresented at 27\% of
the cases in this report, but not in a recent case-control epidemiological study (data analyzed post Todd Green Master’s Ohio State University 2008).

No clinical signs were noted in 46% of IHC cats. Other clinical signs were largely related to gastrointestinal signs, including mild weight loss (18%), chronic constipation (5%), vomiting and decreased appetite. IBD was diagnosed in 6% of the IHC cats of this study. Lower urinary tract signs may be observed, especially if urolithiasis is present. Uroliths or renoliths were observed in 15%, and calcium oxalate stones were specifically noted in 10% of cases. Polyuria/polydipsia has not been frequently reported in cats with IHC.

In many instances, hypercalcemia based on measurement of total serum calcium is fortuitously discovered following submission of serum samples from wellness examinations, pre-anesthetic evaluation of seemingly healthy individuals, those with routine medical conditions, and those from cats forming calcium-oxalate stones. Hypercalcemia is also sometimes discovered following submission of samples from cats with seemingly trivial clinical complaints like intermittent vomiting of hairballs. Though many cats with IHC do not have obvious clinical signs at first look, a more careful review of the history and physical examination often discloses some abnormality that could be explained by persistence of chronic ionized hypercalcemia. This includes low-grade weight loss, loss of muscle mass, and lethargy. Intermittent vomiting and constipation are also possibly due to adverse effects of ionized hypercalcemia on gut motility. Chronic ionized hypercalcemia is a risk factor for the genesis of calcium oxalate urolithiasis and for the development of chronic renal injury resulting in CKD that may take months to years to develop.

**How is the diagnosis of IHC established?**

The diagnosis of IHC is one of exclusion after initially confirming that the ionized calcium is increased. All the known causes of hypercalcemia should ideally be eliminated – this kind of workup can be exhaustive and expensive. The increase in circulating ionized calcium in IHC can be mild, moderate, or severe, as it can also be with other causes of hypercalcemia. Often mild increases in total or ionized calcium that are discovered fortuitously tend to increase over time, but to a varying magnitude. We have observed the ionized calcium concentration to fluctuate into and above the reference range, especially when the hypercalcemia is marginal in magnitude. We have observed large fluctuations in total and ionized calcium concentrations on occasion in some cats with IHC and those with primary hyperparathyroidism.

In order to exclude other causes of hypercalcemia, a minimum database including a CBC, biochemistry profile and urinalysis, should be performed. Additionally, analysis of PTH and 25-hydroxyvitamin D are necessary to rule out hyperparathyroidism and hypervitaminosis D as the cause of the hypercalcemia. The typical pattern for calcium regulatory hormones in IHC would be for the PTH concentration to be within the reference range (often lower end), the PTHrP concentration to be undetectable, and to have a normal serum ionized magnesium concentration. Most 25-hydroxyvitamin D and calcitriol concentrations are usually within the reference range, but a few cats with IHC have been noted to have values increased above the reference range.

Chest radiographs are useful to rule out metastatic pulmonary nodules and mediastinal lymphoma that may be associated with hypercalcemia. Unlike in dogs, mediastinal lymphoma is not common in cats. A combination of abdominal radiographs and ultrasonography can be useful to determine the presence of urolithiasis (kidney, ureter, bladder, urethra), obstructive nephropathy from the stones, or the presence of inflammatory/infiltrative masses that could be associated with the genesis of the hypercalcemia. Treatment recommendations and prognosis may change with the presence of stones and their location.

**Should all cats with IHC receive treatment?**

Cats with minimal increases in circulating calcium concentrations are often ignored in clinical practice since many of these cats have mild or no apparent clinical signs. Even though obvious clinical signs are often not apparent, subtle clinical signs often exist. Excess calcium can be toxic to cells, exerting either physiological or structural effects particularly in the central nervous system, gastrointestinal tract, heart, and kidneys. Mineralization of soft tissues is an important potential complication related to the presence of ionized hypercalcemia that is in part determined by the concomitant concentration of serum phosphorus, but this does not develop in all IHC cats. The clinical outcome for cats with IHC that have not been treated has not been established following the initial diagnosis. An argument can be made to withhold treatment when an IHC cat has no recognizable signs, no identified risk factors for urolithiasis or CKD, and the increase in ionized calcium is minimal. A stronger argument can be made to treat IHC cats in which the ionized calcium concentration continues to escalate. The strongest argument to start treatment exists for cats that have ongoing weight loss, depression, vomiting, constipation, urinary stones, emergence of CKD and or development of sub-maximally concentrated urine.

**Treatment of IHC – diet**

Management of IHC usually begins with a dietary recommendation to attempt to restore normocalcemia. Reports of treatment outcome following dietary change are quite limited, so diet recommendations are largely based on expert opinion and uncontrolled case studies in small numbers of cats. We have observed decreased circulating ionized calcium in some cats following dietary change, but the magnitude and duration of this decrement can be quite variable. Future studies comparing test and control diets are needed to
determine the effects, if any, of altering intake of nutrient(s) on concentrations of the calcium regulatory hormones PTH, calcidiol, calcitriol, and 24,25(OH)2-vitamin D in addition to that for ionized calcium.

**Is there one specific dietary nutrient on which we should focus that will consistently decrease circulating ionized calcium?**

Regulation of the circulating calcium concentration is dynamic and complex. It has not been determined how much of the hypercalcemia in IHC cats results from too much dietary calcium intestinal absorption, increased bone resorption, reduced renal excretion of calcium, or combinations of these processes. Many of the nutrients in the diet interact with each in ways that affect dietary calcium absorption and not all calcium in the diet is biologically available for absorption. Vitamin D is one obvious dietary nutrient that can affect intestinal absorption of calcium and it also has effects on osteoclastic bone resorption that can contribute to the degree of calcemia. Vitamin A has effects on the osteoclast that can work in concert with vitamin D to increase bone resorption.

**What do we know about dietary calcium content in the management of IHC?**

Some veterinary nutritionists recommend diets to treat IHC based on a decreased calcium content on a g calcium/1000 kcal (Mcal) energy basis. Minimal and maximal nutrient recommendations for cat food are provided by the Association of American Feed Control Officials (AAFCO) and the National Research Council (NRC). Most diets sold over-the-counter should meet AAFCO requirements; however, veterinary therapeutic diets may be specifically modified in order to provide certain nutrients at concentrations less than AAFCO minimums. The average calcium content of grocery store foods in the USA is approximately 2.0 to 3.0 g calcium per Mcal (200-300 mg/100 kcal), though some contain up to 6.0 g calcium per Mcal (600 mg per 100 kcal). Some of the highest calcium diets are “high-fiber” diets; thus one must carefully weigh the pros and cons of recommending a high-fiber diet for dietary management of IHC when there is some evidence that reducing dietary calcium may be effective in restoring normocalcemia. Nutrient concentrations of diets can be found either in product guides or by contacting the diet manufacturer, but this information is not readily available from the routine diet label. Nutrient profiles are constantly evolving and this information may change up to every 6-12 months. For feline adult maintenance, the NRC recommended allowance (RA) is 0.72 g calcium per Mcal and the AAFCO minimum is 1.5 g calcium per Mcal.

Feeding of a high protein and low carbohydrate food similar to what cats would eat in the wild (i.e., 40-60% of calories from protein; 30-50% of calories from fat, and <15% of calories from carbohydrates) has been recommended to effectively lower serum calcium concentration in some cats with IHC, especially those with low magnitude hypercalcemia. This nutrient profile is what would be expected from veterinary therapeutic diets designed for cats with diabetes mellitus and also many over-the-counter canned feline diets. In reviewing these types of diets however, it should be noted that calcium content varies from about 1.5 to 5.5 g per Mcal.

**What do we know about dietary vitamin D content in the management of IHC?**

IHC is not the result of obvious excess dietary vitamin D intake since serum concentrations of 25(OH)-vitamin D have been within the reference range in most cats with IHC. However, the minimal requirement for vitamin D in cats is debatable since reference ranges have been established in cats fed vitamin D–supplemented diets. Normal concentrations of 25(OH)-vitamin D could still potentially be associated with IHC in cats if there are up-regulating mutations in the VDR (vitamin D receptor). These possibilities have not yet been investigated.

For adult cats, the NRC-RA for dietary vitamin D3 (cholecalciferol) is 70 IU per Mcal. The safe upper limit (SUL) is listed as 7,520 IU per Mcal. AAFCO minimum and maximum recommendations for feline adult maintenance are 125 and 2,500 IU per Mcal, respectively. Clearly, there is a wide range of acceptable dietary vitamin D in commercial cat foods. Feeding a diet formulated to be low in vitamin D content at < 200 IU per Mcal has been recommended in dietary treatment of cats with IHC.

**How helpful are high fiber diets in restoration of normocalcemia in cats with IHC?**

Higher fiber diets were associated with the restoration of normocalcemia in 5 of 5 cats with calcium oxalate stones and a likely diagnosis of IHC (high ionized calcium concentration) in one report. The effects of fiber on intestinal absorption of calcium are complex and depend on the type and amount of fiber in the diet and the interactions with other nutrients in the diet. It has been theorized that supplemental fiber may lead to increased binding of intestinal calcium, preventing its absorption, and also to decreased intestinal transit time through the small intestine, reducing calcium absorption. The salutary effect of a higher fiber diet, if any, is not simply due to the binding of calcium to fiber. It appears to be common practice for most manufacturers to increase the concentration of calcium in high-fiber diets to offset the potential for decreased absorption.

**How helpful are higher salt diets in management of IHC?**

Treatment with higher salt content diets has not been studied in IHC cats, with or without calcium oxalate stones. Higher salt intake potentially could promote increased water intake, volume expansion, and a dilution effect that would decrease circulating ionized calcium to some degree. Increased water turnover would then create more dilute urine that should help prevent calcium oxalate stone growth by reducing RSS. Increasing salt intake up to 3.7 g per Mcal has been reported to be safe without detection of deleterious effects on renal function, cardiovascular function, and systemic blood pressure when studied in normal cats, geriatric cats, and cats with surgically reduced renal mass. Future studies of higher dietary salt intake for treatment of cats with IHC are warranted.
Treatment of IHC- glucocorticosteroids and oral alendronate

We do not recommend starting drug therapy immediately after the diagnosis of IHC since dietary treatment is effective in restoration of normocalcemia in some cats. Treatment with glucocorticoids restores normocalcemia or dramatically reduces the ionized calcium concentration in most cats with IHC, at least initially. A maximal decline in calcium to within the reference range often requires dose escalation and the beneficial effect may be transitory. Approximately 80% of cats with IHC become normocalcemic with 1.5 to 2.0 mg/kg/day prednisone per day, but some may require increasing doses to remain normocalcemic over time.46 It is important to not prescribe glucocorticosteroids before the diagnosis of the hypercalcemia has been established with some certainty, otherwise cytolytic effects in LSA and myeloproliferative disorders will make definitive diagnosis difficult or impossible. A mild calcium-lowering effect can be exerted by use of glucocorticosteroids in other forms of malignancy-associated hypercalcemia and in those with primary hyperparathyroidism. It is also preferred to have biopsy-proven IBD before the start of glucocorticosteroids. Oral prednisolone achieves greater maximal concentration in the circulation than does oral prednisone in the cat, possibly due to greater GI absorption of prednisolone or less hepatic conversion of prednisone to prednisolone.37 Prednisolone is given orally at 5 – 10 mg/cat/day for 1 month before reevaluation. Though prednisolone can be effective in restoration of normocalcemia in IHC cats, we now usually consider prednisolone as treatment after oral bisphosphonate treatment has failed to restore normocalcemia. In these instances, prednisolone is prescribed in addition to the oral bisphosphonate, but much lower doses of prednisolone may now be effective during combination drug therapy. Long-term treatment with prednisolone contributes to muscle wasting46 and possible induction of diabetes mellitus in some cats.

Bisphosphonate treatment for IHC cats

Historically, oral bisphosphonates have been recommended to treat IHC cats when dietary modification and prednisolone treatment have been unsuccessful in restoration of normocalcemia. Oral alendronate has become our preferred option to treat IHC cats after dietary modification has failed to restore normocalcemia.28 Even though not extensively reported, we now consider bisphosphonate therapy a safer alternative to glucocorticosteroid use in cats that failed dietary intervention. Treatment with bisphosphonates may be useful to decrease the magnitude of hypercalcemia in cats with IHC by altering osteoclastic bone resorption. IV treatment with bisphosphonates is almost never needed in IHC since the hypercalcemia is chronic and the cats are usually not in an acute crisis.

The long-term safety and efficacy of oral alendronate therapy has not been reported in cats. The safety and efficacy of oral alendronate treatment given once weekly for 6 months was reported in 12 cats with IHC.38 Two of the 12 cats developed mild ionized hypocalcemia at 6 months of treatment. We have followed some IHC cats undergoing alendronate treatment for over 2 years without reported clinical side effects.36 The safety of oral alendronate treatment for cats with IHC and CKD has not been specifically studied, but we have not observed any documented decreases in renal function that we could attribute directly to the alendronate. Drug-induced esophageal damage (erosive esophagitis and esophageal stricture) and gastritis are of concern in humans taking oral bisphosphonates.39-42 We have not observed the development of these lesions, nor have they been reported by others, following oral alendronate treatment in IHC cats.

An increased risk for bone fracture has been reported in humans on long-term bisphosphonate treatment presumably because of the increased brittleness of bone due to bisphosphonate therapy.43 Bisphosphonate treatment in humans generally does not exceed 3 years due to concerns that acquired bone pathology outweighs previous benefits.44 We have become aware of two cats that developed pathologic fractures following 9 and 5 years of treatment with weekly oral alendronate.

Any food in the stomach can drastically reduce the absorption of alendronate to near zero – bisphosphonates are poorly absorbed at best under optimal conditions. To maximize intestinal absorption of alendronate, we recommend fasting cats overnight for 12 hours prior to the administration of medication, giving the pills in nothing other than tap water, and then feeding the cat two hours later. Though not specifically studied, an 18-hour fast prior and 4-hour fast post-pill might be a better protocol to achieve the highest possible intestinal absorption.45 We do not recommend the administration of alendronate in pill pockets due to concern about decreased intestinal absorption that could occur. For the same reason, we do not recommend alendronate that has been formulated by compounding pharmacies in flavored solution or suspension.

Given the risk of esophagitis and stricture associated with oral bisphosphonate treatment in humans, we advise extra caution to prevent esophageal tissue damage following oral alendronate administration in cats. The starting dose is usually 10 mg/cat (NOT per kg) per week initially. We recommend administration of whole tablets only, as cut tablets may increase exposure of the esophagus and stomach to adverse effects. We recommend “buttering” the cat’s lips/nose as this has been shown to increase salivation and swallowing which contributes to decreased transit time and less time for mucosal contact from the pill.46 The effect of butter on intestinal absorption of alendronate has not been specifically studied, but use of butter as part of our treatment protocol has effectively restored normocalcemia in many cats. Five to 6 ml of tap water is administered via syringe to provide an additional measure to prevent the pills from getting caught in the esophagus.47 Using these preventative measures, we have not yet observed any signs of esophagitis in cats treated with alendronate.

Some cats return to normocalcemia on 10 mg oral alendronate per week, whereas other cats require dose escalation to do so. If the ionized calcium remains above the reference range at the 4 to 6 week visit, increase the dose to 20 mg once each week, or alternate
giving 10 mg one week followed by 20 mg the next week to provide an average of 15 mg per week. Once the ionized calcium enters the reference range, we recommend reevaluation in 1, 3, and 4 to 6 months if the ionized calcium remains stable within the reference range. Many IHC cats return to normocalcemia following a 10 mg once weekly dose of oral alendronate, whereas some IHC cats will require 20 mg weekly to achieve normocalcemia. Rarely, 30 or 40 mg/cat/week oral alendronate will be needed to restore normocalcemia. Alendronate dose reduction should be prescribed for cats that achieve very low reference range ionized calcium in order to prevent the development of overt hypocalcemia. For cats that develop overt hypocalcemia, alendronate treatment should be discontinued, at least temporarily.

**When should bisphosphonate treatment be stopped for IHC cats?**

Alendronate treatment should be stopped in IHC cats that fail to regain normocalcemia despite 30 to 40 mg weekly doses after ascertaining strict adherence to the pre-pill fasting protocol. Alternatively, prednisolone can be added on top of alendronate to see if a beneficial effect can be gained to lower circulating calcium during combination therapy.

It is not known how long oral alendronate treatment should be continued in those IHC cats that have regained normocalcemia for long periods of time. It is possible that the salutary effects to keep circulating calcium concentrations within the reference range may last long after alendronate is discontinued due to its long half-life in bone, but this has not been specifically studied.

Though bisphosphonate treatment is very often effective in restoration of normocalcemia in IHC cats, it would be far preferable to find the underlying cause(s) of IHC so that drug therapy would no longer be needed. Guidelines as to how long bisphosphonate treatment can safely be given to cats with any disease have yet to be established. We are concerned that some cats are now receiving bisphosphonate therapy for years that may be detrimental to the cat’s long-term bone health (based on emerging reports of pathological fractures in some cats). It may not be enough to just monitor calcium and renal function status in IHC cats during treatment interventions. The measurement of calcium regulatory hormones (PTH, calcitonin, calcidiol, calcitriol, 24,25(OH)2-vitamin D, FGF-23, Klotho) before and after treatment interventions will likely reveal important components for the pathophysiology of IHC in cats and may provide targets to be altered during therapy, and also information to ensure long-term safety. Our new recommendation is to include baseline long bone radiographs for all IHC cats being treated with oral bisphosphonates for more than one year, and then yearly thereafter to more readily detect early bone injury that may be developing. Long-term safety studies in cats treated with oral alendronate are needed.

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