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Topical Review

Endocrine Causes of Calcium Disorders

Deborah S. Greco, DVM, PhD, Diplomate ACVIM

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Nestle Purina Pet Care, St. Louis, MO.

Address reprint requests to: Deborah S. Greco, DVM, PhD, Diplomate ACVIM, Nestle Purina Pet Care, St. Louis, MO 63164.

E-mail: drdebgreco@hotmail.com.

A B S T R A C T

Endocrine diseases that may cause hypercalcemia and hypocalcemia include hyperparathyroidism, hypoparathyroidism, thyroid disorders, hyperadrenocorticism, hypoadrenocorticism, and less commonly pheochromocytoma and multiple endocrine neoplasias. The differential diagnosis of hypercalcemia may include malignancy (lymphoma, anal sac carcinoma, and squamous cell carcinoma), hyperparathyroidism, vitamin D intoxication, chronic renal disease, hypoadrenocorticism, granulomatous disorders, osteolysis, or spurious causes. Hypocalcemia may be caused by puerperal tetany, pancreatitis, intestinal malabsorption, ethlyene glycol intoxication, acute renal failure, hypopararthyroidism, hypovitaminosis D, hypomagnesemia, and low albumin. This article focuses on the endocrine causes of calcium imbalance and provides diagnostic and therapeutic guidelines for identifying the cause of hypercalcemia and hypocalcemia in veterinary patients.

Calcium and Phosphate Metabolism

Calcium homeostasis is so tightly controlled that adjustments are made within a range of 5% of normal. Calcium is important for a number of intracellular reactions, including muscle contraction, nerve cell activity, the release of hormones through the process of exocytosis, and the activation of several enzymes. Calcium is important for coagulation of blood and for maintaining the stability of cell membranes and the linkage between cells. On a less acute basis, calcium is important for the structural integrity of bone and teeth.

Phosphate concentrations are controlled by the same systems that control calcium concentrations. Inorganic phosphate in the blood serves as the source of phosphate, which is important for the structure of bone and teeth. Inorganic phosphate also functions as an important H^+ buffering system in blood. Organic phosphate is an important part of the cell, including the plasma membrane and intracellular components, such as nucleic acids, adenosine triphosphate, and adenosine monophosphate.

Almost all the calcium (99%) in the body is in the bones in the form of hydroxyapatite crystals, which contain calcium, phosphate, and water. The next largest pool of calcium is intracellular calcium. As stated previously, calcium is important for the response of cells in carrying out their physiological activities, including the secretion of hormones. In the inactive cell state, calcium concentrations are relatively low in the cytosol; calcium is bound to proteins or contained within the mitochondria or granules of the endoplasmic reticulum. Increased intracellular calcium concentrations are indicative of increased cell activity.

The smallest pool of calcium, which resides in the extracellular fluid (ECF), is the most important pool for physiological control of calcium concentrations in the blood. This component comprises interstitial calcium, blood calcium, and a small (0.5%) but important part of the bone-calcium pool, which exists as amorphous crystals or in solution. The soluble bone-calcium pool allows access to the large reserve of calcium that resides in bone.

The regulation of calcium levels involves control of the movement of calcium between the ECF and 3 body organs: bone, gastrointestinal (GI) tract, and kidneys. The exchange of calcium ions between the ECF and intracellular fluid occurs in conjunction with the control of intracellular metabolism, with little effect on plasma concentrations of calcium.

The absorption of calcium from the GI tract is by passive diffusion and active transport. The passive diffusion of calcium across the intestinal mucosa occurs in the presence of high concentrations and, as such, is not an important aspect of calcium absorption. Active transport involves the movement of calcium into the intestinal cells down a concentration gradient, which is facilitated by carrier proteins located on the luminal side of the mucosal cell. Calcium is moved through the serosal side of the mucosal cell into the interstitial fluid through a calcium pump system. The active transport system adjusts according to the amount of calcium in the diet, becoming more active when calcium concentrations in the diet are lower and less active when calcium concentrations are higher. Calcium excretion into the GI tract is not affected by calcium uptake, and this can exacerbate conditions involving hypocalcemia. The GI tract serves as the source of calcium for the body, even though both absorption and excretion of calcium occur through the tract. As discussed later, vitamin D plays an important role in the absorption of calcium from the GI tract.

The kidneys serve as the route of excretion of calcium. Most of the calcium that passes into the kidneys is reabsorbed, with a net loss of only about 2%. This amount is matched by the net absorption of calcium by the GI tract. Most of the calcium filtered by the kidneys is reabsorbed in the proximal tubules; the next largest amount is absorbed by the distal tubules, and a lesser amount is absorbed by the ascending loop of Henle. The distal

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tubules are under hormonal control and therefore are the sites of regulation of calcium in the kidneys.

The most important regulation of calcium metabolism between bone and ECF involves the soluble portion of calcium in the bones. Amorphous crystals and soluble calcium, which form the source of ready exchange of ions with the blood, are located between the osteoblasts, which line the blood vessel channels, and the osteocytes, which are deeper in the bone. These 2 cell types have cytoplasmic projections that interact intimately through the presence of tight cell junctions. for labile bone calcium to reach the blood, calcium must cross the membrane barrier created by the osteoblasts and osteocytes. Movement of calcium from stable bone into the ECF also occurs but has little effect on the acute regulation of calcium concentrations. The process of remodeling the bone, which occurs on a continuous basis, involves the breakdown of hydroxyapatite crystals by osteoclasts, a laying down of organic matrix by osteoblasts in the tunnels made by the osteoclasts, and the mineralization of the organic matrix by hydroxyapatite crystals.

Parathyroid Hormone (PTH)

The main endocrine organ involved in the control of calcium and phosphate metabolism is the parathyroid gland. Most domestic animals have 4 pairs of parathyroid glands that are generally located at the poles of the 2 lobes of the thyroid gland; the pig has only 1 pair of parathyroid glands, which lies anterior to the thyroid. The cranial pair of parathyroid glands in dogs and cats is at the craniolateral poles of the thyroid and the caudal pair of parathyroid glands in dogs and cats is located within the medial surface of the thyroid. The parathyroid cells that are in the active process of hormone secretion are called chief cells, whereas inactive, or degenerate, cells are called oxyphil cells.

The synthesis of PTH is similar to the synthesis of other protein hormones; a prepro-PTH of 115 amino acids is synthesized in the rough endoplasmic reticulum and then 25 amino acids are cleaved to form pro-PTH. A "pro" portion of 6 amino acids is removed by the Golgi apparatus; the resulting PTH has 84 amino acids. PTH is secreted by the process of exocytosis. It is rapidly metabolized by the liver and kidneys and has a relatively short half-life (5-10 minutes) in blood.

The effect of PTH is to increase calcium and decrease phosphate concentrations in ECFs. PTH has direct effects on bone and kidney metabolism of calcium and indirect effects on GI metabolism of calcium. The initial effect of PTH on bone is to promote the transfer of calcium across the osteoblast-osteocyte membrane. This level of action occurs without the movement of phosphate and therefore has no effect on phosphate concentrations in blood. PTH has additional effects on stable bone, which results in the resorption of the bone. This effect involves increased osteoclast activity and an inhibition of osteoblast activity. The effect of PTH on stable bone results in the release of both calcium and phosphate.

PTH acts on the distal convoluted tubules of the kidneys to increase absorption of calcium and decrease renal phosphate reabsorption through an effect on the proximal tubules. PTH is also involved in the activation of vitamin D at the kidney level. PTH mediates the absorption of calcium from the gut indirectly through its effect on vitamin D. PTH secretion is controlled by free (ionized) calcium concentrations in blood; a decrease in calcium levels stimulates PTH secretion, and an increase in calcium turns off secretion. Both the actions are mediated by an effect on cAMP metabolism. Epinephrine stimulates PTH secretion through stimulation of adrenergic receptors. Magnesium affects PTH secretion in the same manner as calcium, but its physiological effect is much less. Sleep affects the secretion of PTH; values are highest immediately after waking up.

Calcitonin

Calcitonin, a hormone produced by cells in the thyroid gland, also affects calcium metabolism. Cells of the type involved in the synthesis of calcitonin—parafollicular, or C cells—are scattered throughout the thyroid gland and are distinctly different from the cells that synthesize thyroid hormones. During the early studies of calcitonin in animal classes such as fish, amphibians, reptiles, and birds, which have separate thyroid and ultimobranchial glands, it was found that all the calcitonin activity was in the ultimobranchial glands. Therefore, the calcitonin cells represent ultimobranchial gland tissue that has been incorporated into the thyroid during embryonic development.

Calcitonin, synthesized as a preprohormone, has 32 amino acids; a ring structure at the amino terminus contains a disulfide link that bridges between amino acids 1 and 7. The processing of the molecule is interesting because calcitonin is located in the middle of procalcitonin, so an additional enzyme cleavage is required for the formation of the active molecule. The secretion of calcitonin is by exocytosis from granules.

Calcitonin acts as a counterbalance to PTH because it causes hypocalcemia and hypophosphatemia. The effect of calcitonin on mineral metabolism is mainly seen in the bones. Calcitonin decreases the movement of calcium from the labile bone-calcium pool (behind the osteoblast-osteocyte barrier) to the ECF and decreases bone resorption through an inhibitory effect on the osteoclasts. Although the inhibition of bone resorption explains 1 aspect of the hypophosphatemic effects of calcitonin, calcitonin also increases movement of phosphate from the ECF into bones. Calcitonin decreases GI activity directly by inhibiting gastric acid secretion and indirectly by inhibiting gastrin secretion. The physiological importance of this is not known. Calcitonin also increases renal excretion of calcium and phosphate.

The control of calcitonin secretion is by calcium; increased calcium concentrations cause increased secretion of calcitonin. The physiological control of calcium metabolism by calcitonin operates in situations of hypercalcemia with increased secretion of calcitonin and concomitant inhibition of PTH secretion. During hypocalcemic conditions, calcitonin synthesis is inhibited, and PTH becomes responsible for re-establishing normal calcium concentrations in the ECFs. GI hormones, including gastrin, cholecystokinin, secretin, and glucagon, stimulate the secretion of calcitonin, with gastrin being the most potent. These hormones limit postprandial hypercalcemia.

Vitamin D

Vitamin D is important for the absorption of calcium from the gut. It is a steroid-like molecule, and because it is produced in one tissue and transported by the blood to a distant site of action, it should probably be called a hormone instead of a vitamin. All the vitamin D produced by the body is produced in the skin. Epithelial cells of the skin synthesize the immediate precursor of vitamin D, 7-dehydrocholesterol, from acetate. Exposure of the skin to ultraviolet light results in cleavage of the C-9 and C-10 bonds of 7-dehydrocholesterol, which results in the formation of vitamin D. The vitamin D molecule, as such, is inactive and must be transformed by both the liver and the kidney before the molecule is biologically activated. The liver first hydroxylates the molecule at the C-25 position, and the kidney subsequently hydroxylates the molecule at C-1 to produce the active compound, 1,25-$(OH)_2$-vitamin D (1,25-vitamin D).

Control of the C-1 hydroxylase in the kidney by PTH is the most important control linkage for the synthesis of 1,25-vitamin D. Decrease in calcium concentrations stimulates PTH secretion, which in turn favors the synthesis of active vitamin D and increased intestinal absorption of calcium. Phosphate also regulates vitamin D metabolism. Increased serum phosphate concentrations stimulate an enzyme that promotes hydroxylation of C-24 (instead of C-1) by the kidney, which leads to the formation of 24,25-$(OH)_2$-vitamin D, an inactive molecule. The active molecule, 1,25-vitamin D, also regulates itself by decreasing C-1 hydroxylase and increasing C-24 hydroxylase activity, resulting in decreased amounts of active vitamin D. Because of its lipid nature, 1,25-vitamin D is transported by binding to proteins in the plasma. Most of vitamin D is carried out in association with a specific globulin called transcalciferin, a molecule synthesized by the liver.

The most important effects of vitamin D involve increased absorption of calcium by the GI tract. Vitamin D stimulates the synthesis of protein within the mucosal cells, which aids the rate-limiting step in calcium absorption; movement of calcium into the mucosal cell. Because the intestinal effect of vitamin D depends on the activation of protein synthesis by mucosal cells, the effect on calcium absorption usually requires several hours. Although the stimulation of protein synthesis relates mostly to active transport of calcium, vitamin D also stimulates passive transfer of calcium. Vitamin D also affects the bone, promoting the movement of calcium ions from the labile pool into ECFs and the resorption of bone, as well as enhancing the effects of PTH on bone metabolism of calcium.

PTH and phosphate control the synthesis of 1,25-vitamin D. A decrease in calcium concentrations results in increased PTH secretion and increased formation of 1,25-vitamin D through enhancement of C-1 hydroxylation. This action leads to the correction of hypocalcemia by increasing absorption of calcium by the gut. A decline in phosphate concentrations results in decreased inhibition of the C-1 hydroxylation, which indirectly results in increased 1,25-vitamin D production and increased absorption of phosphate. some evidence suggests that hormones associated with pregnancy, such as growth hormone and prolactin, increase 1,25-vitamin D production by stimulating C-1 hydroxylation.

In the overall control of calcium metabolism, PTH is primarily responsible for the maintenance of calcium homeostasis. The primary target tissue for PTH in calcium homeostasis is the labile pool in bone; changes in renal absorption of calcium are also important. In the case of long-term calcium deficit in the diet, both PTH and 1,25-vitamin D are important for correction of the deficit. Decreased dietary calcium leads to decreased concentrations of calcium in the ECFs and the release of PTH. PTH affects resorption of calcium by the kidneys, but most importantly for long-term correction of the problem, it causes increased 1,25-vitamin D secretion with increased absorption of dietary calcium. PTH also contributes to the overall calcium pool through its effect on stable bone, that is, the promotion of resorption.

Hypercalcemia

Clinical Presentation

The initial clinical signs of hypercalcemia are a result of hyperpolarization of cell membranes which affect the neuromuscular, GI, cardiac, and renal tissues.[1] Early renal signs of hypercalcemia, such as polydipsia and polyuria, are caused by increased renal blood flow, reduced renal medullary hypertonicity, decreased solute transport from the loop of Henle, and impaired response of distal renal tubules to antidiuretic hormone.[2] Listlessness, depression, and muscle weakness result from depressed excitability of neuromuscular tissue. Mild GI signs of hypercalcemia include inappetence, vomiting, and constipation. Persistent mild elevations in serum calcium (12-14 mg/dL) may cause uroliths and signs of urinary-tract disease such as hematuria and stranguria.[3] However, severe hypercalcemia (>14 mg/dL) can progress rapidly to acute renal failure (ARF) because of mineralization of renal tissue and other factors including renal blood flow.

Differential Diagnosis of Hypercalcemia

Hypercalcemia has a variety of causes including malignancy, hyperparathyroidism, fungal disease, osteoporosis, hypoadrenocorticism, chronic renal disease, and hypervitaminosis D; however, this article focuses on the endocrine causes of hypercalcemia such as hyperparathyroidism. Some unusual endocrine disorders, such as pheochromocytoma, hypoadrenocorticism, and multiple endocrine neoplasia (MEN) types 1 and 2 may also cause hypercalcemia. The diagnostic approach to hypercalcemia consists of ruling out the most common cause: hypercalcemia of malignancy. A thorough history and physical examination, including lymph node and rectal examination (for anal sac adenocarcinoma), complete blood cell count, urinalysis, serum chemistry profile, and chest and abdominal radiographs are necessary to search for underlying neoplastic processes. If lymphoma is not detected on the minimum database, a bone marrow examination and survey skeletal radiographs may be necessary. Once a diagnosis of neoplasia has been excluded, the next primary differential for hypercalcemia is chronic renal failure (CRF); CRF is difficult to exclude because hypercalcemia itself may result in renal damage associated with soft-tissue mineralization of the kidneys. Therefore, an animal with hypercalcemia, azotemia, and hyperphosphatemia could have primary hyperparathyroidism, primary renal failure with secondary renal hyperparathyroidism, or vitamin D intoxication. Furthermore, patients with hypercalcemia secondary to renal disease may exhibit elevations of intact PTH.

Laboratory Abnormalities Associated With Hypercalcemia

Serum calcium may be affected by laboratory error, age of the animal (young and growing animals have higher values), acid-base status, and plasma protein concentrations. Serum calcium is bound by albumin (50%), chelated (5%), or found in the ionized form (45%).[4] Laboratory assessment of hypercalcemia should include measurement of ionized calcium to document hypercalcemia and interpretation of the serum phosphorus (which should be low unless azotemia is present).[5] The serum chemistry profile may be examined for the presence of azotemia (increased blood urea nitrogen, creatinine, and phosphorus) and signs of ARF (metabolic acidosis, electrolyte abnormalities, etc). Assessment of blood bicarbonate and pH is important because a decrease in pH causes an increase in ionized Ca as calcium ions are displaced from albumin by positively charged hydrogen ions; conversely, alkalosis results in a decrease in ionized calcium. Electrocardiographic changes with hypercalcemia include shortening of the QT interval; severe hypercalcemia may be associated with Osborn waves (J waves), ventricular irritability, and ventricular fibrillation with arrest.[6]

Although some parathyroid tumors may be palpable, most are not. Therefore, ultrasonographic examination of the cervical region is indicated to search for a parathyroid mass. Cervical ultrasonography has been reported to be a reliable diagnostic tool for identifying parathyroid masses; however, it does require

experience and expertise.[7] Demonstration of a cervical nodule in the region of the thyroid gland, coupled with high or normal PTH and elevated ionized calcium provides more evidence for cervical exploratory surgery. Recently, a rapid intraoperative PTH assay has been developed to provide surgeons with guidance in cases where the functional parathyroid nodule is not immediately obvious.[8] Nuclear scintigraphy using technetium (Tc 99m) can also be used to demonstrate the presence of a parathyroid tumor[9]; however, nuclear imaging can be expensive and available only at large referral centers. The patient should be prepared for surgery by saline diuresis and administration of calcitriol in anticipation of the serum calcium levels dropping precipitously both during the operation and immediately postoperatively.

Hyperparathyroidism

Primary hyperparathyroidism occurs uncommonly in older dogs and cats.[10,11] There is no sex predilection; however, Keeshond, Siberian husky, and Golden retriever dogs have a higher incidence of the disorder.[11,12] Siamese cats are at an increased risk for the disease.[13,14] Clinical signs are often related to chronic, mild hypercalcemia; therefore, urolithiasis, vague GI signs, and polydipsia/polyuria are the most common presenting complaints.[3] Severe and rapid increases in serum calcium are more likely to be the result of hypercalcemia of malignancy.

Diagnosis of primary hyperparathyroidism is based on hypercalcemia (ionized), hypophosphatemia (unless azotemic), normal to elevated serum PTH concentrations, and a mass in the cervical region (usually identified by ultrasound or at surgery). Intact PTH, demonstrated by a "sandwich" assay validated for use in dogs and cats, should be measured. A normal PTH concentration (2-13 pmol/L) in the presence of elevated total calciumor ionized calcium or both is considered inappropriate for the calcium level and would be considered diagnostic for primary hyperparathyroidism. For suspected cases of hypercalcemia of malignancy in which the diagnostic approach has failed to identify a neoplastic process, PTH-related protein concentrations may be measured; however, dogs with hypercalcemia of malignancy usually have low PTH and high ionized calcium.[4] Patients with CRF usually have low or low normal ionized calcium and high PTH concentrations. In one study, dogs with CRF had approximately twice the PTH concentrations of dogs with primary hyperparathyroidism.[4]

Treatment of Hyperparathyroidism

Initial treatment of severe hypercalcemia (>14 mg/dL total calcium, or >1.5 mmol/L ionized calcium or both) should be instituted with fluid diuresis using sodium-containing fluids such as normal (0.9%) saline. Once the animal has been rehydrated and ECF volume has been expanded by 3%-5% using fluid therapy, pharmacologic diuresis may be induced with furosemide. A dosage of 5 mg/kg intravenous (IV) bolus followed by a 5 mg/kg/h infusion is recommended.[1] Thiazide diuretics enhance distal tubular reabsorption of calcium and are therefore contraindicated.[1] Once the cause of the hypercalcemia is identified, corticosteroids (2 mg/kg BID) may be used to increase renal excretion of calcium. Although, hypercalcemia of malignancy responds to corticosteorid therapy, other causes of hypercalcemia, such as hyperparathyroidism, do not. Furthermore, use of corticosteroids prior to establishing a definitive diagnosis may obscure the cause of hypercalcemia of malignancy. Phosphonates, compounds related to pyrophosphate which inhibits osteoclastic activity, may be used to lower serum calcium; however, their use in dogs is limited. Calcitonin (4.5 U/kg, subcutaneous [SQ]) can be used to treat hypercalcemia; however, it is expensive. Bicarbonate decreases the ionized fraction of serum calcium at a dosage of 1-4 mEq/kg.

Definitive treatment of hyperparathyroidism involves surgical removal of the parathyroid tumor; however, several alternative therapies have been developed.[15] Ultrasound-guided radiofrequency heat ablation and ethanol chemical ablation of parathyroid tumors have been reported as safe and effective treatments for hyperparathyroidism. However, complications associated with these procedures include damage to the recurrent laryngeal nerve, hypocalcemia, and recurrence of the parathyroid tumor. Surgical removal of parathyroid tumors is not without complication either, as removal of large and invasive parathyroid masses may cause recurrent laryngeal nerve damage and postoperative hypocalcemia.[15]

Preoperative treatment of hypercalcemia may be necessary if concentration of serum calcium and ionized calcium is high; however, the calcium phosphorus product (>60) was not predictive of renal failure in dogs with primary hyperparathyroidism.[10] Treatment with saline diuresis followed by furosemide diuretics may promote renal excretion of calcium. If the patient is dehydrated, fluid deficits should be corrected using normal saline over a 6- to 8-hour period. Most often, fluid therapy with 0.9% saline for 12-24 hours before anesthesia is sufficient to lower serum calcium. Dogs and cats undergoing parathyroidectomy for hyperparathyroidism may be started on an appropriate dose of vitamin D prior to surgery to prevent severe hypocalcemia after the surgical procedure.

Hypocalcemia

Clinical Presentation

Clinical signs of hypocalcemia can affect nearly all body systems. Early signs of hypocalcemia are nonspecific and include anorexia, facial rubbing, growling, nervousness, and a stiff and stilted gait.[16] Later the signs progress to paresthesias, hyperventilation, and generalized tetany which may culminate in seizures. Initially, the GI system may be affected resulting in nonspecific signs such as anorexia and vomiting (cats).[17] Progressive hypocalcemia and neuromuscular signs such as seizures, tetany, ataxia, and weakness are seen as a result of decreased neuron membrane stability. Cardiopulmonary signs of hypocalcemia include bradycardia and panting, associated with muscular weakness (diaphragm) and anxiety.[18] A rare sign of hypocalcemia is posterior lenticular cataracts.[16]

Causes of hypocalcemia include hypoparathyroidism, iatrogenic (postthyroidectomy), chronic, and acute renal failure, acute pancreatitis, hypoalbuminemia, puerperal tetany (eclampsia), ethylene glycol intoxication, intestinal malabsorption, phosphate-containing enemas, toxins or drugs (piperazine), and nutritional secondary hyperparathyroidism. Endocrine causes of hypocalcemia include hyperadrenocorticism and hypoparathyroidism.

Laboratory Findings and Electrocardiographic Signs of Hypocalcemia

Serum calcium may be affected by laboratory error (lipemia and ethylenediaminetetraacetate), age of the animal (young and growing animals have higher values), acid-base status (alkalosis decreases ionized calcium and acidosis increases it), species, and plasma protein concentrations (hypoalbuminemia may cause decreased total serum calcium). In general, serum calcium concentrations in excess of 12 mg/dL should warrant an investigation and calcium over 14 mg/dL is considered a metabolic emergency.

Table 1
Vitamin D Preparations

Vitamin D Preparation	Dose	Maximal Effect	Size
1,25-Dihydroxycholecalciferol (active vitamin D_3, calcitriol)	0.03–0.06 mcg/kg/d	1-4 d	0.25 and 0.5 μg capsules, 1.0 μg/mL oral solution, 1 or 2 mcg/mL injectable
Ergocalciferol (vitamin D_2)	I: 4000-6000 U/kg/d M: 1000-2000 U/kg/d/wk	5-21 d	25,000 and 50,000 U capsules 8000 U/mL syrup

Abbreviations: I, Initial; M, maintenance.

Although several formulas for "correction" of serum calcium have been developed, a better approach is to measure the ionized form of calcium with pH species-specific correction.[5] Ionized calcium concentrations should be in the range of 1.25-1.45 mmol/L. The classic biochemical changes in animals with primary hypoparathyroidism include hypocalcemia (both total and ionized) and hyperphosphatemia.[18] Electrocardiographic signs of hypocalcemia may include sinus bradycardia with wide T waves, T-wave alternans, and prolongation of the QT and ST segments.[6]

Hypoparathyroidism

Primary hypoparathyroidism in dogs appears to be an immune-mediated disorder.[16,18,19] In cats, hypoparathyroidism is usually iatrogenic and secondary to damaged parathyroid glands during thyroidectomy for hyperthyroidism.[20] Uncommonly, cats may develop immune-mediated parathyroiditis.[17] In dogs, toy poodles, German shepherd dogs, Labrador retrievers, Terriers, St. Bernards, and Miniatures Schnauzer are predisposed. In dogs, there is a female predilection and in cats a male predisposition.[16,21,22]

Primary hypoparathyroidism is diagnosed by means of an intact PTH assay. Serum or plasma PTH concentrations should be measured on a freshly drawn morning sample in a fasting animal.[18] Handling of the sample is crucial to an appropriate diagnosis because PTH may degrade if subjected to warm temperatures.[4] Intact PTH refers to the entire 85–amino acid sequence of PTH; this is measured in a double-antibody "sandwich" assay in most endocrine laboratories that perform PTH measurement. For the diagnosis of primary hypoparathyroidism, the sample should be analyzed for both ionized calcium and intact PTH. Low ionized calcium (< 1.25 mmol/L) and low (< 2 pmol/L) or low normal (inappropriate in the presence of low ionized Ca) intact PTH concentrations are diagnostic for hypoparathyroidism.[4]

Treatment of Hypoparathyroidism

Treatment of hypocalcemia results in rapid resolution of clinical signs. IV calcium chloride or calcium gluconate is required to immediately resolve tetany and seizures.[22] Calcium chloride contains more calcium per unit volume; however, perivascular injection can result in calcinosis cutis and severe tissue trauma. Calcium gluconate has the advantage of not being as irritating when injected outside the vein; however, a larger volume must be administered to achieve the same effect. The dosage of IV calcium is 5-15 mg of calcium/kg over a 10- to 30-minute period. Patient response should dictate the final dose of calcium while the patient is monitored using an electrocardiogram for cardiovascular abnormalities such as bradycardia, ventricular premature complexes/contractions, or shortening of the QT interval. Maintenance of normal serum and ionized calcium can be achieved via SQ injections of diluted 10% calcium gluconate q 4-6 hours. The same dose used previously to control tetany intravenously should be diluted in an equal volume of saline before administering subcutaneously. However, caution should be exercised in small dogs and cats as calcinosis cutis has been observed in animals receiving diluted 10% calcium gluconate subcutaneously, particularly if the animal is also hyperphosphotemic.[23] The SQ dose interval should be gradually increased

Table 2
Calcium Preparations

Calcium Salt	Dose of Elemental Calcium	Available Calcium	Size Available (convert to elemental calcium)
Calcium carbonate	Canine: 1-4 g/d Feline: 0.5-1 g/d	40%	Tablets: 500, 600, 650, 1250, and 1500 mg Capsules: 1250 mg Oral suspension: 250 mg/mL
Calcium gluconate	Canine: 1-4 g/d Feline: 0.5-1 g/d	10%	Tablets: 500, 650, and 975 mg Chewable tablets: 500 mg Capsules: 500 and 700 mg Powder for suspension: 70 mg/mL
Calcium acetate	Canine: 1-4 g/d Feline: 0.5-1 g/d	25%	Tablets, gelcaps, and capsules: 667 mg
Calcium citrate	Canine: 1-4 g/d Feline: 0.5-1 g/d	21%	Tablets: 950 and 1150 mg Capsules: 850 and 1070 mg Powder for oral suspension: 725 mg/ml
Calcium glubionate	Canine: 1-4 g/d Feline: 0.5-1 g/d	30%	Syrup: 360 mg/mL

to 12-hour intervals as oral vitamin D and calcium take effect and until serum calcium concentration remains stable (> 8 mg/dL).

Long-term treatment of hypoparathyroidism consists of therapy with synthetic 1,25-dihydroxycholecalciferol (calcitriol), ergocalciferol (vitamin D2), and oral calcium (Tables 1 and 2).[18] The most convenient form of vitamin D therapy is vitamin D_3 or calcitriol. The advantage of calcitriol is that if hypercalcemia occurs, it will resolve within 48 hours of discontinuation of the drug; however, a recent study showed no difference in response based on the type of vitamin D therapy prescribed.[18] The standard dose of 0.03-0.06 μg/kg/day for dogs and slightly lower for cats. A short-term course of calcitriol at a dosage of 0.25 μg can be given per os (PO) q 48 hours in cats following surgical thyroidectomy to prevent hypocalcemia caused by inadvertent parathyroid gland damage. Oral calcium carbonate may be given at a dosage of 1-4 g/day and provides approximately 40% bioavailable elemental calcium; therefore, a 1000 mg tablet would contain 400 mg of elemental calcium. A small dog would require approximately 1250 mg of calcium carbonate per day.

Other Endocrine Causes of Calcium Disturbances

Medullary thyroid tumors (calcitonin positive) have been sporadically reported in dogs[24]; most often, these tumors occur secondary to MEN type 1[25] (concurrent pituitary, parathyroid, and pancreatic adenomas) and MEN type-2A (pheochromocytoma, C-cell hyperplasia, and parathyroid hyperplasia).[26] Increased serum calcium concentrations can occur in cats with hyperthyroidism and cats with concurrent adenomas of the thyroid and parathyroid glands.[27,28] Hypercalcemia secondary to congenital hypothyroidism is the result of decreased renal clearance and increased GI absorption of calcium. Hyperadrenocorticism may be associated with disturbed calcium metabolism, adrenal secondary hyperparathyroidism (increased PTH and normal ionized calcium), dystrophic calcification of the lungs and skin (calcinosis cutis), and calcium oxalate urolithiasis.[29,30]

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