

HOW I WORK UP HYPERCALCEMIA

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Pathophysiology

Most calcium in the body is found in the bones and teeth, while the blood contains only 0.1% of it. Serum total calcium consists of three fractions: Protein-bound (~35%), ionized (~55%), and complex (10%). Ionized calcium is the only biologically active form, and should be measured in all patients with hypercalcemia.

Serum calcium (Ca) levels are primarily regulated by PTH (parathyroid hormone) and vitamin D. Both of these also affect phosphorus (P) homeostasis. PTH is released in response to hypocalcemia and/or hyperphosphatemia; PTH release is inhibited by vitamin D and hypercalcemia. PTH has three major functions: stimulation of the release of Ca and P from bones; reabsorption of Ca and excretion of P from the kidneys; and activation of vitamin D in the kidneys. PTH excess causes the Ca concentration to rise. Renal excretion of P is more important than the increased release of P from bone. Therefore, in cases of PTH excess, P concentrations DECREASE. PTH deficiency causes hypocalcemia and hyperphosphatemia.

Vitamin D increases absorption of both Ca and P from the proximal small intestine. It does this by increasing production of Ca-binding protein. Once the protein is made, its effects last for several weeks. Excess vitamin D (such as with calcipotriene/psoriasis cream intoxication) leads to both hypercalcemia and hyperphosphatemia.

Vitamin D inhibits further production of PTH via negative feedback. In cases of renal failure, decreased activation of vitamin D in the kidney leads to INCREASED secretion of PTH. Among other things, increased PTH increases osteoclastic activity, leading to the renal-secondary hyperparathyroidism and “rubber jaw” seen in some patients with CRF. Ca concentration is variable in patients in renal failure. It may be low initially and increase as the disease progresses, and more PTH is secreted.

PTHrp, or parathyroid hormone related protein, is released during various neoplastic conditions, such as lymphoma and multiple myeloma. The effects of PTHrp are similar to those of PTH.

Diagnosis

Many patients that are diagnosed with hypercalcemia are not clinical at the time of diagnosis; the finding appears on routine bloodwork. Of the canine patients that are clinical, the most common clinical signs of hypercalcemia are PU/PD and decreased appetite; vomiting, weakness and depression may also occur. PU/PD is much less common in cats than in dogs. The most common clinical sign associated with hypercalcemia in cats is anorexia; vomiting, depression, weakness, and constipation may also occur. Other clinical signs depend on the underlying cause (eg, vomiting with lymphosarcoma, and tenesmus with anal sac adenocarcinoma).

There are relatively few causes for hypercalcemia, compared with other non-specific clinicopathologic abnormalities. In patients with multiple, non-specific problems (including vomiting and diarrhea), ruling out the various causes of hypercalcemia is often the most efficient method for arriving at a diagnosis. The most common cause of hypercalcemia in dogs is neoplasia (specifically lymphoma and apocrine gland adenocarcinoma), followed by Addison's disease and primary hyperparathyroidism. Idiopathic hypercalcemia is the most common cause in cats, followed by neoplasia and renal failure. The majority of the causes of hypercalcemia can be remembered using the mnemonic "HARD IONS."

H: Hyperparathyroidism

A: Addison's disease

R: Renal disease (including grapes and raisins in dogs)

D: Hypervitaminosis D (old rodenticide poisonings, calcipotriene—Devonex, plants), Diet

I: Idiopathic (CATS), infectious/inflammatory (granulomatous disease—fungal, schistosomiasis, other)

O: Osteolytic (osteomyelitis, osteosarcoma, growing puppy)

N: Neoplasia (Paraneoplastic—lymphoma, anal sac adenocarcinoma, multiple myeloma, other)

S: Spurious, Supplementation

The work-up for hypercalcemia begins with a thorough history, including questioning for potential toxin exposure (ask about plants, rat bait, and psoriasis cream specifically), travel history (fungal disease), and past medical problems. Physical examination may reveal enlarged lymph nodes (lymphoma) or anal sac adenocarcinoma on rectal examination. It may also reveal bone pain secondary to osteosarcoma. (However, hypercalcemia is very uncommon in patients with osteosarcoma, and it is more likely that these patients would present because of pain than hypercalcemia).

Before proceeding with the work-up, serum total calcium should be rechecked in conjunction with an ionized calcium to rule-out a spurious result. Adjustment formulas used to correct total calcium based on albumin concentration are no longer recommended because they do not accurately predict ionized calcium concentration.

A minimum data base including a CBC, serum chemistry, and urinalysis should be performed. Evaluation of a serum chemistry panel may be suggestive of Addison's disease (hyperkalemia and hyponatremia). Increased BUN and creatinine may be suggestive of renal failure, although pre-renal azotemia must be ruled out. Additionally, evaluation of the serum calcium and phosphorus concentrations may help elucidate the cause. Patients with increased levels of PTH are usually hypercalcemic and hypophosphatemic. Neoplasia associated with PTHrp production often causes hypophosphatemia in addition to hypercalcemia, as well. Patients with hypervitaminosis D (or granulomatous disease) should have increased levels of both calcium and phosphorus.

Imaging studies should be performed if necessary to search for neoplasia, granulomatous disease, or to provide further insight into another disease process. Radiographs of bones should obviously be performed if pain is elicited upon palpation. Abdominal radiographs may reveal uroliths that were

formed secondary to hypercalcemia. Thoracic radiographs may reveal enlarged lymph nodes or metastasis (anal sac adenocarcinoma, other carcinomas). Abdominal U/S may also show enlarged lymph nodes, and help the clinician evaluate the status of the kidneys. U/S of the cervical region may reveal enlarged parathyroid glands (1 or more).

Serum PTH and PTHrp concentrations can be very useful in the diagnostic workup of hypercalcemia. An increased PTHrp is highly suggestive of neoplasia, but a normal PTHrp does NOT rule it out. PTH levels must be evaluated based on what is “appropriate,” not what is “normal.” A mid-range PTH level is appropriate in a dog with a calcium in the lower to middle part of the reference range. However, a dog with hypercalcemia should have a LOW or undetectable PTH. Therefore, if a hypercalcemic dog’s PTH level is midrange, this is inappropriate and indicates parathyroid pathology, such as primary hyperparathyroidism.

Depending on the status of the patient, bone marrow aspirate/core biopsy may be recommended prior to receiving results of the PTH/PTHrp assays, to allow treatment for lymphoma, if necessary. In the author’s experience, it is not common to identify lymphoma with bone marrow aspirate if there are no other indications of it in the CBC, peripheral lymph nodes or abdomen (spleen, liver, lymph nodes), BUT IT IS POSSIBLE.

Based on initial diagnostics, additional testing may be warranted. This may include an ACTH stimulation test and/or lymph node aspirates.

Obviously, not all diagnostics are necessary in each patient with hypercalcemia. The severity of clinical signs and hypercalcemia help direct testing. Since the diagnosis of hypercalcemia is an incidental finding in many patients (particularly dogs with primary hyperparathyroidism and cats with idiopathic hypercalcemia), a more methodical, step-wise approach can be taken. In these cases, following minimum data base and confirmation of ionized hypercalcemia, I often recommend submitting samples for baseline cortisol (if warranted to rule out Addison’s disease) and PTH/PTHrp prior to imaging. However, if the patient presents with more acute signs, imaging is prudent prior to receiving results of the PTH/PTHrp.

Treatment

Definitive treatment of hypercalcemia is aimed at the primary disease, if applicable (lymphoma, Addison’s, hyperparathyroidism, etc.). Patients with lymphoma often respond to treatment within 24-48 hours, as do patients with hypoadrenocorticism. Direct therapy aimed at decreasing the calcium concentration depends upon the severity of the hypercalcemia and associated clinical signs.

Intravenous saline infusion is the primary treatment for acute clinical signs, as it decreases calcium concentration by correcting dehydration and increasing renal excretion of calcium. Furosemide can be used for severe hypercalcemia, but only following rehydration. Although prednisone will help treat hypercalcemia, it MUST NOT be used until diagnostics have been completed, since it often significantly delays a diagnosis of lymphoma. A bisphosphonate (such as zoledronate via infusion) may be given to

alleviate hypercalcemia for treatment of hypercalcemia while completing, or following, diagnostics. Bisphosphonates inhibit osteoclastic activity, thus decreasing Ca concentrations from many causes. However, samples for serum chemistry and PTH/PTHrp analysis should be collected prior to bisphosphonate administration. Calcitonin has also been recommended for severe hypercalcemia, but bisphosphonates are more effective. Oral bisphosphonates can also be used long-term in cats with symptomatic idiopathic hypercalcemia (alendronate, 10 mg/cat/week initially), but owners must be warned of possible esophageal strictures. It must be given on an empty stomach to enhance absorption, so overnight fasting and fasting for 4 hours after administration is recommended. After pilling the cat, administer 5-10 mL of water orally and place a small amount of butter on the cat's nose to enhance salivation and propel the pill into the stomach. Note that nutritional management of idiopathic hypercalcemia, using diets with <200 mg Ca/100kcal and with a Ca:P<1:4, may also be successful.

Feline Hyperthyroidism

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Etiology

Feline hyperthyroidism is the most common endocrinopathy in cats, and is caused by excessive production of thyroid hormones (T3 and T4). It is usually caused by benign adenomatous hyperplasia or adenoma, and is bilateral in most cases (approximately 80%). Thyroid carcinoma is rare (1-2% of cases), but may develop in cats treated with methimazole long-term.

The prevalence of hyperthyroidism has increased significantly since the first cases were reported in 1979, and epidemiologic studies have demonstrated that its incidence has increased at a rate greater than that of other geriatric diseases. The underlying cause is unclear, but likely multifactorial. Iodine-deficient diets and goitrogens, such as soybean isoflavones and bisphenol A (found in the can lining of pop-top canned foods), have been implicated.

Diagnosis

Hyperthyroidism is generally a disease of older cats, with a mean age of 13 years. Common clinical signs include weight loss, polyphagia, and hyperactivity. Conversely, some cats (~10%) present with the apathetic form of the disease, in which they are less active and have decreased appetite. The reason for this presentation is unclear, but it may be due to concurrent disease or very chronic hyperthyroidism. Whereas cats diagnosed with hyperthyroidism used to be noticeably underweight on physical examination, clinicians' ability to diagnose the disease earlier, combined with the prevalence of obesity in the feline population, has led to the diagnosis in many cats that are either overweight or in apparently good body condition, although most have lost weight. A palpable thyroid nodule is suggestive of hyperthyroidism, but may also be present in cats without the disease. About half of hyperthyroid cats have cardiac abnormalities, including tachycardia, murmur, and gallop rhythm.

Definitive diagnosis of hyperthyroidism usually relies upon an increased total T4 concentration. However, a minimum database, including complete blood count, serum biochemistry, and urinalysis, is recommended to help identify concurrent disease. Since hyperthyroidism causes an increase in the glomerular filtration rate, it is critical to evaluate the renal values. Treatment of hyperthyroidism may unmask underlying renal disease or exacerbate renal disease that is already present. Other abnormalities associated with hyperthyroidism include mild erythrocytosis (probably due to increased erythropoiesis), increased phosphorus due to altered bone metabolism, and increased ALT and ALP. However, an increased ALT >500 U/L may be suggestive of concurrent hepatic disease and require further investigation.

Thyrotoxic cardiomyopathy is not uncommon in cats with hyperthyroidism, and this author rarely performs an echocardiogram on hyperthyroid cats with only a murmur but no clinical signs of cardiac disease. If the murmur does not resolve following normalization of the T4, an echocardiogram may be warranted at that time. Blood pressure measurement and fundic exam

are, however, evaluated in each patient. Most cases of mild hypertension will resolve with normalization of the T4, but if the hypertension is severe (>200 mm Hg) or causing retinal lesions (tortuous vessels, retinal hemorrhage) or other clinical signs, anti-hypertensive therapy is indicated.

T3 measurement is insensitive for the diagnosis of hyperthyroidism, and is not routinely used. Total T4 concentration is increased in >90% of hyperthyroid cats. However, in approximately 10% of affected cats, total T4 is within the upper half of the reference range. This can be due to mild disease, daily fluctuation of T4 into and out of the reference range, or to non-thyroidal illness. In these cases, a repeat total T4 will often be increased. Alternatively, a free T4 (by equilibrium dialysis) may be evaluated. An increased free T4 (ED) is more sensitive for the diagnosis of hyperthyroidism than a tT4, but less specific. This means that the free T4 (ED) is more likely to be increased in a mildly hyperthyroid cat or one with concurrent illness. However, the fT4(ED) is also more likely than the tT4 to be increased in a euthyroid cat with non-thyroidal illness. Diagnostic accuracy is improved when the tT4 is evaluated together with a fT4(ED). A patient with a tT4 in the upper half of the reference range, and with a fT4(ED) above the reference range, is very likely to be hyperthyroid. Conversely, a euthyroid patient with concurrent illness and a high fT4 is likely to have a tT4 concentration in the lower half of the reference range.

Recently, measurement of TSH has been evaluated for diagnosis of hyperthyroidism. The most commonly used assay is the canine assay, which has a lower limit of detection (0.03 ng/mL) that is too high to differentiate between hyperthyroid cats and some normal cats. Whereas 98% of hyperthyroid cats have a TSH lower than the limit of detection, 30% of euthyroid cats also have a TSH below the limit of detection.

Nuclear scintigraphy is useful in confirming hyperthyroidism, differentiating whether unilateral or bilateral disease, identifying ectopic (intrathoracic tissue), and differentiation of carcinoma vs. adenoma. It can also be used to help calculate dose of I-131 for treatment.

Treatment

Current treatments include medical, radioactive iodine, and dietary options. Thyroidectomy is much less common now that radiation therapy is available.

In the United States, medical therapy generally consists of methimazole administration. Methimazole inhibits thyroid hormone synthesis by inhibiting the enzyme thyroid peroxidase. The medication is relatively inexpensive and is reversible, which is advantageous if the patient has renal disease. However, this means it must also be given for the life of the patient, and the long-term monitoring cost should be factored into the cost of treatment. There are also several potential side effects associated with methimazole therapy. Gastrointestinal upset (vomiting, diarrhea) is the most common of these (in approximately 10% of patients), and should resolve with discontinuation of the medication. Following discontinuation, the drug can usually be restarted at a lower dose and gradually increased. Facial excoriation is uncommon but generally

requires discontinuation of the medication. Neutropenia, thrombocytopenia, and hepatotoxicity are the most life-threatening of the side effects but are usually reversible if caught in time. This means that regular monitoring of the CBC and serum chemistry (q2 weeks x 3 months) is recommended.

Transdermal methimazole administration is also possible in patients that will not tolerate oral medication, or for owners that don't want to deal with pilling their cats. The pluronic lecithin organogel (PLO) formulation appears to be effective in most cats, although there are some cats that don't respond to it as well as they would to the pill. It also appears to cause fewer GI side effects than the oral formulation. Keep in mind, however, that the effects of this gel on humans (including children) have not been evaluated. Thus, it might not be ideal to use on a cat in a household with a child who frequently handles the cat and may get the medication on his/her skin.

Interestingly, although only 1-2% of cats with hyperthyroidism have a carcinoma at diagnosis, up to 20% of cats that have been treated for 4 or more years with methimazole may develop thyroid carcinomas.

Radioactive iodine is a definitive therapy for hyperthyroidism and is currently the treatment of choice in hyperthyroid cats with normal renal function. I-131 is injected IV or SQ, and then the I-131 is concentrated in the hyperactive thyroid tissue. Beta particles from the I-131 then travel short distances (<2 mm) and destroy the hyperactive tissue. Thus, normal tissue is usually spared. This is a very effective therapy, and most cats have a normal T4 3 months following treatment. However, some (10-20%) patients develop clinical hypothyroidism, diagnosed with concurrent low tT4 and increased TSH. Iatrogenic hypothyroidism is associated with the development of azotemia and decreased survival in some cats, and supplementation of levothyroxine improves survival.

Dietary therapy is another option for the treatment of hyperthyroid cats. This diet is severely iodine restricted, and since iodine is necessary for thyroid hormone synthesis, should result in decreased thyroid hormone synthesis. Studies have been promising, provided that the cat will eat the diet, and that it is the ONLY diet that the cat eats. Although euthyroid cats can eat the diet, they MUST be supplemented with a normal iodine-containing diet. In one study, although T4 concentrations normalized in most cats receiving the diets, there was not an overall increase in body weight or decrease in heart rate, so optimal clinical control is unlikely.

The prognosis for hyperthyroid cats is variable and dependent upon the cat's physical condition at diagnosis, in addition to concurrent disorders. One study showed a median survival of 2 years with methimazole treatment, and 4 years with I-131 therapy.