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Renal Secondary Hyperparathyroidism in Dogs

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Abstract: *The parathyroid glands secrete parathyroid hormone (PTH), which is important for maintaining calcium homeostasis. Parathyroid gland hyperplasia and subsequent hyperparathyroidism can occur secondary to chronic renal failure in dogs, resulting in significant alterations in calcium metabolism. Renal secondary hyperparathyroidism is a complex, multifactorial syndrome that involves changes in circulating levels of calcium, PTH, phosphorus, and 1,25-dihydroxycholecalciferol (calcitriol). An increased PTH level can have deleterious effects, including soft tissue mineralization, fibrous osteodystrophy, bone marrow suppression, urolithiasis, and neuropathy. Dietary phosphorus restriction, intestinal phosphate binders, and calcitriol supplementation may slow the progression of renal disease and decrease PTH concentrations in animals with secondary hyperparathyroidism; however, the prognosis for these animals is guarded to poor.*

At a Glance

The four canine parathyroid glands are embedded in the poles of the two lobes of the thyroid gland, although they share no anatomic or physiologic connections with the thyroid gland. The main function of the parathyroid glands is to maintain calcium metabolism in the body. In response to decreasing levels of serum ionized calcium (iCa), chief cells in the parathyroid gland secrete parathyroid hormone (PTH). PTH acts on the bones, kidneys, and, indirectly, intestinal mucosa to elevate the serum calcium level.[1,2]

Patients with parathyroid hyperplasia and hyperparathyroidism secondary to chronic renal failure (CRF) have significant alterations in calcium metabolism[2,3] as well as changes in circulating levels of PTH, phosphorus, and 1,25-dihydroxycholecalciferol (calcitriol). The diagnosis, treatment, and prevention of renal secondary hyperparathyroidism are important because excess PTH may complicate treatment and cause progression of renal disease in dogs. This article reviews the normal physiology and metabolism of calcium as they relate to the pathogenesis, diagnosis, and treatment of renal secondary hyperparathyroidism.

Importance of Calcium

The control of calcium metabolism is important because calcium plays an integral role in many physiologic processes. Serum calcium must be maintained in a narrow range for normal nerve and muscle function, heart muscle contraction, cell membrane stability and linkage, coagulation, and, to a small degree, structural integrity of bones and teeth. Calcium in the extracellular fluid helps regulate the cellular functions of several organs, including the kidneys, thyroid C cells, and parathyroid glands. Calcium ions also serve as messengers, conveying signals from cell surfaces into cells.[3]

Calcium Distribution

Most calcium (99%) is found in bone in the form of hydroxyapatite crystals, which contain phosphate, water, and calcium.[1,2] Intracellular calcium accounts for most of the remaining calcium in the body. In inactive cells, the intracellular iCa level is low because most calcium is bound to protein or contained in the mitochondria or endoplasmic reticulum. As cell activity increases, so does the intracellular iCa

QuickNotes

Serum ionized calcium, not total calcium, should be measured in dogs with chronic renal failure to diagnose and monitor changes in the calcium level.

level. The smallest pool of calcium in the body is the extracellular fluid component, which comprises complexed calcium (bound to phosphate, sulfate, bicarbonate, citrate, and lactate), iCa, and protein-bound calcium. Extracellular iCa is the most important factor in controlling the calcium serum concentration.[1,2]

Regulation of Calcium in the Body

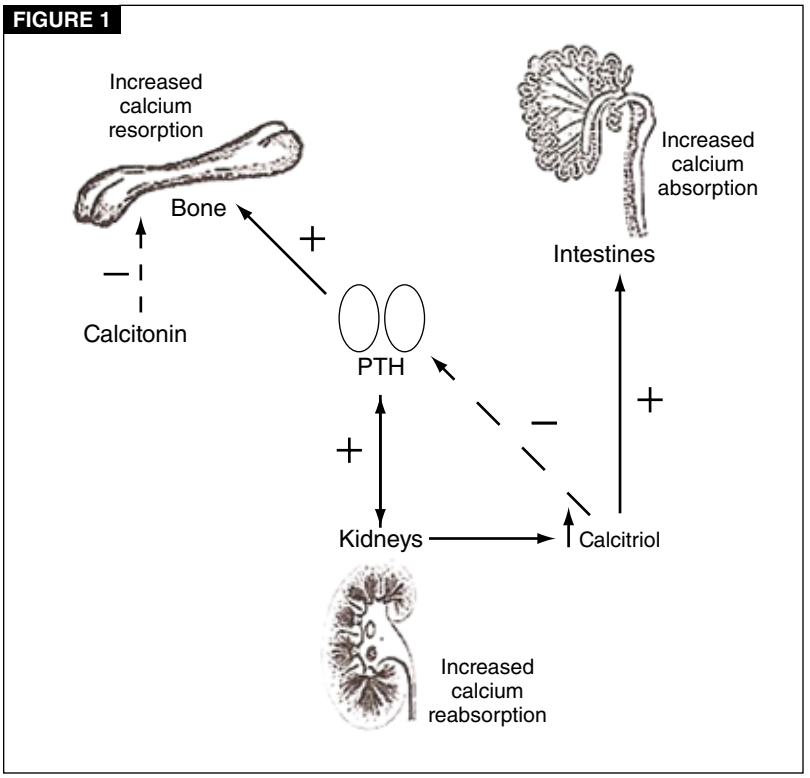
Normal calcium homeostasis is maintained principally by the actions of three hormones: PTH, calcitriol, and calcitonin (**FIGURE 1**). These hormones control the movement of calcium between the extracellular fluid, gastrointestinal tract, kidneys, and bones. Phosphorus is also an important regulator of calcium.

Parathyroid Hormone

The serum calcium level is monitored by specific membrane calcium receptors on the surface of the chief cells of the parathyroid gland. PTH is synthesized and secreted by these cells in response to a low serum iCa level. Increased PTH secretion leads to an increase in serum concentrations of total calcium and iCa and a decrease in the serum phosphate concentration. If the serum calcium level is chronically decreased, such as in animals with renal failure or those that are pregnant or lactating, hyperplasia of the parathyroid glands occurs.[3] The enlarged glands are more sensitive to small reductions in the calcium level and secrete PTH more efficiently.

PTH acts on the kidneys to increase the serum calcium level by increasing calcium reabsorption from the renal proximal tubules.[1,2] It acts on bone tissue to increase calcium resorption from the bone matrix to elevate the serum calcium level, principally by stimulating osteoclasts, which digest bone matrix and increase the calcium ion level in the matrix fluid. Calcium ions are then transported from the bone fluid to the extracellular fluid via an extensive membrane system formed by the processes of osteocytes and osteoblasts.[1,3] PTH indirectly increases intestinal absorption of calcium and phosphorus through the conversion of calcidiol to calcitriol in the proximal renal tubules.[2]

FIGURE 1



Hormonal regulation of calcium homeostasis. Normal calcium homeostasis is maintained principally by the actions of parathyroid hormone (PTH), calcitriol, and calcitonin. These hormones control the movement of calcium between the extracellular fluid, gastrointestinal tract, kidneys, and bones. Positive feedback (+) is indicated by the solid lines; negative feedback (–) is indicated by the dashed line. (Adapted from Polzin DJ, Osborne CA, Ross S. Chronic renal failure. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine Diseases of the Dog and Cat.* 6th ed. St Louis: Elsevier; 2005:1756-1785.)

Calcitriol

Dogs ingest vitamin D (calciferol) in their food, and it is absorbed from the intestines. Calciferol is hydroxylated in the liver to produce 25-hydroxyvitamin D (calcidiol), which is further hydroxylated to calcitriol in the kidneys.[2] In response to hypocalcemia, PTH is secreted from the parathyroid glands and stimulates the synthesis and secretion of calcitriol by the kidneys. Calcitriol acts directly on enterocytes to increase intestinal absorption of calcium and phosphorus. In the kidneys, calcitriol increases reabsorption of phosphorus and calcium from the glomerular filtrate. It also exerts negative feedback on the kidneys to inhibit the production of more calcitriol and on the parathyroid glands to decrease PTH synthesis and secretion when the serum calcium level is high.[1–3]

Calcitonin

Calcitonin is secreted by the parafollicular C cells of the thyroid gland in response to increases in serum calcium. It acts on bone tissue to decrease the serum calcium level by

stimulating osteoblasts to increase calcium absorption and deposition in the skeleton and inhibiting osteoclasts to decrease bone resorption of calcium.[1] In a healthy animal, the action of calcitonin is less important than that of PTH for minute-to-minute regulation of serum calcium. However, it is important in growing, pregnant, and lactating animals, in which it protects the bones from excess calcium loss.[1]

Phosphorus

In a healthy animal, PTH acts on the kidneys to increase renal excretion of phosphate ions and reabsorption of serum calcium, thereby increasing the serum calcium level.[1,2] Decreases in serum phosphate lead to an increase in extracellular calcium.[3] Sudden elevations in extracellular phosphate have been shown to directly stimulate PTH secretion in vivo.[4] However, no clinical studies have yet been done to determine whether acute elevations in phosphate have an effect on PTH secretion in animals with conditions leading to chronic phosphate retention. Dogs fed diets high in phosphorus and low in calcium can develop nutritional secondary hyperparathyroidism. These dogs are typically young and fed a predominantly meat diet.[1,3]

Renal Secondary Hyperparathyroidism

Parathyroid gland hyperplasia and hyperparathyroidism can occur secondary to CRF. The accepted explanation of the pathogenesis of this syndrome involves the kidneys' progressive inability to excrete phosphorus[3,5] (**FIGURE 2**). Dogs with CRF have a progressive loss of nephrons and a decreased glomerular filtration rate (GFR). The reduced GFR leads to increases in serum concentrations of substances that are normally filtered from the blood by the kidneys, including phosphate. As the serum phosphate concentration increases, the iCa level decreases, stimulating the release of PTH. Because the serum phosphate level remains high, the parathyroid glands are chronically stimulated to increase the serum calcium level, leading to parathyroid hyperplasia.

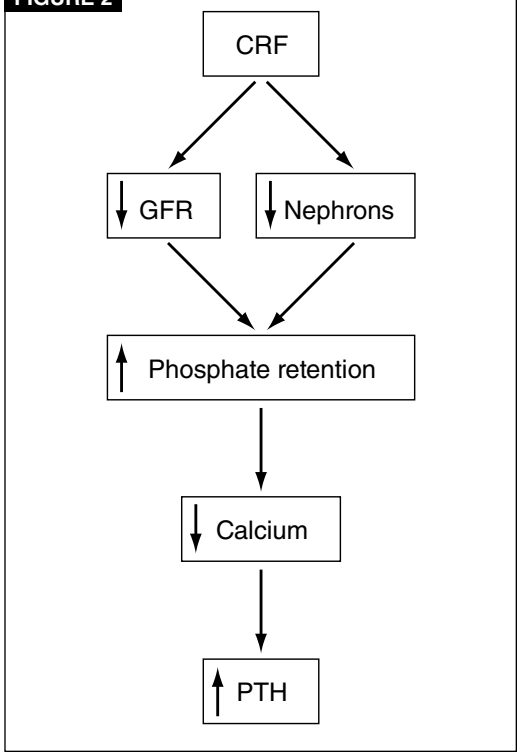
A calcitriol deficit in may also explain renal secondary hyperparathyroidism[3,5,6] (**FIGURE 3**). Along with severe electrolyte abnormalities, a calcitriol deficit may occur in CRF secondary to decreased synthesis from damaged renal proximal tubules. This deficit precedes the increase in the serum phosphate level. Extracellular iCa subsequently decreases due to reduced intestinal absorption of calcium, which is mediated by calcitriol. Because calcitriol acts directly on the parathyroid glands to regulate PTH secretion, a decrease in calcitriol also leads to a lack of negative feedback and a further increase in the PTH level. This mechanism may coexist with decreased renal phosphorus excretion.

Other factors that may contribute to the development of hyperparathyroidism in CRF include alterations in the set point for the response of the parathyroid glands to calcium and decreased breakdown of PTH by the diseased kidneys.[2]

Chronic Renal Failure and Calcium

Unlike primary hyperparathyroidism, in which the parathyroid glands function autonomously and lead to a high total serum calcium level secondary to increased production of calcitriol and calcium absorption from the gut, total

FIGURE 2

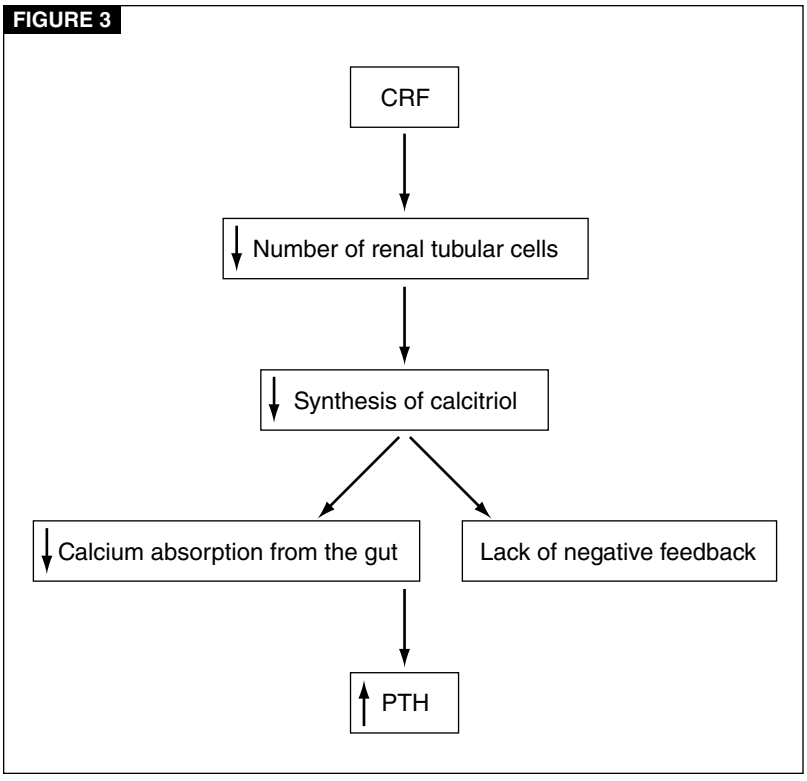


The phosphate theory of renal secondary hyperparathyroidism. With chronic renal disease, a decreased glomerular filtration rate (GFR) leads to an increased serum phosphate concentration and a decreased iCa level, which stimulates the release of PTH.

*Quick*Notes

Ionized hypercalcemia is relatively uncommon in dogs with chronic renal failure because of concurrent hyperphosphatemia and decreased calcitriol synthesis by the kidneys.

FIGURE 3



Calcitriol deficiency and renal secondary hyperparathyroidism. Calcitriol deficit occurs in chronic renal disease secondary to decreased synthesis by damaged renal proximal tubules. Extracellular iCa subsequently decreases due to reduced intestinal absorption of calcium, which is mediated by calcitriol. A decrease in calcitriol also leads to a lack of negative feedback and a further increase in the PTH level.

*Quick***Notes**

Dogs with renal secondary hyperparathyroidism may present with lameness, pathologic fractures, or facial swelling due to bone demineralization and fibrous osteodystrophy of the jaw and long bones.

calcium concentrations in dogs with renal secondary hyperparathyroidism can be normal, elevated, or low.[3] Studies looking at calcium concentrations in dogs with CRF have mainly focused on the total calcium concentration. Hypercalcemia, based on total calcium levels, has been observed in approximately 10% of dogs with CRF, and the prevalence appears to increase with the severity of azotemia.[2,7,8]

In contrast to an elevated total calcium level, ionized hypercalcemia is relatively uncommon in dogs with CRF because of concurrent hyperphosphatemia and decreased calcitriol synthesis by the kidneys.[2,3] Early in renal disease, an elevated PTH level can maintain a normal serum phosphate level by increasing the amount of phosphate lost in the urine. However, as renal disease progresses, the kidneys cannot excrete enough phosphate to prevent hyperphosphatemia. Calcitriol synthesis also decreases with progressive loss of functional nephrons, leading to decreased calcium absorption from the gut.[9] Therefore, as renal disease progresses, the iCa concentration may be normal or low. However, ionized hypercalcemia can develop as a consequence of CRF or can contribute to renal azotemia by mineralizing renal tubules (nephrocalcinosis), decreasing GFR, altering renal blood flow, and impairing renal concentrating ability, leading to polyuria and polydipsia.[2,10] Treatment with calcium-containing phosphate binders or calcitriol supplementation can also lead to increased iCa.[2]

Measurement of total calcium is not a reliable assessment of calcium status in dogs with CRF.[11] The measured total calcium level has been shown to correlate poorly with the iCa level. A recent study[12] of serum iCa levels in dogs with CRF found that measurement of total calcium underestimated hypocalcemia, with 56% of the dogs diagnosed as hypocalcemic based on iCa levels and only 8% based on total calcium levels. Another study[11] of total calcium levels adjusted for albumin concentrations in dogs with CRF showed total calcium to underestimate hypocalcemia and overestimate hypercalcemia compared with iCa. Because of this variability, iCa, the most physiologically relevant form of calcium in the body, should be evaluated in dogs with CRF instead of total calcium. In-house blood analyzers are available to measure serum iCa.

Clinical Signs

With renal secondary hyperparathyroidism, serum calcitriol and iCa levels initially return to normal as a result of an increased serum PTH level. However, they can remain normal only if PTH secretion remains increased, which has deleterious effects on the body. As renal disease progresses, the kidneys synthesize and secrete less calcitriol and excrete less phosphorus. Hyperphosphatemia and decreased calcium absorption from the gut lead to a chronically increased PTH level. The resulting mobilization of calcium stores can lead to conditions such as fibrous osteodystrophy, bone marrow suppression, soft tissue mineralization, urolithiasis, and neuropathy.[2]

Bone demineralization occurs in progressive renal disease as osteoclastic activity increases to maintain normal calcium and phosphorus concentrations. The bones most vulnerable to demineralization are dental alveolar bone and the cancellous bone of the maxilla and

mandible.[13] Radiographs may reveal loss of the lamina dura around the teeth, decreased bone density, and soft tissue mineralization of the gastric mucosa or other tissues[14] (**FIGURE 4**). Symmetric swelling of the maxilla and mandible, a soft pliable mandible or "rubber jaw," pathologic fractures, and bone pain are all suggestive of fibrous osteodystrophies seen with renal failure. Affected dogs may present with lameness or a stiff gait. Because of the higher skeletal metabolic rates in growing animals, young dogs generally develop proliferative bone lesions, whereas generalized osteodystrophy and rubber jaw are more common in older dogs.[13] When the product of serum calcium and phosphate concentrations exceeds 60 to 70 mg/dL, soft tissue mineralization occurs,[2,6] predominantly in damaged tissue. In the kidneys, mineralization may cause further deterioration of renal function and worsen hyperphosphatemia and secondary hyperparathyroidism.

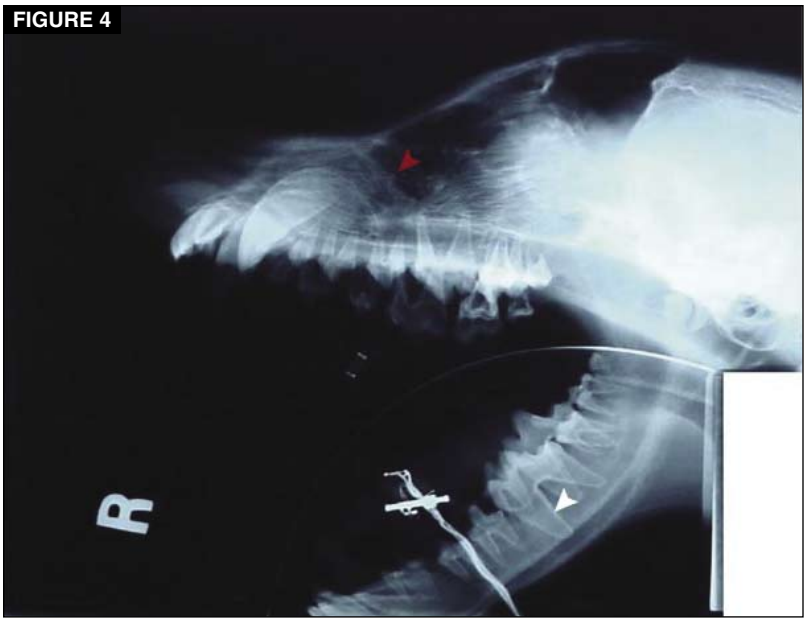
A thorough evaluation is necessary to help differentiate hypercalcemic animals with CRF and secondary hyperparathyroidism from those with another cause of hypercalcemia (**BOX 1**). A complete physical examination, thorough history, complete blood count, urinalysis, thoracic radiography, abdominal ultrasonography, and cervical ultrasonography to evaluate the parathyroid glands are recommended. On ultrasonography and gross examination of the parathyroid glands, dogs with primary hyperparathyroidism usually have a solitary adenoma, although they can have carcinoma or nodular hyperplasia, which may affect more than one gland.[3] Secondary hyperparathyroidism is characterized by diffuse parathyroid gland hyperplasia.[3,15] Dogs with primary hyperparathyroidism may have clinical signs similar to those in animals with secondary hyperparathyroidism from other causes, but their signs are generally subtle or absent compared with animals with primary renal failure (**TABLE 1**).

BOX 1

Causes of Hypercalcemia in Dogs

- Malignancy
  - Lymphosarcoma
  - Apocrine gland carcinoma of anal sac
  - Other malignancies (rare)
- Hypoadrenocorticism
- Chronic renal failure
- Primary hyperparathyroidism
- Hypervitaminosis D
- Hyperthyroidism (rare)
- Nutritional secondary hyperparathyroidism
- Granulomatous disease

FIGURE 4



Right lateral skull radiograph of a 7-month-old golden retriever with CRF secondary to renal dysplasia. Note the absence of the lamina dura around the tooth roots (*white arrowhead*) and thickening of the maxilla (*red arrowhead*).

Diagnostic Testing

Serum Ionized Calcium

Measurement of the serum iCa concentration can help distinguish between primary hyperparathyroidism and renal secondary hyperparathyroidism (**TABLE 2**). As previously discussed, the serum iCa level is usually high with primary hyperparathyroidism and normal to low with renal secondary hyperparathyroidism.

Changes in blood pH can affect the iCa level. An acidic pH increases the amount of iCa in a sample; an alkaline pH causes a decrease.[2] For in-house analysis, blood should be drawn and analyzed immediately to prevent the changes in pH that occur as a result of loss of carbon dioxide. For laboratory analysis, anaerobically obtained and stored serum is preferred because iCa and pH are more stable in serum than in heparinized or whole blood. Some

*Quick*Notes

Dietary phosphorus restriction and the use of phosphate binders can lower the serum phosphate level and, subsequently, the parathyroid hormone level, which has been shown to slow the progression of renal disease and extend the life of chronic renal failure patients.

blood analyzers mathematically manipulate the pH value and iCa concentration to yield an adjusted value, allowing samples to be obtained in a routine manner. Because differences exist between in-house analyzers, reference ranges for an individual analyzer should be established before use.[3]

Serum PTH

The serum PTH level is one of the most important diagnostic aids in dogs suspected of having parathyroid disease (**TABLE 2**). PTH is measured in serum by radioimmunoassay. Most human and veterinary laboratories currently use the two-site PTH assay system,[3] which depends on the production of two polyclonal antibodies that bind to intact PTH. Samples obtained for this assay should be stored and shipped frozen to prevent degradation of PTH. Serum collected with EDTA is adequate.[2]

It is important to evaluate serum PTH relative to serum total and iCa concentrations. In primary hyperparathyroidism, in which PTH secretion is not suppressed by an increased calcium concentration, the PTH level will remain normal to high in the presence of an elevated serum iCa level. In dogs with renal secondary hyperparathyroidism, the serum PTH level may be elevated, but serum iCa is usually normal to low. In general, dogs with hypercalcemia not related to parathyroid disease should have low to normal serum PTH levels.[2,16]

A recent study[17] demonstrated hyperparathyroidism secondary to hyperadrenocorticism in dogs. As in dogs with renal secondary hyperparathyroidism, serum PTH levels were elevated in these patients, but serum iCa was normal to low. Therefore, in patients with clinical signs of Cushing's disease, the adrenal and parathyroid glands should be evaluated in conjunction with the iCa level.

Serum Parathyroid Hormone-Related Protein

Parathyroid hormone-related protein (PTHrP) is a protein similar to PTH in structure and sequence. It is found in many types of cells (e.g., endocrine, central nervous system, mesenchymal, epithelial) and plays a key role in the development of hypercalcemia associated

*Quick***Notes**

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TABLE 1

Clinical Signs of Chronic Renal Failure and Primary Hyperparathyroidism in Dogs

System Affected	Signs of Chronic Renal Failure	Signs of Primary Hyperparathyroidism
Urinary	Polyuria/polydipsia Isosthenuria Urinary tract infection	Polyuria/polydipsia Urinary incontinence Dysuria Pollakiuria Hematuria Cystic calculi
Neuromuscular	Weight loss Poor body condition Lethargy Depression Dehydration	Listlessness Weakness Exercise intolerance Shivering Muscle wasting Stiff gait
Gastrointestinal	Vomiting Diarrhea Anorexia	Inappetence Vomiting Constipation
Cardiovascular	Hypertension	—

with malignancy.[2,3] In a hypercalcemic animal, measuring serum PTHrP can help distinguish between hypercalcemia due to primary hyperparathyroidism and hypercalcemia of malignancy. Serum PTHrP levels are elevated in animals with hypercalcemia of malignancy and should be undetectable in animals with hypercalcemia due to primary hyperparathyroidism (**TABLE 2**). However, this test alone cannot differentiate between renal secondary hyperparathyroidism and hypercalcemia of malignancy because animals with renal disease can have increased immunoreactivity to PTHrP fragments.[3] In a hypercalcemic patient, malignancy is usually diagnosed based on further diagnostic tests, such as aspiration of lymph node, liver, and spleen tissue; abdominal ultrasonography; and chest radiography. Therefore, serum assays for PTHrP are rarely indicated and should not be conducted in patients with renal disease.

Serum Calcitriol

Measurement of serum calcitriol can help distinguish between primary and secondary hyperparathyroidism (**TABLE 2**). Calcitriol levels are generally elevated in patients with primary hyperparathyroidism because of increased calcitriol production. They are decreased in patients with renal secondary hyperparathyroidism because of decreased renal production of calcitriol. Animals with vitamin D intoxication secondary to ingestion of cholecalciferol or ergocalciferol rodenticide, calcipotriene psoriasis medication, or plants that contain glycosides of calcitriol can present with hypercalcemia, hyperphosphatemia, and renal azotemia similar to animals with secondary hyperparathyroidism.[3] However, the hypercalcemia seen with vitamin D toxicosis is usually severe and rapid in onset, often escalating within 24 hours after ingestion.[2] A history of ingestion or sudden onset of clinical signs, such as vomiting, anorexia, tremors, or polyuria, can also help differentiate hypervitaminosis D from CRF. With vitamin D toxicosis, the PTH level should be normal to low and the serum calcitriol level elevated.[3] The serum level of 25-hydroxyvitamin D (calcidiol), a vitamin D metabolite, is elevated in cases of cholecalciferol or ergocalciferol rodenticide ingestion.[2]

Additional Diagnostics

A common cause of elevated serum total calcium is hypoadrenocorticism (Addison's disease). These animals are often azotemic, hyperphosphatemic, and significantly ill on presentation, similar to animals with CRF and vitamin D toxicosis. However, with Addison's, serum iCa and PTH levels are usually normal.[3] A diagnosis of hypoadrenocorticism should be confirmed or ruled out with an ACTH stimulation test.

Management

Phosphorus Restriction Therapy

While there is no cure for CRF, the progression of disease and development of second-

QuickNotes

Measurement of serum calcitriol can help distinguish between primary and secondary hyperparathyroidism.

TABLE 2

Expected Diagnostic Test Results for the Most Common Causes of Hypercalcemia

Serum Concentration Measured	Primary Hyperparathyroidism	Chronic Renal Failure	Malignancy	Vitamin D Toxicosis
Total calcium	↑	N, ↑, ↓	↑	↑
Ionized calcium	↑	N to ↓	↑	↑
Phosphorus	↓	↑	N	↑
Calcitriol	↑	N to ↓	N to ↓	↑
PTH	↑	↑	N to ↓	N to ↓
PTHrP	Absent	Absent to ↑	↑	Absent

N = normal, ↓ = decreased, ↑ = increased (Adapted from Schenck PA, Chew DJ, Nagode LA, Rosol TJ. Disorders of calcium: hypercalcemia and hypocalcemia. In: DiBartola SP, ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice.* 3rd ed. St. Louis: WB Saunders; 2006:122-194.)

ary hyperparathyroidism may be slowed by controlling the serum phosphate level. A low-phosphate diet should be instituted in animals with signs of renal failure. Clinical studies suggest that dietary phosphorus restriction may delay the progression of renal disease by dampening renal secondary hyperparathyroidism and preventing renal interstitial mineralization.[6] Studies in dogs have shown not only a decrease in serum phosphate and PTH but also an increased survival time in animals fed phosphorus-restricted diets compared with those fed an unrestricted diet.[18,19] Progression of renal failure may also be slowed, as suggested by a stabilized GFR and a lower serum creatinine concentration, in dogs fed phosphorus-restricted renal diets.[18,19]

In addition to feeding a phosphorus-restricted diet, administration of oral phosphate binders such as aluminum hydroxide (Amphojel; Wyeth Laboratories, Collegeville, PA), calcium carbonate, or sevelamer hydrochloride (RenaGel; Genzyme, Cambridge, MA) can help lower serum phosphate levels (**TABLE 3**). These drugs indirectly decrease the serum phosphate level by binding phosphates in the intestinal tract and preventing their absorption. Aluminum hydroxide is a better phosphate binder than calcium carbonate in the more acidic environment of the stomach. However, in the more alkaline environment of the intestines, calcium carbonate works equally well. Common adverse effects of phosphate binders include constipation and nausea. Also, hypercalcemia can develop when calcium-containing phosphate binders are used. This risk can be minimized by administering these agents with a meal to maximize the binding of calcium to phosphorus and thereby decrease calcium absorption.[20]

Sevelamer hydrochloride is a metal- and calcium-free polymer resin phosphate binder that works by binding phosphorus in exchange for chloride. It has been shown to reduce hypercalcemic episodes and subsequent vascular and renal calcification in people with CRF compared with calcium-containing phosphate binders.[21] There is some concern that the release of chloride ions with phosphate binding may create or worsen metabolic acidosis, with a subsequent decrease in the serum bicarbonate level. Newer forms of sevelamer contain carbonate instead of chloride to address this concern.[22] Studies comparing the efficacy of sevelamer and calcium-containing binders in controlling phosphorus levels have yielded mixed results.[23–25] Sevelamer is a more expensive drug and can cause gastrointestinal upset.[20] Specific clinical trials have yet to be performed in dogs.

Calcitriol Therapy

Lowering serum PTH levels in animals with CRF is important because it has been suggested that PTH itself may contribute to the progression of renal disease.[15] The use of phosphate binders and a reduction in dietary phosphorus intake usually lowers but does not always normalize an elevated serum PTH level. In animals with normal serum phosphate and normal to low calcium levels, calcitriol supplementation has been used to further decrease PTH concentrations. Calcitriol works by binding to specific receptors within parathyroid chief cells to block PTH synthesis and secretion. It may also restore a lower calcium set point, which further inhibits PTH secretion and prevents or reverses parathyroid gland hyperplasia.[26] Studies have shown that calcitriol supplementation lowers serum PTH levels and reduces the severity of secondary hyperparathyroidism in dogs with CRF.[5,26,27] It may also prolong survival time in dogs with stage III or IV kidney disease.[28]

Calcitriol has been shown to increase serum calcium and phosphorus levels; therefore, normal serum phosphate and calcium concentrations should be established before starting calcitriol therapy.[6,27,28] Calcitriol should be used with caution in combination with calcium-containing phosphate binders because of the increased risk of hypercalcemia. Human dialysis patients treated with calcitriol in combination with sevelamer hydrochloride or calcium carbonate have shown equal improvements in phosphorus levels and in parathyroid-induced

*Quick***Notes**

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TABLE 3

Available Oral Phosphate Binders and Recommended Dosages for Use in Dogs

Drug	Dosage
Aluminum hydroxide[5]	30–90 mg/kg/day PO with food
Calcitriol[21,25]	2.5 ng/kg PO once daily
22-Oxacalcitriol[23]	0.025–0.05 µg/kg PO once daily

bone disease. However, serum calcium levels increased in patients treated with calcitriol and calcium carbonate, whereas they remained unchanged in the group treated with calcitriol and sevelamer hydrochloride.[23]

It is hypothesized that calcitriol therapy should be initiated earlier in the course of CRF and secondary hyperparathyroidism in conjunction with a phosphorus-restricted diet.[6,27] Early intervention is important because the PTH level can be high even with mild azotemia.[6] Dogs with CRF usually present with clinical signs of illness such as anorexia, weight loss, vomiting, diarrhea, and dehydration and should be medically stabilized before starting calcitriol therapy. Stabilization therapy usually includes intravenous fluids to correct dehydration and reduce azotemia as well as antiemetics and histamine-receptor antagonists (H_2 blockers) to control vomiting. Use of antibiotics may be indicated by urine culture results. Dietary phosphorus restriction to lower the serum phosphate level should be started once the patient has regained an appetite.

Human formulations of calcitriol (Rocaltrol, Roche) contain too much calcitriol for use in small animals. These 250- and 500-ng capsules cannot be readily divided, and custom reformulation by a pharmacist has been recommended to obtain appropriate dosages for individual pets.[6,26] The current recommended dose for calcitriol in dogs is 2.5 ng/kg/day.[27]

Vitamin D Analogs

Because of the risk of hypercalcemia with calcitriol supplementation, several vitamin D analogs, including 22-oxacalcitriol (OCT), have been studied as alternatives to calcitriol in CRF patients. These analogs are thought to suppress calcitriol and PTH levels but with a lower occurrence of hypercalcemia.[29] Clinical trials in human dialysis patients receiving intravenous OCT showed decreases in serum PTH and increases in serum calcium to be highly dose dependent.[30] Experimental studies in dogs have shown that both daily oral and intermittent intravenous OCT administration lower serum PTH levels without elevating iCa concentrations.[31] However, despite some promising experimental studies, further clinical trials need to be done to prove the relative safety and efficacy of OCT compared with calcitriol.

Monitoring Response to Treatment

PTH, serum calcium, phosphorus, and creatinine levels should be closely monitored during treatment with calcitriol. Serum calcium and phosphorus levels should be measured once weekly for 2 weeks after initiating therapy and then at least once a month for the first 6 months of therapy. If hypercalcemia develops, calcitriol supplementation should be discontinued. Only after a normal serum calcium level is restored should supplementation be reinstituted at a lower dose. Serum PTH and creatinine levels should be measured 4 to 6 weeks after initiating therapy to document calcitriol efficacy and to monitor the progression of renal disease. If the PTH level is not suppressed by 4 to 6 weeks, the dose of calcitriol can be cautiously increased or therapy can be discontinued.[5] The owner and veterinarian should monitor the patient's clinical signs, including changes in appetite, thirst, urination, vomiting, diarrhea, and energy level, for evidence of progression of renal or parathyroid disease.

Conclusion

Although renal secondary hyperparathyroidism is rare, it is an important disease to diagnose and treat. Excess PTH may complicate the treatment of CRF and cause progression of renal disease in dogs. Early diagnosis of renal disease and disturbances in calcium and phosphorus homeostasis are important to prevent the development of hyperparathyroidism. The diagnosis of secondary hyperparathyroidism may be complicated if the serum calcium level is elevated. Physical examination, historical findings, and comprehensive and specific diagnostics to rule out primary hyperparathyroid disease and other causes of hypercalcemia are important for making a diagnosis of renal secondary hyperparathyroidism.

Dietary phosphorus restriction and the use of phosphate binders can lower serum phosphate and, subsequently, PTH levels, which has been shown to slow the progression of renal disease and extend the length of life of CRF patients. It is also important to treat the clinical signs of renal failure with appropriate fluid therapy, antiemetics, and H_2 blockers and antibiotics if indicated. Therapy with calcitriol may decrease serum PTH levels further and may extend the quality and length of life in patients with renal secondary hyperparathyroidism.

During treatment with calcitriol, it is important to monitor serum calcium, phosphorus, creatinine, and PTH levels. There is a risk of hypercalcemia with calcitriol supplementation, and calcitriol should be used with caution in combination with calcium-containing phosphate binders. Owners and veterinarians should monitor clinical signs associated with progression of renal disease and hyperparathyroidism, such as appetite, thirst, urination, and vomiting, to assess treatment efficacy. Even with early diagnosis and treatment, CRF is a progressive and irreversible disease for which there is no cure, and the prognosis for animals with renal hyperparathyroidism is guarded to poor. **C**

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3 CE CREDITS

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1. **Before starting treatment with calcitriol, which of the following should be done?**
   - **a.** correct dehydration with intravenous fluids
   - **b.** control vomiting and nausea with antiemetics and H_2 blockers
   - **c.** start a phosphorus-restricted diet
   - **d.** all of the above

2. **_____ is not a hormone involved in the control of calcium homeostasis.**
   - **a.** Calcitriol
   - **b.** Cortisol
   - **c.** PTH
   - **d.** Calcitonin

3. **What diagnostic test(s) can be done to differentiate CRF from other causes of hypercalcemia?**
   - **a.** serum lactate measurement
   - **b.** lymph node aspiration
   - **c.** serum calcitriol measurement
   - **d.** b and c

4. **Which mechanism(s) may cause hyperparathyroidism secondary to CRF?**
   - **a.** decreased renal calcitriol synthesis
   - **b.** increased serum phosphate level
   - **c.** high serum protein levels
   - **d.** a and b

5. **An elevated serum PTH level can cause**
   - **a.** pathologic fractures.
   - **b.** cardiac arrhythmias.
   - **c.** symmetric swelling of the maxilla and mandible.
   - **d.** a and c

6. **Which statement regarding the PTH radioimmunoassay test is correct?**
   - **a.** Dogs with hypercalcemia unrelated to parathyroid disease always have decreased PTH levels.
   - **b.** The PTH level should be evaluated relative to total calcium and iCa concentrations.
   - **c.** Only dogs with primary hyperparathyroidism have elevated PTH levels.
   - **d.** PTH concentrations can be measured on an in-house blood analyzer.

7. **_____ generally causes an increase in the serum calcitriol level.**
   - **a.** Primary hyperparathyroidism
   - **b.** Hypothyroidism
   - **c.** CRF
   - **d.** Hyperadrenocorticism

8. **Which therapy is used to treat renal secondary hyperparathyroidism?**
   - **a.** dietary phosphorus restriction
   - **b.** oral calcium binders
   - **c.** calcidiol supplementation
   - **d.** parathyroid gland ablation

9. **_____ is a potential adverse effect of calcitriol therapy.**
   - **a.** Hepatic failure
   - **b.** Gastric ulceration
   - **c.** Hypercalcemia
   - **d.** Muscle weakness

10. **Serum _____ should be monitored during treatment with calcitriol.**
    - **a.** calcium
    - **b.** phosphorus
    - **c.** creatinine
    - **d.** all of the above