SECTION 5 | PARATHYROID GLAND

CHAPTER 15

Hypercalcemia and Primary Hyperparathyroidism

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CHAPTER CONTENTS

CALCIUM REGULATION AND HYPERCALCEMIA

CALCIUM FUNCTION AND CONTROL

Overview

Calcium serves two principal physiologic functions. First, insoluble calcium salts (primarily hydroxyapatite) provide the structural characteristics that allow bones to protect internal organs and bear weight. Second, soluble calcium ions in the extracellular fluid (ECF) and cytosol are critically important for a myriad of biochemical intracellular and extracellular functions. For example, calcium is necessary for various enzymatic reactions, transport of substances across membranes and membrane stability, blood coagulation, nerve conduction, neuromuscular transmission, muscle contraction, smooth muscle tone, hormone secretion, bone formation, hepatic glycogen metabolism, cell growth, and cell division (Rasmussen, 1989; Brown et al, 1995; Rosol et al, 2000; Wysolmerski and Insogna, 2012). Approximately 1% of total body calcium is contained within the ECF and soft tissue, 99% is found in bone. The skeleton, therefore, is a reservoir of available calcium when ECF concentrations decline, and it acts as a storehouse for excess calcium. About 50% of circulating calcium (0.5% of total body calcium) is bound to serum proteins, primarily albumin, and to a lesser extent, complexed with anions, such as citrate or sulfate. The remaining 50% is in the ionized biologically active form (Fig. 15-1).

The concentration of serum ionized calcium (iCa) and the calcium content of skeleton is maintained within narrow limits by a complicated homeostatic system involving multiple organs and several hormones. The organs involved in the regulation of calcium metabolism are the parathyroid glands, kidneys, skeleton, and gut (Fig. 15-2). The hormones include parathyroid hormone (PTH), vitamin D, and PTH-related protein (PTHrP). The actions of PTH on bone resorption, renal calcium excretion, and metabolism of vitamin D are responsible for maintaining homeostasis (Fig. 15-3; Table 15-1). Abnormalities in any of these organs, hormones, or receptors may cause disturbances in calcium metabolism that can lead to hypercalcemia or hypocalcemia.

Parathyroid Hormone

PTH is an 84–amino acid, single-chain polypeptide, synthesized, stored, and secreted by chief cells in the four parathyroid glands (Fig. 15-4). PTH is synthesized initially as a single-chain, preproparathyroid peptide. The 25 residue presequence is cleaved twice to generate the biologically active full-length protein (PTH 1-84). PTH has a half-life of minutes in circulation and is degraded in the liver and kidneys. The degradative process releases carboxy-terminal (C-terminal) fragments of PTH into the circulation. In

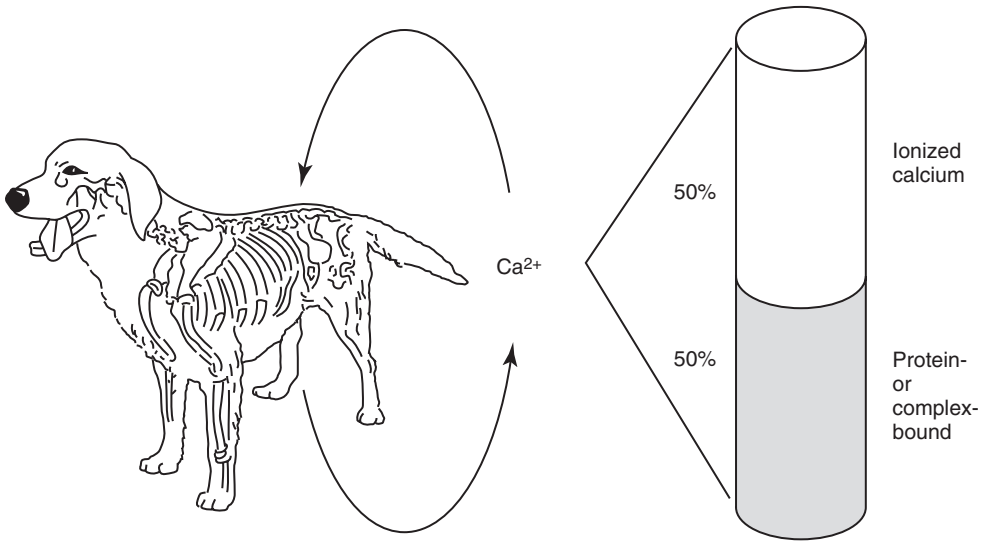


FIGURE 15-1 Skeletal calcium acts as a reservoir so that calcium can be stored or mobilized, depending on need. (From Skelly BJ: Hyperparathyroidism. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology,* ed 4, Gloucester, England, 2012, British Small Animal Veterinary Association; used with permission.)

response to subtle hypercalcemia, proteases found within parathyroid secretory granules digest the amino-terminal portions of PTH, leaving the inactive C-terminal fragments to be secreted. Thus, biologically inactive C-terminal fragments, known to accumulate in the circulation of patients with chronic kidney disease (CKD), are a product of both parathyroid secretion and peripheral metabolism of full-length PTH (Wysolmerski and Insogna, 2012).

PTH secretion is regulated by the extracellular iCa concentration. A steep inverse sigmoidal relationship exists between PTH secretion and calcium concentration. The steep portion of this curve encompasses the normal physiologic range for extracellular calcium, over which small changes in serum concentrations of iCa elicit large changes in the rate of PTH secretion. Increased serum calcium concentrations inhibit secretion of PTH and decreased concentrations stimulate PTH synthesis and secretion (Aurbach et al, 1985; Brown et al, 1999; see Fig. 15-3). For parathyroid cells to regulate PTH secretion, they must sense changes in extracellular calcium concentration. This is accomplished through a G protein-coupled receptor (GPCR) known as the *calcium-sensing receptor (CaR).* Calcium binding to the CaR activates downstream signaling pathways, primarily induction of phospholipases, and intracellular calcium transients (Stewart, 2004). This, in turn, suppresses PTH secretion. In addition to parathyroid cells, the CaR is prominently expressed in kidneys, where they regulate the calcium handling by renal tubules. Subtle hypercalcemia activates the CaR, suppressing renal calcium reabsorption. In this manner, hypercalcemia directly promotes calcium excretion in urine, and hypocalcemia directly enhances its reabsorption (Wysolmerski and Insogna, 2012; see Fig. 15-2).

The actions of PTH are mediated by the type 1 PTH/PTHrP receptor (PTH1R). The calcium-regulating effects of the receptor appear to be primarily the result of activating adenylyl cyclase. During usual conditions, this receptor is activated equally well by the amino-terminal portions of PTH and PTHrP (see later). The PTH1P is most abundant in bone and kidney, where it mediates the systemic functions of PTH. However, PTH1P is also expressed in cells throughout the body, where it serves as a PTHrP receptor. In this capacity, PTH1P has important functions during bone development, and it mediates many of PTHrP's effects on

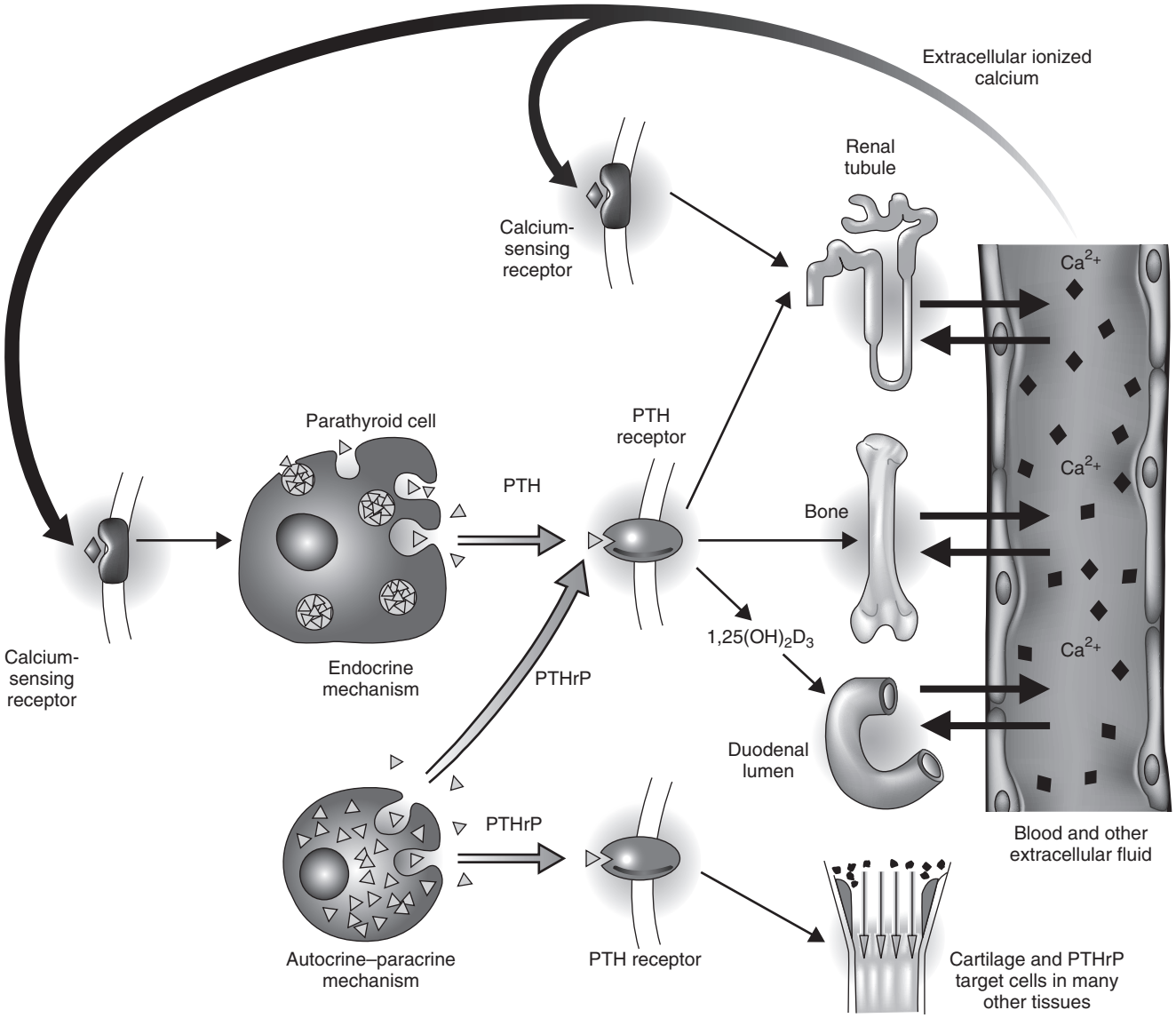


FIGURE 15-2 The parathyroid axis. The synthesis of parathyroid hormone *(PTH)* and parathyroid hormone–related protein *(PTHrP)* is shown on the left and the target sites on the right. Both act by means of the same receptor (also called the *type 1 receptor*). Negative feedback of 1,25-dihydroxyvitamin D_3—*$1,25(OH)_2D_3$*—is not shown. (Modified from Marx SJ: Hyperparathyroid and hypoparathyroid disorders, *N Engl J Med* 343:1863, 2000.)

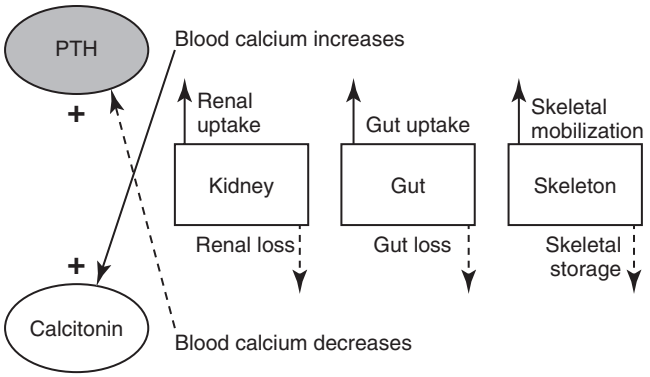


FIGURE 15-3 Calcium homeostasis. The release of parathyroid hormone *(PTH)* causes increased uptake of calcium in the kidney and gut and mobilization from the skeleton. (From Skelly BJ: Hyperparathyroidism. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology,* ed 4, Gloucester, England, 2012, British Small Animal Veterinary Association; used with permission.)

TABLE 15-1 **APPROXIMATE REFERENCE INTERVALS FOR SERUM CONCENTRATIONS OF TOTAL CALCIUM, IONIZED CALCIUM, PARATHYROID HORMONE, PARATHYROID HORMONE–RELATED PROTEIN, AND CALCITRIOL**

	DOG	CAT
Total calcium (TCa)		
(mg/dL)	9.0-11.7	8.0-10.5
(mmol/L)	2.2-2.9	2.0-2.6
Ionized calcium (iCa)		
(mg/dL)	4.6-5.6	4.5-5.5
(mmol/L)	1.1-1.4	1.1-1.4
Parathyroid hormone (PTH) (variability among laboratories)		
(pmol/L)	0.5-5.8	0-4
(pg/mL)		6-16*
Parathyroid hormone–related protein (PTHrP)		
(pmol/L)	< 2	< 2
1,25-Dihydroxyvitamin D_3 (calcitriol) (pg/mL)		
Adults	20-50†	20-40†
10 to 12 weeks old (pg/mL)	60-120†	20-80†

*From Pineda et al.: Feline parathyroid hormone: validation of hormonal assays and dynamics of secretion, *Domest Anim Endocrinol* 42:256, 2012.
†From Rosol et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice,* ed 2, Philadelphia, 2000, WB Saunders, pp. 108-162.

cellular proliferation, apoptosis, and differentiation (Wysolmerski and Insogna, 2012).

The amino acid sequence of PTH is known for humans, dogs, cows, pigs, rats, chickens, and cats. Based on immunologic reactivities, most mammals appear to have similar amino-terminal portions of the molecule (Toribio et al, 2002). It is recognized that the amino terminal of PTH binds to CaR, whereas the carboxyl

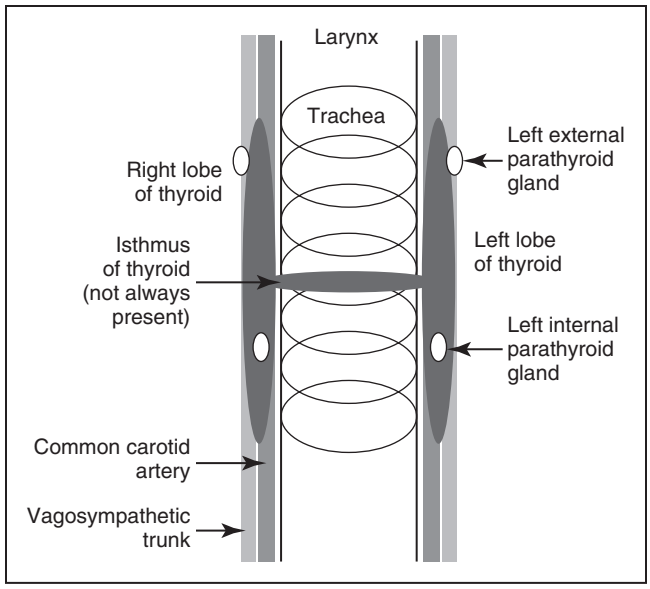


FIGURE 15-4 Schematic representation of the anatomical position of the parathyroid glands. (From Skelly BJ: Hyperparathyroidism. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology,* ed 4, Gloucester, England, 2012, British Small Animal Veterinary Association; used with permission.)

terminus is thought to serve only as a guide for PTH through the cellular secretory pathway (Orloff and Stewart, 1995). A synthetic 1-34 amino-terminal fragment is biologically active, but relatively minor modifications, especially at the first two residues, can completely abolish this effect (Marx, 2000).

Parathyroid Hormone–Related Protein

PTHrP was discovered in the course of exploring the pathogenesis of humoral hypercalcemia of malignancy (HHM). PTH and PTHrP share structural features suggesting that they arose from a common ancestor: in people eight of the first 13 amino-terminal amino acids are identical. This amino-terminal homology allows both PTH and PTHrP to bind to the receptor PTH1P with equal affinity, thereby activating the same pathways. PTH is made only in parathyroid glands and is secreted into the circulation. PTHrP is synthesized in many cells, is secreted locally, and acts in a paracrine or autocrine fashion to activate PTH1P on neighboring cells. In veterinary medicine, PTHrP is best recognized as having a central role in the pathogenesis of HHM and is used as a "tumor marker" in both dogs and cats (Williams et al, 2003; Henry, 2010). Since its discovery in the early 1980s, assay of PTHrP has been used in the evaluation of hypercalcemic patients in whom cancer is a possibility (Philbrick et al, 1996).

Vitamin D

Inactive vitamin D is produced in skin and is available in some foods. It appears that dogs are less able to synthesize vitamin D in the skin than are other mammals (Gross et al, 2000; Mellanby et al, 2005). Thus, dogs have a greater requirement for dietary vitamin D. PTH stimulates activity of renal enzymes responsible for synthesizing biologically-active 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$), also known as calcitriol. The main function of vitamin D is to support circulating calcium concentrations. Vitamin D stimulates calcium (and phosphorus) absorption from the gut lumen by enterocytes, and it stimulates bone resorption via osteoblastic release of cytokines (see Figs. 15-2 and 15-3).

PATHOPHYSIOLOGY OF PRIMARY HYPERPARATHYROIDISM

Introduction: Extensive Effects of Excess PTH

Hypercalcemia in primary hyperparathyroidism (PHPTH) is the result of PTH inducing osteoclast-mediated bone resorption, stimulating intestinal absorption of calcium, and stimulating renal tubular resorption of calcium (Mundy, 1988; Hruska and Teitelbaum, 1995).

Kidney

In the setting of accelerated bone resorption, the kidneys become the principal defense against hypercalcemia (Bilezikian, 1992a; Hruska and Teitelbaum, 1995). In the kidney, PTH has three principal effects. First, PTH acts on proximal tubules to inhibit reabsorption of phosphate. Second, it stimulates the activity of renal 1α-hydroxylase in proximal tubular cells leading to formation of biologically active $1,25(OH)_2D_3$ from its circulating precursor 25-hydroxyvitamin D (25[OH]D) (also known as calcidiol) while inhibiting synthesis of inactive vitamin D forms. Third, PTH increases kidney calcium reabsorption. Most calcium is reclaimed from glomerular filtrate in the proximal tubules via a PTH-independent process. The primary target of PTH's action to promote calcium reabsorption is in distal tubules, where it stimulates directional, transcellular calcium transport from the tubule lumen, across the cell, and into the ECF. Early in the course of PHPTH, when hypercalcemia is mild, urinary calcium excretion is relatively low. PTH action, at the renal level, enhances tubular resorption of calcium. When serum calcium concentrations are greater than 12 to 14 mg/dL, the renal tubular mechanism for reabsorbing calcium becomes overwhelmed. Here, the kidney's adaptive mechanism for correcting hypercalcemia becomes operative despite excessive concentrations of PTH. This hypercalciuria, however, is not sufficient to correct the hypercalcemia but can lead to nephrocalcinosis. Nephrocalcinosis may be mild and reversible or severe and progressive, leading to continued renal damage and uremia. Most dogs with PHPTH have normal blood urea nitrogen (BUN) and serum creatinine concentrations. As has been described in people with PHPTH untreated for as many as 10 years, virtually no changes in serum renal or other biochemical profiles (aside from increasing calcium and decreasing phosphate concentrations) are noted (Silverberg et al, 1999).

Bone

In the skeleton, PTH activates bone turnover and liberates stored calcium. The immediate action of PTH is to stimulate the transport of calcium across bone lining cells from an easily mobilized pool of calcium at the bone surface (Attie, 1989). The activity of these cells, caused by PTH or PTHrP, is the foundation for virtually all cases of marked hypercalcemia. Associated with accelerated osteocytic and osteoclastic bone resorption, mineral is removed and replaced by immature fibrous connective tissue. The bone lesion of fibrous osteodystrophy in afflicted dogs is reported to be generalized throughout the skeleton but accentuated in certain areas, such as the cancellous bone of the skull (Capen and Martin, 1983). Iliac crest bone biopsies from virtually all humans with PHPTH reveal histomorphometric evidence of the effects of excess PTH (Arnaud and Kolb, 1991; Hruska and Teitelbaum, 1995). These findings may include increased bone resorption surfaces, increased numbers of osteoclasts, osteocytic osteolysis, and marrow fibrosis. Bone histomorphometric findings in dogs with PHPTH were similar to those reported in humans (i.e., parallel increases in osteoblastic and osteoclastic activity) (Meuten et al, 1983a; Weir et al, 1986). Excessive absorption of calcium from the gastrointestinal tract is not usually an important cause of hypercalcemia, although it is a contributor to the hypercalcemia resulting from vitamin D toxicosis.

Uroliths and Urinary Tract Infections

Hypercalciuria resulting from PHPTH is a cause of the urolithiasis and urinary tract infections that are "common" with this disorder. The incidence of urinary tract infection is about 20% to 30% of afflicted dogs and about 25% to 40% have urinary calculi (Berger and Feldman, 1987; Klausner et al, 1987). Hypercalciuria from increased glomerular filtration of calcium predisposes individuals to urolithiasis. Additional factors may play a role in urolith formation or urinary solute saturation, including pH, ionic strength, and crystal aggregation inhibitors. Calcium phosphate, for example, is markedly less soluble in alkaline urine than in acidic urine. Other hypercalcemic conditions are not usually associated with urolithiasis. This discrepancy may be explained, perhaps, by the chronic nature of the hypercalcemia in dogs with PHPTH as opposed to the short-term nature of hypercalcemia in dogs with neoplasia, toxin exposure, and other such conditions. In these other conditions, dogs tend to develop their clinical signs quickly, which either resolve or worsen in the short-term.

In PHPTH, hypercalcemia is aggravated by increased production of vitamin D and decreased amount of serum phosphate available to form complexes with serum iCa. The result is decreased tubular resorption of phosphate, hyperphosphaturia, and hypophosphatemia. These actions are responsible for the development of the biochemical triad classic for PHPTH: hypercalcemia, hypophosphatemia, and hyperphosphaturia. Vitamin D deficiency, after chronic PTH-stimulated use of vitamin D stores, is a possible natural adaptive mechanism to PHPTH in people. People with vitamin D deficiency caused by PHPTH may develop osteomalacia, a problem considered uncommon or not clinically relevant in animals (Meuten et al, 1983a; Weir et al, 1986).

Calcitonin

Calcitonin, a 32–amino acid polypeptide hormone produced by parafollicular or "C cells" located in the thyroid, is secreted in response to increases in serum calcium (Mol et al, 1991). This hormone has the primary responsibility of limiting postprandial hypercalcemia in normal mammals. Calcitonin decreases bone resorption by reducing the size of osteoclast brush borders, the number of osteoclasts, and osteoclast motility. Calcitonin does not affect the kidney or intestine. It may, however, influence the satiety center, decreasing appetite. The role of calcitonin in dogs with PHPTH is not known. Increased calcitonin secretion in response to hypercalcemia seems a reasonable physiologic response. Parafollicular cells are markedly hyperplastic and appear as small white foci in the thyroid gland of dogs with PHPTH (Capen and Martin, 1983). Hyperplastic parafollicular cells may displace colloid-containing follicles lined by thyroid follicular cells, implying the presence of an adaptive response by the parafollicular cells. Studies in humans suggest that this adaptive mechanism is inconsistent (Arnaud and Kolb, 1991).

ASSAYS

Total Calcium

Serum or heparinized plasma samples are suitable for routine analysis of total calcium (TCa). Fasted blood samples may reduce problems with lipemia. Mean serum TCa concentrations in healthy mature dogs is about 10.5 mg/dL (reference interval of about 9.6 to 11.6 mg/dL; 2.4 to 2.9 mmol/L). Results from healthy cats are usually slightly lower. Dogs younger than 3 months of age have slightly higher results than dogs older than 1 year (Schenck and Chew, 2012). Oxalate, citrate, and ethylenediaminetetraacetic acid (EDTA) anticoagulants should not be used because they bind calcium. Calcium status of dogs and cats is often initially based on the *total* concentration because this is the result provided in most general biochemistry "profiles." Estimation of iCa based on the TCa is not a perfect science. For example, when estimating the iCa based on the TCa in dogs, there is a tendency to overestimate the number of normocalcemic patients and underestimate those with hypocalcemia. In cats, using the TCa to estimate the iCa tends to underestimate normocalcemia and hypercalcemia, overestimating hypocalcemia (Schenck and Chew, 2005a; 2005b). Adjustment formulas previously used to predict the iCa are not recommended (Schenck and Chew, 2012). Because iCa is available to most veterinary clinicians, it is wise to assess the iCa directly whenever there is suspicion of a calcium imbalance.

Ionized Calcium

Typically, serum is analyzed for iCa measurement, but heparinized plasma or whole blood can be used. Results from heparinized whole blood samples tend to be lower than results using serum (Schenck and Chew, 2008). The analysis of serum eliminates potential interference by heparin and allows longer storage periods. Silicone separator tubes should not be used. Analysis utilizing an ion-selective electrode allows easy and accurate measurement. Serum iCa concentration in healthy adult dogs and cats is about 1.1 to 1.4 mmol/L. Young dogs and cats have slightly higher values. Accurate determination of iCa requires that samples be collected and processed correctly. Therefore, adhering to laboratory protocol is imperative.

Parathyroid Hormone

The development of an assay for serum PTH in 1963 by Berson and colleagues was a major breakthrough in the diagnosis of human parathyroid disorders. It is now appreciated that complete (84–amino acid) molecules of PTH and numerous incomplete "pieces" of PTH are found in the circulation of all animals. Primary bioactivity resides in the intact molecule, the major secretory product of parathyroid glands (see Fig. 15-4). Excellent valid assays are available for PTH in dogs and cats. It is imperative for clinicians to follow their laboratories' protocols regarding sample collection and processing, usually including shipping samples on ice (Torrance and Nachreiner, 1989a; 1989b). Development of the "two-site" PTH assay system used by many laboratories depended on production of two different polyclonal antibodies. The two-site immunoradiometric assay (IRMA) system for intact human PTH was demonstrated to be valid for measurement of dog and cat PTH (Torrance and Nachreiner, 1989a; Flanders and Reimers, 1991; Barber et al, 1993). One antibody binds only the midregion and C-terminal 39-84 amino acids of human PTH. The other antibody binds only the N-terminal amino acids of human PTH. Samples being assayed are incubated simultaneously with both antibodies, with a "sandwich" comprised of the N-terminal antibody plus the patient's intact hormone plus the 39-84 antibody. Only these "sandwiches" are detected by the assay system, eliminating interference by midregion or C-terminal fragments, even if present in large concentrations. These assays usually require several days to receive results.

Two-site immunochemiluminometric assays for intact PTH in humans use similar antibodies and a similar range of applicability to animal sera (Michelangeli et al, 1997; Estepa et al, 2003). One chemiluminescent PTH assay system required only about 20 minutes to perform, making this method potentially of use during surgery (Bilezikian et al, 2001; Ham et al, 2009; Cortadellas et al, 2010). As can be appreciated, assay systems often become unavailable for various reasons. A whole intact molecule PTH assay system is now being used that has lower reference values, but good correlation with previously-used systems (Refsal and Nachreiner, 2012). Currently, enzyme-linked immunosorbent assay (ELISA) is the most common assay used to measure PTH in the Great Britain and Europe. A canine-specific intact ELISA, which is also validated for cats, is available (Skelly, 2012). Reference intervals and units used in reporting results vary among laboratories, necessitating good communication to avoid confusion. Assay of 1-84 amino acid PTH is now considered to be most reliable (Gao et al, 2001).

Determination of the serum PTH concentration is a useful diagnostic aid in the evaluation of dogs and cats suspected of having parathyroid disease. As with most hormone assays, evaluation of the serum hormone concentration "out of context" is not as consistently informative as evaluation in the proper context is. With this in mind, the serum PTH concentration must be evaluated relative to the total and, ideally, ionized serum calcium concentrations. Decreases in the serum calcium concentration are normally associated with increases in the serum PTH concentration. Increases in the serum calcium concentration are normally associated with decreases in the PTH concentration (Fig. 15-5). As with any laboratory value, a single PTH result may not be the "expected" value. Therefore practitioners are encouraged to complete a thorough evaluation of hypercalcemic dogs or cats. If any test result does not seem logical, it may need to be repeated. Serum hormone concentrations may fluctuate significantly.

Vitamin D

Measurement of vitamin D metabolites, although not commonly used in veterinary medicine, would occasionally be helpful in the diagnosis of calcium disorders. 25(OH)D (calcidiol) and $1,25(OH)_2D_3$ (calcitriol) are the metabolites of greatest clinical interest for detection of hypovitaminosis or hypervitaminosis D syndromes and in CKD (Carothers et al, 1994). These metabolites are stable during refrigeration and freezing, but samples should not be exposed to light for any length of time. Both metabolites are chemically identical among species, therefore receptor-binding assays or radioimmunoassays (RIAs) used for people may be satisfactory for dogs and cats (Hollis et al, 1996). Young growing individuals have higher calcitriol concentrations than adults.

Calcitriol assays have demonstrated genetic errors of vitamin D metabolism and normal-to-increased concentrations in PHPTH, whereas patients with hypercalcemia of malignancy have levels that may be low, normal, or high. Dogs and cats with possible exposure to rat and mouse poisons containing vitamin D may present challenging diagnostic problems. Serum concentrations of vitamin D have been increased in these animals (Dougherty et al, 1990).

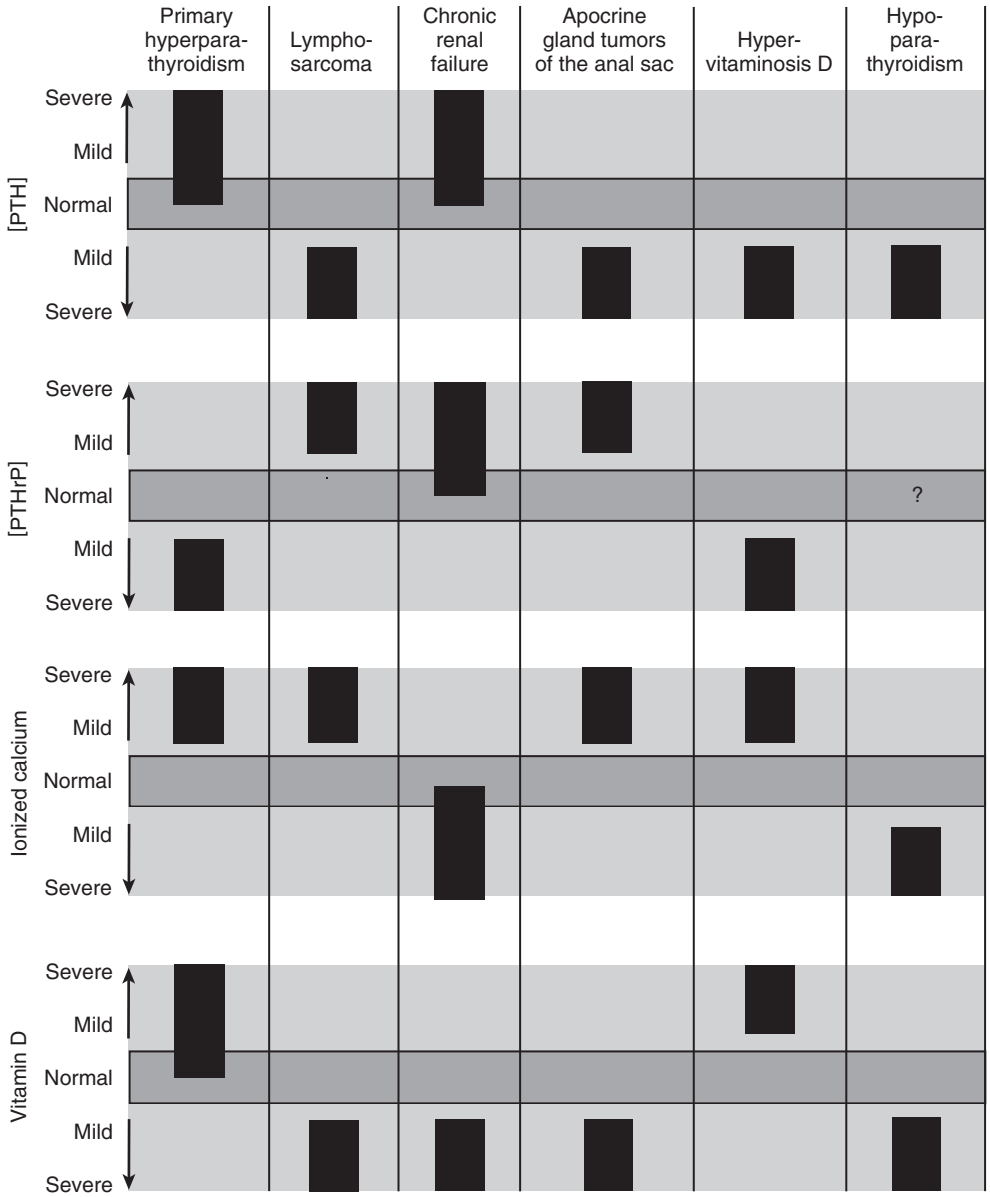


FIGURE 15-5 Graph showing the serum parathyroid hormone *(PTH),* parathyroid hormone–related protein *(PTHrP),* ionized calcium (iCa), and vitamin D concentrations in the most common causes for hypercalcemia of dogs.

Parathyroid Hormone–Related Protein

PTHrP resembles PTH not only in terms of its genetic sequence but also in terms of structure (Fig. 15-6); thus, PTHrP is a second member of the PTH family of hormones (Broadus and Stewart, 1994). In marked contrast to PTH, found only in parathyroid glands, PTHrP is found in many tissues (Table 15-2; Fig. 15-7) (Strewler, 2000). Two-site IRMA and N-terminal RIAs are available for the measurement of human PTHrP, and these same assay systems have been validated for the dog (Brown et al, 1987; Burtis, 1992). Because PTHrP is susceptible to degradation by serum proteases, assays should use fresh or frozen plasma using EDTA as anticoagulant. The EDTA complexes with plasma calcium, limiting the action of most proteases. The addition of protease inhibitors, such as aprotinin, may provide further protection. Use of serum is not recommended (Budayr et al, 1989; Henderson et al, 1990; Rosol et al, 2000). Valid assays for dog and cat PTHrP can be used to screen for certain cancers. Simultaneously assaying PTH and PTHrP in hypercalcemic dogs and cats has the potential to be a quick, reliable, noninvasive, and inexpensive aide in distinguishing HHM from nonmalignant hypercalcemia. Animals with renal insufficiency may also have increased concentrations of PTHrP (see Fig. 15-5).

DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA

See Box 15-1.

Primary Hyperparathyroidism

See the next section.

Hypercalcemia of Malignancy

General Overview

Malignancies are the most common causes of hypercalcemia in dogs and cats (Messinger et al, 2009). Neoplasms can cause hypercalcemia by several recognized physiologic processes (Fig. 15-8): HHM is caused by secretion of PTHrP, while some lymphomas

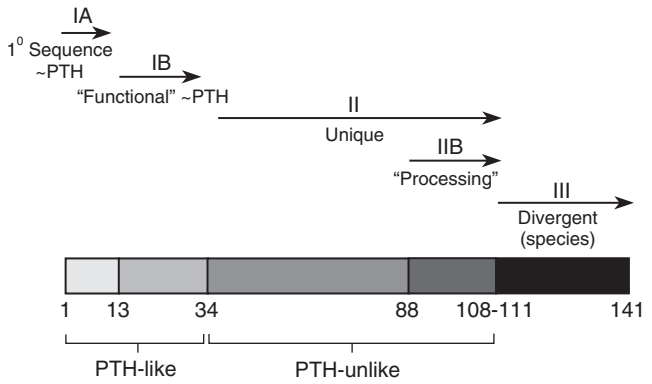


FIGURE 15-6 Structural and functional domains of parathyroid hormone–related protein (PTHrP). The 1 to 13 region of PTHrP is 70% homologous with the corresponding region of parathyroid hormone *(PTH)* and is believed to be involved in activation of adenylate cyclase and other second-messenger systems in target tissues. The 14 to 34 region shares no homology with the 14 to 34 region of PTH but has been shown to bind effectively to the PTH receptor. The 35 to 108 region of PTHrP is unique, sharing no homology with any other known peptide. This region is extraordinarily highly conserved among species, which suggests that it has a crucial but as yet unknown function or functions. The 88 to 108 region of the peptide is rich in potential proteolytic cleavage sites and contains several amidation signals and is therefore presumed to be the site of posttranslational processing, at least in some tissues. The 112 to 141 region of the peptide is poorly conserved among species. Preliminary evidence suggests that at least in some situations, C-terminal fragments derived from this region enter the circulation. The functional consequences of this are unknown. (From Broadus AE, et al.: Humoral hypercalcemia of cancer: identification of a novel parathyroid hormone-like peptide, *N Engl J Med* 319:556, 1988.)

synthesize vitamin D in addition to PTHrP. Hypercalcemia is then induced by marked increase in osteoclastic bone resorption in areas surrounding the malignant cells within the marrow (Rosol et al, 2000; Stewart, 2005). Ectopic PTH synthesis and secretion is a rare cause of hypercalcemia in people (Stewart, 2005). Some dogs with lymphosarcoma, apocrine gland carcinomas of the anal sac, or multiple myeloma are hypercalcemic. Some tumors that metastasize to bone can cause hypercalcemia through the induction of local bone resorption. These include malignancies of mammary tissue, prostate, liver, and lung. Primary bone tumors do not typically cause hypercalcemia. Hypercalcemia has been associated with nasal adenocarcinomas, thyroid carcinoma, thymoma, squamous cell carcinoma of the gastrointestinal system or vagina, and melanoma (Pressler et al, 2002; Schenck and Chew, 2012).

Humoral Hypercalcemia of Malignancy

Humoral Factors, Including Parathyroid Hormone–Related Protein. Tumor tissue at a site distant from bone may synthesize and secrete PTHrP, stimulating bone resorption, leading to hypercalcemia. Excessive secretion of biologically active PTHrP plays a central role in the pathogenesis of hypercalcemia in most forms of HHM. Cytokines, such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNFα), transforming growth factor-a (TGF-a), transforming growth factor-b (TGF-b), or calcitriol, can have synergistic or cooperative actions with PTHrP (Fig. 15-9) (Rosol et al, 2000). PTHrP binds to the PTH1R, as described earlier. PTHrP, via interaction with PTH1R, stimulates osteoclastic bone resorption, increases renal tubular calcium resorption, and decreases renal tubular phosphate resorption. IL-1 and the transforming growth factors (TGFs) also have the potential to stimulate bone resorption (McCauley et al, 1991; Rosol et al, 2000). Identification of PTHrP provides an explanation of why some tumors (those that do not synthesize PTHrP) are not associated with hypercalcemia. PTHrP concentrations are abnormal usually only in individuals with malignancies and renal failure (see Fig. 15-5). Serum PTH concentrations in dogs with malignancy-associated hypercalcemia are typically low or undetectable. This should be seen as a normal response by the parathyroid glands to hypercalcemia. Assay of PTH and PTHrP concentrations should not be viewed as a replacement for a complete physical examination, thoracic radiography, abdominal ultrasonography, or any other key parameter used to identify neoplasia. These assay results are as integral as other components of an evaluation.

Hematopoietic Neoplasia. T cell lymphoma is the most common cause of hypercalcemia in dogs, accounting for almost 60% of dogs with hypercalcemia and almost 80% of dogs with hypercalcemia due to cancer (Messinger et al, 2009). Lymphoma afflicts dogs of any age and either sex. Approximately 20% to 40% of

TABLE 15-2 **SITES AND PROPOSED ACTIONS OF PARATHYROID HORMONE–RELATED PROTEIN (PTHrP)**

SITE	PROPOSED ACTIONS
Mesenchymal Tissues	
Cartilage	Promotes proliferation of chondrocytes; inhibits terminal differentiation and apoptosis of chondrocytes
Bone	Stimulates or inhibits bone resorption
Smooth muscle	Released in response to stretching; relaxes smooth muscle in the vascular system, myometrium, and urinary bladder
Cardiac muscle	Positive chronotropic stimulus; indirect positive inotropic stimulus
Skeletal muscle	Unknown
Epithelial Tissues	
Mammary	Induces branching morphogenesis; secreted in milk; possible roles in lactation
Epidermis	Unknown
Hair follicle	Inhibits anagen
Intestine	Unknown
Tooth enamel	Induces osteoclastic resorption of overlying bone
Endocrine Tissues	
Parathyroid glands	Stimulates placental transport of calcium (?)
Pancreatic islets	Stimulates insulin secretion and somatic growth
Pituitary	Unknown
Placenta	Calcium transport (?)
Central Nervous System (CNS)	Released from cerebellar granular neurons in response to activation of L-type calcium channels; receptors in cerebellum, hippocampus, hypothalamus

From Strewler GL: The physiology of parathyroid hormone–related protein, *N Engl J Med* 342:177, 2000.

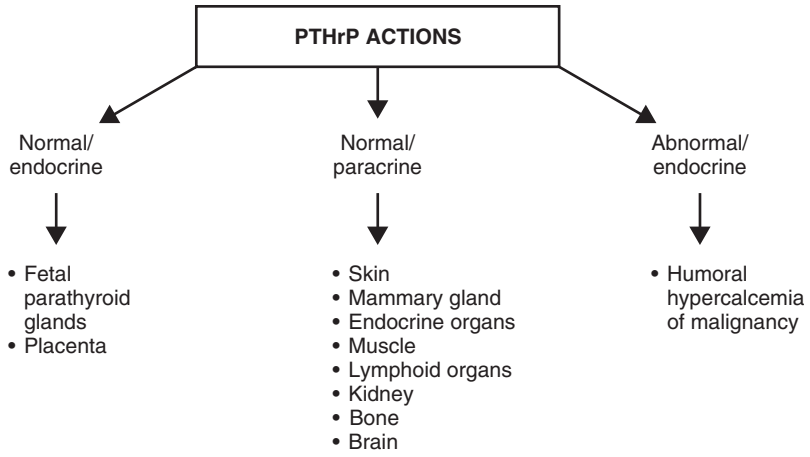


FIGURE 15-7 Actions of parathyroid hormone–related protein *(PTHrP).* (From Rosol TJ, et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice,* ed 2, Philadelphia, 2000, WB Saunders, pp. 108-162.)

BOX 15-1 Differential Diagnoses for Hypercalcemia

Non-Pathologic
Spurious, laboratory error
Young growing animal

Common
Lymphosarcoma
Hypoadrenocorticism
Primary hyperparathyroidism (PHPTH)
Chronic kidney disease (CKD)
Idiopathic hypercalcemia of cats (IHC)

Less Common
Apocrine gland carcinoma of the anal sac
Multiple myeloma
Vitamin D toxicosis
- Overzealous dietary supplementation
- Plants (calcitriol glycosides)
- Rodenticides (cholecalciferol)
- Anti-psoriasis creams (calcipotriol or calcipotriene)

Uncommon to Rare
Hemoconcentration, hyperproteinemia
Carcinomas
- Lung
- Mammary
- Nasal
- Pancreas
- Testicular
- Thymus
- Thyroid
- Vaginal
- Adrenal medullary

Melanoma
Acute kidney injury (AKI)
Hyperthyroidism
Nutritional secondary hyperparathyroidism
- (Serum calcium concentrations usually within reference intervals)

Granulomatous disease
- Blastomycosis
- Histoplasmosis
- Schistosomiasis

Hypervitaminosis A
Raisin/grape toxicity

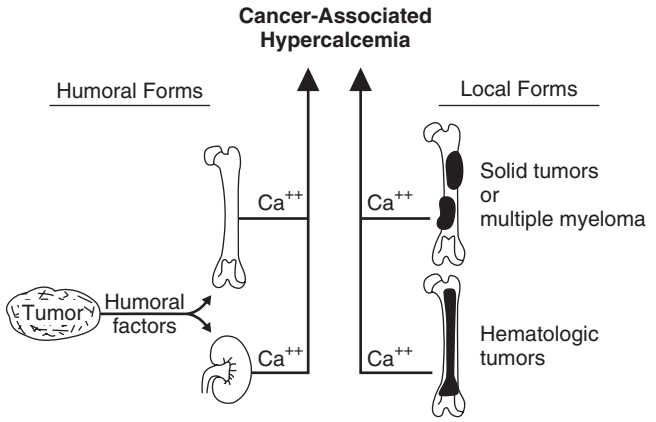


FIGURE 15-8 Pathogenesis of cancer-associated hypercalcemia. Humoral and local forms of cancer-associated hypercalcemia increase circulating concentrations of calcium by stimulating osteoclastic bone resorption and increased renal tubular resorption of calcium. (From Rosol TJ, et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice,* ed 2, Philadelphia, 2000, WB Saunders, pp. 108-162.)

dogs with lymphosarcoma are hypercalcemic (Weller et al, 1982; Matus et al, 1986; Rosol et al, 2000). Clinical signs may be subtle, moderate, or severe. About one-third of cats with lymphoma are hypercalcemic (Savary et al, 2000). Studies on affected dogs have demonstrated parameters consistent with influence by PTHrP, including increased fractional excretion of phosphorus, increased nephrogenous cyclic adenosine monophosphate (cAMP), and increased osteoclastic bone resorption. PTHrP appears to differ from natural PTH in its inability to stimulate renal formation of $1,25(OH)_2D_3$ and its lack of cross-reactivity with specific, two-site, intact PTH assays. A significant percentage of these dogs have increased serum concentrations of PTHrP (Fig. 15-10) (Weir et al, 1988a; 1988b; 1988c). Studies in cats have revealed similar findings (i.e., some cats with cancer have hypercalcemia secondary to tumor-synthesis and secretion of PTHrP). In seven cats with HHM and increases in serum or plasma PTHrP, one had lymphoma, four had lung carcinomas, one had a thyroid carcinoma, and one had an undifferentiated carcinoma. These authors demonstrated that IRMA assays for human 1-84 PTHrP can be used to measure PTHrP in cats and that malignancies in cats, particularly carcinomas, may secrete PTHrP and induce HHM in cats (Bollinger et al, 2002).

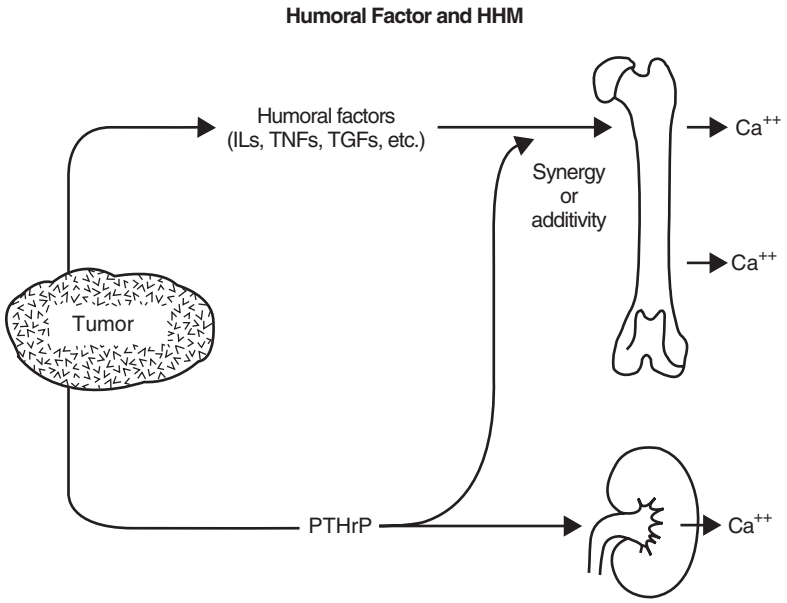


FIGURE 15-9 Humoral factors, such as parathyroid hormone–related protein *(PTHrP),* interleukin-1 (IL-1), tumor necrosis factors *(TNFs),* and transforming growth factors *(TGFs)* produced by tumors induce humoral hypercalcemia of malignancy *(HHM)* by acting as systemic hormones and stimulating osteoclastic bone resorption or by increasing tubular resorption of calcium. (From Rosol TJ, et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice,* ed 2, Philadelphia, 2000, WB Saunders, pp. 108-162.)

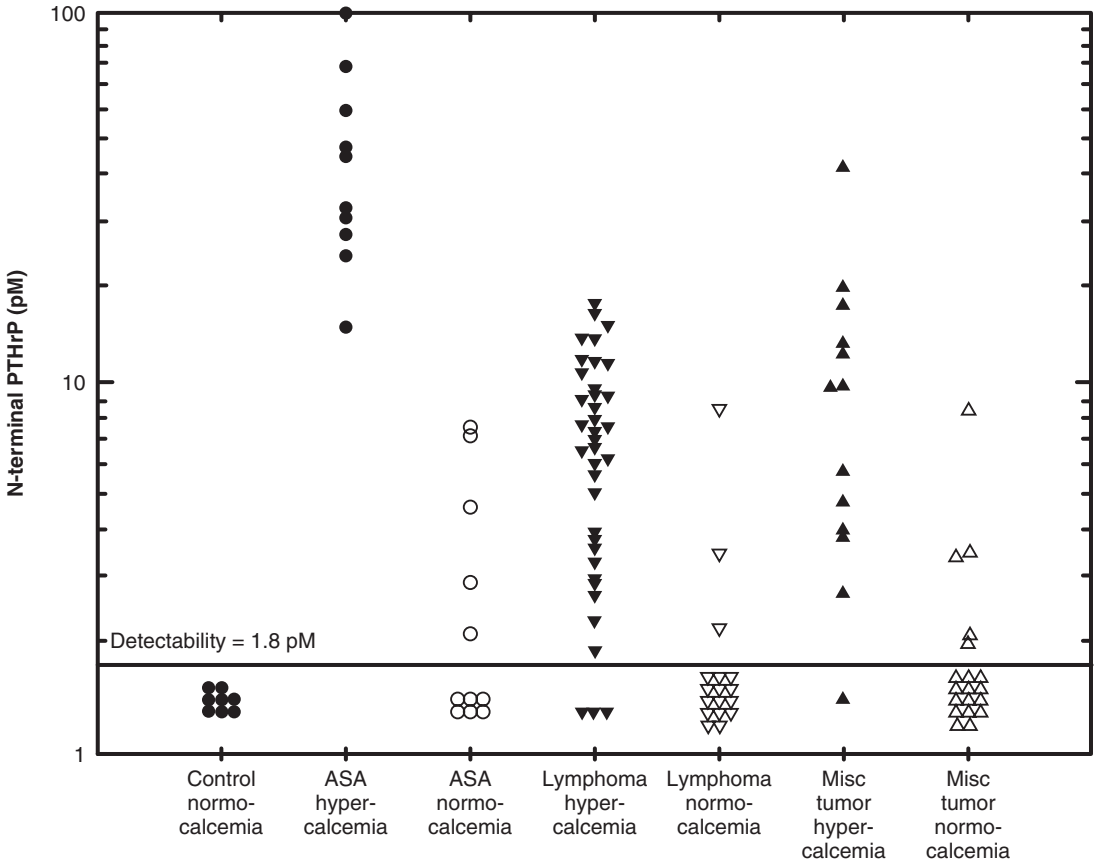


FIGURE 15-10 Circulating N-terminal parathyroid hormone–related protein *(PTHrP)* concentrations in normal dogs (control); dogs with hypercalcemia (>12 mg/dL) and anal sac adenocarcinoma *(ASA),* lymphoma, or miscellaneous tumors *(misc tumor);* and dogs with normocalcemia (< 12 mg/dL) and anal sac adenocarcinoma, lymphoma, or miscellaneous tumors. (From Rosol TJ, et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice,* ed 2, Philadelphia, 2000, WB Saunders, pp. 108-162.)

Lymphomas can synthesize vitamin D in addition to PTHrP, in which case afflicted patients would not only have the expected increases in serum PTHrP but also would have increased vitamin D concentrations (Seymour and Gagel, 1993). Some lymphocytes contain the 1α-hydroxylase (similar to that found in renal tubules) that converts 25(OH)D to the active metabolite, $1,25(OH)_2D_3$ (Rosol et al, 2000). Therefore lymphomas that retain this capability may synthesize excessive amounts of calcitriol, which would increase calcium absorption from the intestinal tract and exacerbate the hypercalcemia resulting from PTHrP synthesis and secretion (see Figs. 15-1 and 15-5).

Although the clinical signs associated with lymphoma are variable, a dog with lymphoma and HHM is typically far more ill than dogs with PHPTH. Lymphoma must remain a possible explanation for hypercalcemia in any dog or cat until a different cause has been confirmed. Lymphosarcoma may or may not be apparent to the veterinarian during the physical examination. At least 40% of dogs with both lymphoma and HHM do not have peripheral lymph node, liver, spleen, or renal enlargement. Most of these dogs have a mediastinal mass, usually obvious on thoracic radiographs. The finding of a mediastinal mass in a dog with hypercalcemia should suggest a diagnosis of lymphoma, although other forms of neoplasia (e.g., thymoma) may account for both the mass and the hypercalcemia (Foley et al, 2000). In addition to lymphoma and thymoma, hypercalcemia due to HHM can be caused by melanoma, myeloma, or by carcinomas of the lung, pancreas, thyroid, skin, mammary gland, nasal cavity, or adrenal medulla. Concentrations of PTHrP are highest in dogs with apocrine gland carcinomas of the anal sac (Pressler et al, 2002; Williams et al, 2003; Schenck and Chew, 2012).

Apocrine Gland Adenocarcinoma of the Anal Sac. Adenocarcinomas of the anal sac represent a classic example of cancer associated hypercalcemia. Like lymphosarcoma, this neoplasm is known to synthesize PTHrP (Matus and Weir, 1989; Williams et al, 2003). This is a well-defined but relatively uncommon tumor of older dogs; their mean age at presentation is 10 to 11 years (range, 3 to 17 years) (Bennett et al, 2002). Slightly more than half of the dogs with this cancer were female. Dogs of almost any breed and mixed breed dogs can develop this condition (Ross et al, 1991; Goldschmidt and Shofer, 1992; Bennett et al, 2002; Williams et al, 2003). In one study, the serum calcium concentrations (upper reference value of 12.6 mg/dL) at the time of diagnosis ranged from 12.7 to 21.7 mg/dL (Bennett et al, 2002). Clinical signs associated with this condition include (among many owner observations) recognition of a mass near the rectum, tenesmus, poor appetite or anorexia, polyuria/polydipsia, and lethargy. HHM is reported in about 25% of dogs with apocrine gland carcinoma of the anal sac (Ross et al, 1991; Williams et al, 2003).

Local reappearance of the cancer or metastasis causes recurrence of hypercalcemia if surgery resulted in transient resolution. Dogs afflicted with this form of cancer have increases in urinary cAMP and fractional phosphorus excretion. Serum PTH concentrations are suppressed, PTHrP concentrations are excessive, bone histomorphometry reveals increased bone resorption, and there is no compensatory increase in formation. These changes are consistent with excesses in PTH or PTHrP (Meuten et al, 1983b). Apocrine gland adenocarcinoma cell lines established in mice have also demonstrated potential factors responsible for HHM, although only PTHrP is increased in the serum (Grone et al, 1998). This form of malignancy carries a guarded prognosis (Rosol et al, 1992a; 1992b; Williams et al, 2003).

With recognition of hypercalcemia in any dog, a rectal examination and careful palpation of the anal sac areas should be routine. In affected dogs, rectal examination usually demonstrates a space-occupying mass that may be invasive and occasionally ulcerated. Careful digital rectal palpation is necessary to identify the presence of sublumbar lymph node enlargement. Although radiography may also be used to evaluate the sublumbar area, abdominal ultrasonography has been a sensitive diagnostic aid. Radiography of the thorax and abdomen can be used in searching for pulmonary metastases and/or bony metastases (lytic areas).

Other Nonneoplastic and Solid Tumors That May Synthesize Parathyroid Hormone–Related Protein. Thymoma, melanoma, carcinomas of the lung, pancreas, thyroid, skin, mammary gland, nasal cavity, adrenal medulla, and interstitial cell tumors of the testicle are less commonly encountered solid tumors that cause hypercalcemia without bone metastasis (Grain and Walder, 1982; Meuten et al, 1983a; Pressler et al, 2002; Williams et al, 2003). Dogs or cats with any of these neoplastic conditions are not usually hypercalcemic, but when present, the value of a randomly collected serum or plasma sample for PTHrP measurement can be quite informative. In people, a small percentage of bronchogenic non–small-cell carcinomas, breast cancers, squamous cell carcinomas of the esophagus, renal-cell carcinomas, and hepatomas have synthesized and secreted PTHrP (Harris et al, 2002). PTHrP has also been associated with hypercalcemia in nonneoplastic diseases, such as schistosomiasis (Fradkin et al, 2001).

Hematologic Malignancies of the Bone Marrow: Osteolytic Hypercalcemia

Background. Some types of hematologic malignancies present in bone (e.g., lymphoma and multiple myeloma) produce hypercalcemia by inducing bone resorption locally (Rosol et al, 2000). In humans, metastatic breast cancer is another example, although this association is not common in dogs or cats. A number of paracrine factors may be responsible for the stimulation of local bone resorption in dogs or cats with such tumors, such as the previously discussed cytokines and PTHrP (see Humoral Hypercalcemia of Malignancy; Black and Mundy, 1994). Production of small amounts of PTHrP by a tumor in bone may stimulate local bone resorption without inducing a systemic response. Prostaglandins (especially prostaglandin E_2) may also contribute to local stimulation of bone resorption (Rosol et al, 2000). Together, these cytokines and prostaglandins comprise the osteoclast-activating factors.

Multiple Myeloma. Multiple myeloma is a tumor of B-lymphocytes or plasma cell lines that may be associated with the development of osteolytic bone lesions and, occasionally, hypercalcemia. The hypercalcemia develops secondary to production of the previously described interleukin-1β (IL-1β; previously described as "osteoclast-activating factor"), plus transforming growth factor-β (TGF-β), and the receptor activator of nuclear factor *k*-B ligand (RAN *k*L). The latter is a membrane-associated protein that stimulates osteoclast activity by binding to surface receptors (Henry, 2010). There is correlation between extent of bone destruction, tumor cell burden, and the amount of IL-1β produced by myeloma cell cultures (Durie et al, 1981; Wysolmerski and Insogna, 2012). Approximately 17% of dogs afflicted with this cancer are hypercalcemic and 50% of dogs with multiple myeloma have radiographic evidence of bone lysis (Matus et al, 1986; Henry, 2010).

Bone pain may be associated with the lytic areas. The initial database from afflicted dogs often reveals abnormal increases in the total serum globulin concentration as a result of a monoclonal spike. A "monoclonal gammopathy" can be demonstrated via serum protein electrophoresis. Bone marrow aspiration may aid in confirming the diagnosis. Analysis of urine for light chains of myeloma protein (Bence Jones protein) has not been of value (Matus et al, 1986; Henry, 2010).

Hypercalcemia Induced by Metastases of Solid Tumors to Bone

Certain malignant neoplasms with osseous metastasis may cause hypercalcemia and hypercalciuria. Primary bone tumors, by contrast, do not typically induce hypercalcemia. For example, hypercalcemia would be rare in a dog with osteosarcoma, whereas malignant mammary adenocarcinoma or squamous cell carcinoma are (albeit infrequently) associated with both bone metastasis and hypercalcemia. Several different types of cells may be involved in the actual destruction of bone at sites of metastasis, including osteoclasts, tumor cells, lymphocytes, and monocytes. Lymphocytes and monocytes may accumulate as part of the cell-mediated immune response to a tumor (Mundy et al, 1984). Osteolysis is a result of the physical disruption of bone by proliferating neoplastic cells, but it also can be caused by secretion of cytokines or prostaglandins that stimulate local bone resorption (Garrett, 1993; Henry, 2010).

Epithelial tumors, especially squamous cell carcinomas, are the most likely neoplasms to metastasize to bone in dogs and cats (Quigley and Leedale, 1983). Common metastatic bone sites in the dog include the humerus, femur, and vertebrae, whereas in the cat, local invasion of bone rather than distant metastasis is more common. Although reported, these tumors are not commonly associated with hypercalcemia (Grain and Walder, 1982).

Hypervitaminosis D

Background

Vitamin D can be cumulative in its toxic action if a dog or cat consumes excess quantities in food, for example, and may require weeks before effects on mineral metabolism become clinically obvious. However, acute toxicity after massive ingestion of cholecalciferol appears to be the more commonly reported cause of vitamin D toxicosis in dogs. Hypercalcemia and hyperphosphatemia are the anticipated electrolyte abnormalities in vitamin D toxicity, although normophosphatemia and transient periods of normocalcemia have been reported (Harrington and Page, 1983; Mellanby et al, 2005; Figs. 15-11 and 15-12). Hypercalcemia begins as soon as 12 to 18 hours after massive ingestion, and peak concentrations are usually demonstrated by 48 to 72 hours, coinciding with increases in BUN and creatinine (Rumbeiha, 2000). Increased resorption from bone, coupled with increased gastrointestinal absorption of calcium and phosphorus, are responsible for these abnormalities. Skeletal disease is usually not detectable radiographically, probably because of the acute nature of the toxicosis. The osteoclastic phase of bone resorption occurs early and is followed by osteoid deposition and hyperosteoidosis (Boyce and Weisbrode, 1983). Extensive soft tissue mineralization of the endocardium, blood vessels, tendons, kidney, and lung is frequently associated with vitamin D toxicity (Meuten, 1984).

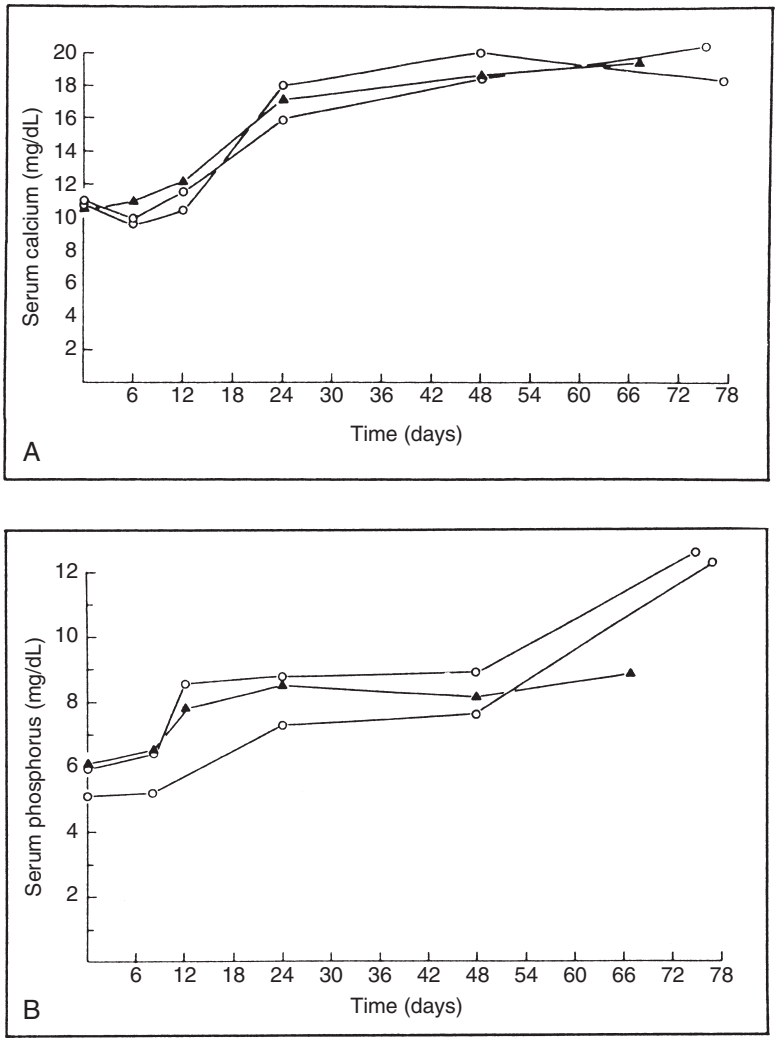


FIGURE 15-11 Serum calcium **(A)** and phosphorus **(B)** concentrations of dogs given vitamin D_3 at a dosage of 10 mg/kg *(circles)* and 20 mg/kg *(triangles)*. (From Gunther R, et al.: Toxicity of a vitamin D_3 rodenticide to dogs, *J Am Vet Med Assoc* 193:211, 1988.)

Rodenticide Toxicosis

Hypercalcemia that develops secondary to cholecalciferol rodenticide toxicosis in dogs and cats is a recognized concern (Gunther et al, 1988; Moore et al, 1988; Bahri, 1990; Dougherty et al, 1990; Fooshee and Forrester, 1990; Rumbeiha et al, 1999; Murphy, 2002). A variety of rat bait products contain cholecalciferol (Nicholson, 2000; Rumbeiha, 2000; Morrow, 2001). Dogs studied after being given this type of poison became weak, lethargic, and anorexic within 48 hours. Within 60 to 70 hours of consumption, all dogs became recumbent, exhibited hematemesis, and progressed into shock before dying or being euthanized (Gunther et al, 1988). Although the median lethal dose of cholecalciferol in dogs is widely reported to be 43 to 88 mg/kg, studies have shown that as little as 10 mg/kg given once orally can be lethal. Dogs that ingest as little as 4 to 6 mg/kg, once, can become ill. Clinically healthy dogs that ingest single doses of 2 mg/kg may develop hypercalcemia (Rumbeiha, 2000).

Most dogs and cats exposed to these toxins have had rapid increases in the serum calcium and phosphate concentrations (see Fig. 15-11). Diffuse gastrointestinal hemorrhage was obvious. Histologic lesions consisting of hemorrhage or mineralization or both were identified in the gastrointestinal tract, kidneys, myocardium, and in the blood vessels of many organs (Gunther et al, 1988). The incidence of acute and/or severe renal failure was variable. Three exposed cats survived (Moore et al, 1988).

Other Causes of Vitamin D Toxicosis (Creams, Plants, and Dietary Supplements)

Since 1997, perhaps the most common accidental cause of vitamin D toxicosis in pets has been ingestion of human psoriasis medications containing the vitamin D analogs calcipotriol or calcipotriene. Excess dietary supplementation and overzealous administration of vitamin D by veterinarians to dogs or cats with hypoparathyroidism have been reported (Mellanby et al, 2005). Vitamin D given after removal of a parathyroid tumor when hypocalcemia is recognized or anticipated can be overdosed. Lilies and *Cestrum diurnum* (day-blooming jessamine) are popular houseplants that should be considered sources of vitamin D toxicity in pets because they contain active metabolite of vitamin D. Jasmine, an indoor climbing plant without active vitamin D metabolites, should not be confused with day-blooming jessamine. Other plants containing glycosides of vitamin D include *Solanum malacoxylon and Trisetum flavescens*.

Diagnosis

The diagnosis of vitamin D toxicosis is based on a history of exposure. In acute cases, one may see dark or bloody feces, azotemia, oliguria or polyuria, proteinuria, and sometimes glucosuria. An additional clue in diagnosing chronic hypervitaminosis D, such as with a dietary excess, would be hyperphosphatemia in a hypercalcemic dog or cat. Most other causes of hypercalcemia are associated with hypophosphatemia or normal serum phosphate concentrations. The history and signs of vitamin D toxicosis can be strikingly similar to those seen in dogs with hypoadrenocorticism, acute kidney injury (AKI), and CKD. Various assays are available as diagnostic aides. Calcidiol (25[OH]D) concentration is a good indicator of vitamin D ingestion and can be used to help identify hypervitaminosis D, because vitamin D metabolites resulting from rodenticides will be measured. The vitamin D analog found in skin creams is not measured with this assay but should be detectable with a calcitriol assay (Peterson, 2012).

Hypoadrenocorticism

Hypoadrenocorticism (Addison's disease) is one of the more common causes of hypercalcemia in dogs, accounting for approximately 10% to 50% of cases (Uehlinger et al, 1998; Rosol et al, 2000). Serum calcium concentrations have been reported to be increased in as many as 33% of dogs with adrenocortical insufficiency (hypoadrenocorticism) (Peterson and Feinman, 1982; Peterson et al, 1996; Scott-Moncrieff, 2010) as well as in a smaller percentage of hypoadrenal cats (Johnessee et al, 1982; Peterson et al, 1989). A correlation has been noted between

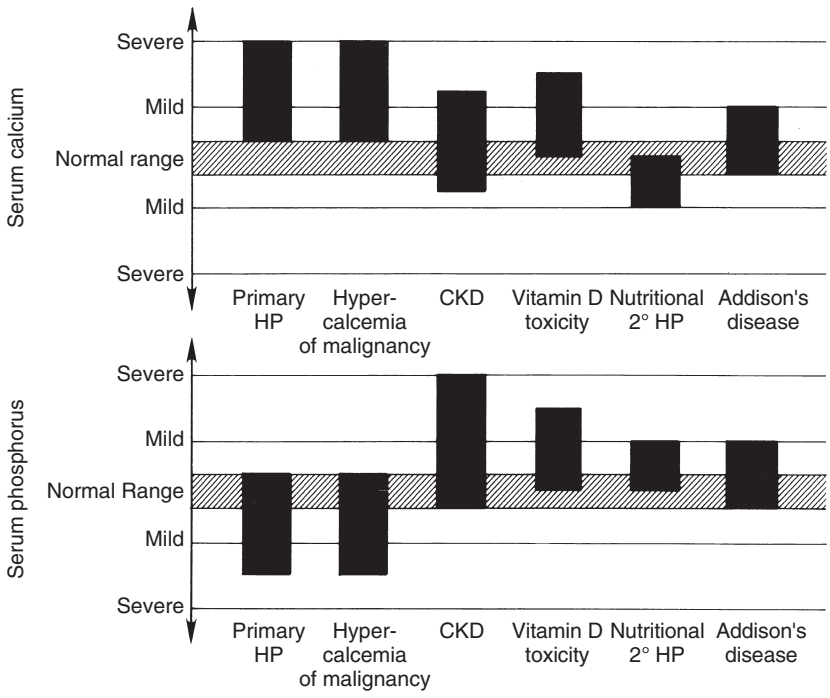


FIGURE 15-12 The range in serum calcium and phosphorus concentrations for the more common causes of hypercalcemia and/or hyperparathyroidism in the dog. CKD, Chronic kidney disease; *HP*, hyperparathyroidism; *2° HP*, secondary hyperparathyroidism.

the degree of hyperkalemia and the level of hypercalcemia (see Chapter 12). If the serum potassium concentration exceeds 6.0 to 6.5 mEq/L, a large percentage of these animals have serum calcium concentrations of 12 to 13.5 mg/dL. Hypercalcemia is not restricted to the extremely ill hypoadrenal dog. It is not common, however, for the serum calcium concentration to exceed 13.5 mg/dL, and it rarely exceeds 15 to 16 mg/dL. Despite the increased serum TCa concentrations, serum iCa concentrations usually remain in the reference range. Serum phosphate concentrations also correlate with serum calcium concentrations, with the hyperphosphatemic animal more likely to exhibit hypercalcemia (see Fig. 15-12).

Clinical signs and laboratory abnormalities associated with hypoaldosteronism (a primary component of Addison's disease) are often striking and overshadow concerns related to hypercalcemia (see Chapter 12). Most dogs and cats with hypoadrenocorticism have hyperkalemia, hyponatremia, azotemia, hyperphosphatemia, and may be severely ill. The only differential diagnoses for this combination of clinical and serum abnormalities are hypoadrenocorticism, significant (acute?) kidney injury, and vitamin D (rodenticide) toxicosis. Hypercalcemia rapidly resolves after saline fluid therapy for adrenal insufficiency, but does not respond as quickly or at all in dogs with vitamin D toxicosis or primary renal disease.

The pathogenesis of the hypercalcemia associated with hypoadrenocorticism is probably multifactorial. Any combination of the following may be involved: volume contraction, decreased glomerular filtration rate (GFR), increased intestinal absorption of calcium, hyperproteinemia resulting from dehydration and hemoconcentration, increased plasma protein binding affinity for calcium, increased concentrations of calcium-citrate complexes, and increased renal tubular resorption of calcium (Peterson and Feinman, 1982; Scott-Moncrieff, 2010).

Chronic Kidney Disease (CKD)

A majority of dogs and cats with CKD have normal serum TCa concentrations, a small minority have hypocalcemia, and a larger minority (14% of dogs and 38% of cats) have increases in TCa, making CKD the second or third most common cause of hypercalcemia (Schenck and Chew, 2012). The prevalence of hypercalcemia increases with CKD severity. The finding of hypercalcemia and renal azotemia presents a diagnostic dilemma because hypercalcemia can lead to renal failure or develop as a consequence of it. Deleterious effects of hypercalcemia only follow increases in serum iCa concentrations, making assessment of this parameter of particular importance. About 10% of dogs and almost 30% of cats with CKD have increases in serum iCa concentrations. The pathogenesis of hypercalcemia associated with CKD usually involves diffuse hyperplasia of the parathyroid glands (Fig. 15-13). The actual presence or incidence of a syndrome involving "autonomously functioning" parathyroid glands that are the result of chronic stimulation due to CKD (i.e., tertiary hyperparathyroidism) is not known. *Tertiary hyperparathyroidism* is the name given to the syndrome of chronic renal secondary hyperparathyroidism, in which one or more of the parathyroid glands begin to autonomously secrete PTH ("tertiary" disease). Dogs or cats with no or minimal clinical signs, persistent hypercalcemia of a magnitude greater than 13.0 mg/dL, and a serum phosphate that is normal or low usually do not have CKD. Those with serum calcium concentrations less than 12.5 mg/dL and hyperphosphatemia are more likely to have CKD. The dog or cat for which the diagnosis remains vague despite these guidelines may need further evaluation. Measurement of serum iCa concentrations should help distinguish primary kidney disease (normal or low) from a primary parathyroid problem (increased) (see Fig. 15-5). Cervical ultrasonography may aid in distinguishing enlargement of more than one gland (consistent with renal secondary hyperparathyroidism) versus identifying one parathyroid nodule (consistent with PHPTH). If the underlying disease process is still uncertain, the results of PTH and PTHrP assays may be helpful (Schenck and Chew, 2012).

Acute Kidney Injury (AKI)

Dogs with acute and severe hyperphosphatemia as a component of AKI usually have normal or low serum calcium concentrations. Mild hypercalcemia is occasionally seen. As with hypercalcemia associated with CKD, the pathogenesis of hypercalcemia induced by AKI is multifactorial. In the oliguric phase of acute failure, deposition of calcium and phosphorus in soft tissues may occur. During the polyuric phase, as kidney function improves, this mineral may be mobilized, and hypercalcemia and hyperphosphatemia may develop (Llach et al, 1981). Alternatively, rapid improvement in both renal function and serum phosphate concentrations may lead to transient hypercalcemia as a result of changing mass law interactions.

Raisin/Grape Toxicity

Of 132 dogs reported to have had raisin or grape ingestion, 33 had no adverse effects, 14 became ill but did not have azotemia, and 43 had clinical signs and AKI. More than 90% of dogs with grape or raisin ingestion associated AKI have had increases in both serum TCa and phosphate concentrations. Ingestion of even small quantities can lead to acute life threatening kidney failure. Any dog suspected of ingesting raisins or grapes should be induced to vomit while gastric lavage and administration of activated charcoal are considered. Intravenous (IV) fluid therapy is recommended for at least 48 hours. Pathogenesis of the kidney injury and of the hypercalcemia is multifactorial (Gwaltney-Brant et al, 2001; Morrow et al, 2001; Eubig et al, 2005; Schenck and Chew, 2012). As many as 50% of these dogs do not survive, whereas many of those who have survived required days or even weeks of fluid therapy or dialysis. Higher serum TCa and TCa x phosphate products are associated with poorer prognosis.

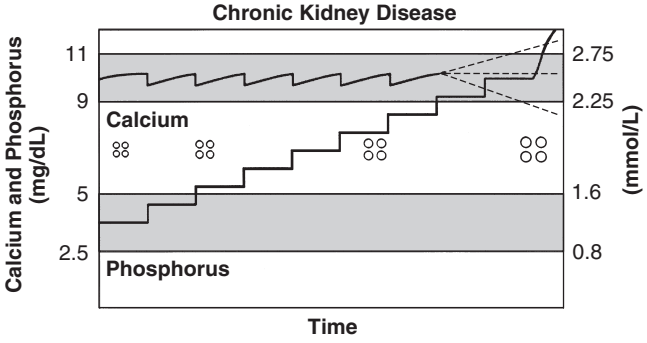


FIGURE 15-13 Diagrammatic illustration of progressive renal failure with time. Note the progressive loss in the ability to excrete phosphate, the small fluctuations in the serum calcium concentration until late in the disease, and the progressive enlargement of all four parathyroids secondary to the progressive renal failure. *Open circles,* Parathyroid gland size over time, illustrating renal secondary hyperparathyroidism.

Nutritional Secondary Hyperparathyroidism

Increased secretion of PTH associated with nutritional secondary hyperparathyroidism represents a normal compensatory response to nutritionally induced hypocalcemia. Dietary mineral imbalances capable of inducing this syndrome include diets low in calcium or vitamin D or diets containing excessive amounts of phosphorus with normal or low calcium levels (Crager and Nachreiner, 1993). Nutritional secondary hyperparathyroidism most commonly develops after the exclusive ingestion of all-meat diets, classically diets consisting solely of liver or beef heart (Capen and Martin, 1983).

Subtle and chronic decreases in the serum calcium concentration (usually not below normal reference concentrations) develop in animals fed these diets. Subtle decreases in serum iCa concentration stimulate the parathyroid glands to secrete PTH. With prolonged stimulation, chief cell hyperplasia and secondary hyperparathyroidism develop. Depletion of skeletal calcium leads to clinical signs in these animals. Pathologic bone fractures are common. Acute lameness is the most common owner observation. Because renal function is normal, hyperparathyroidism diminishes renal tubular resorption of phosphate (hyperphosphaturia) and increases resorption of calcium. These dogs and cats usually have a low-normal serum calcium concentration and a normal serum phosphorus concentration (Schenck and Chew, 2012).

Septic Bone Disease, Sepsis, Schistosomiasis, and Systemic Mycoses

Bacterial or fungal osteomyelitis and primary or secondary tumors of bone are rare causes of hypercalcemia. Neonatal septicemia in puppies with septic emboli and lysis of bone is also rare. Hypercalcemia has been associated with blastomycosis, histoplasmosis, schistosomiasis, aspergillosis, and coccidioidomycosis in dogs without apparent bone involvement (Legendre et al, 1981; Dow et al, 1986; Troy et al, 1987; Meuten and Armstrong, 1989; Rohrer et al, 2000, Fradkin et al, 2001; Parker, 2001). In one of these reports, increases in PTHrP concentration were believed to cause hypercalcemia in two dogs with schistosomiasis (Fradkin et al, 2001). The pathogenesis for sepsis-induced hypercalcemia is not certain, but inflammation associated with sepsis may cause sufficient bone destruction and mobilization of calcium to cause hypercalcemia (Meuten, 1984). The production of bone-resorbing factors such as prostaglandins and cytokines comprise the osteoclast-activating factors produced by monocytes and lymphocytes that may be involved in the pathogenesis (Mundy et al, 1984). Viable macrophages have osteolytic capabilities that may be enhanced by endotoxin (McArthur et al, 1980). Abnormal metabolism of vitamin D may also be involved in the hypercalcemia associated with granulomatous disease (Lemann and Gray, 1984).

Disuse Osteoporosis/Tumors Metastasizing to Bone

Disuse osteoporosis is a rare cause of hypercalcemia seen in animals immobilized because of extensive musculoskeletal or neurologic injury. This form of hypercalcemia is mild and is associated with bone resorption and urinary hydroxyproline excretion, decreased bone production, hypercalciuria, and osteopenia (Chew and Meuten, 1982). While metastasis of cancers to bone is relatively common in dogs and cats, hypercalcemia is not common.

Hemoconcentration, Sodium Bicarbonate Infusion, and Plasma Transfusion

Hypercalcemia occasionally may develop in severely dehydrated animals. Hypercalcemia is usually mild, perhaps resulting from volume contraction and secondary hyperproteinemia. Hypercalcemia should resolve with fluid therapy. Sodium bicarbonate infusions have been demonstrated to decrease the TCa and iCa concentrations (Chew et al, 1989). Increases in the serum TCa concentration and decreases in the iCa concentration can transiently follow plasma transfusion, presumably secondary to excesses in citrate–calcium ion complexes (Mischke et al, 1996).

Hypothermia, Fetal Retention, and Endometritis

A dog and a cat have been described with severe, environmentally induced hypothermia and hypercalcemia (Ross and Goldstein, 1981). Hypercalcemia rapidly resolved after rewarming and fluid therapy. The pathogenesis is not known. Similarly, one dog with a retained fetus and concurrent endometritis had hypercalcemia (Hirt et al, 2000). It remains to be demonstrated whether or not these conditions warrant being included in differential diagnosis lists for hypercalcemia.

Age

See Serum Total Calcium Concentration.

Laboratory Error

See Serum Total Calcium Concentration.

PRIMARY HYPERPARATHYROIDISM IN DOGS

SIGNALMENT

Age, Gender, and Weight

PHPTH is typically diagnosed in older dogs and appears to be much less common, or at least less frequently diagnosed, in cats. The mean age of dogs with PHPTH is about 11 years with a range of about 4 to 17 years (Fig. 15-14). More than 95% of dogs with this condition are 7 years of age or older. There is no apparent gender predilection.

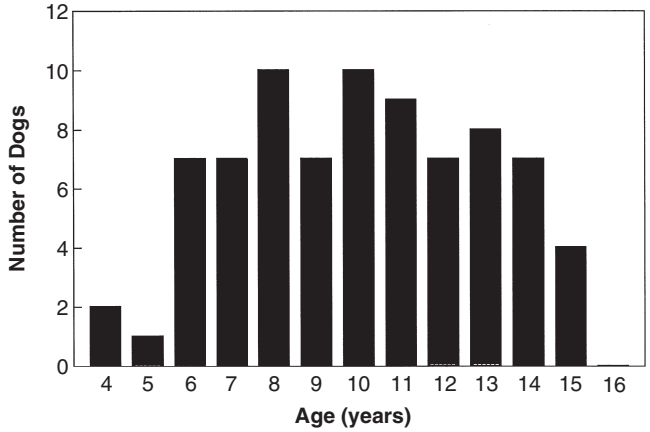


FIGURE 15-14 Age distribution of 78 dogs with primary hyperparathyroidism (PHPTH). Their mean age at the time of diagnosis was 10½ years.

TABLE 15-3 **BREED DISTRIBUTION OF 210 DOGS WITH PRIMARY HYPERPARATHYROIDISM**

BREED	PERCENTAGE
Keeshond	20
Mixed Breed	14
Labrador Retriever	9
German Shepherd dog	6
Golden Retriever	6
Springer Spaniel	5
Poodle	4
Shih Tzu	4
Australian Shepherd	3
Cocker Spaniel	3
Doberman Pinscher	2
Rhodesian Ridgeback	2
Breeds represented once	22

Data from Feldman EC et al.: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004), *J Am Vet Med Assoc* 227:756, 2005.

The mean body weight (22 kg) in one study of dogs with PHPTH included a range of 2.6 to 60 kg (Feldman et al, 2005).

Breed

PHPTH has been diagnosed in dogs from almost every breed and mixed breed. The etiology of the condition in most is unknown. PHPTH has been demonstrated to be an autosomal dominant, genetically transmitted disease in Keeshonden with possible age-dependent penetrance (Skelly and Franklin, 2006; Goldstein et al, 2007). The breeds most commonly encountered, in addition to the Keeshond are dogs of mixed breeding, Labrador Retrievers, German Shepherd dogs, Golden Retrievers, Poodles, Shih Tzu, or Springer Spaniels (Table 15-3). Hereditary neonatal PHPTH (an extremely rare condition) with a possible autosomal recessive mode of inheritance was reported in two German Shepherd dogs (Thompson et al, 1984).

ANAMNESIS: CLINICAL SIGNS

Overview

Between 20% and 50% of owners do not observe clinical signs in their dog with PHPTH, even after being told of the signs to expect. Early, mild, or even more dramatic hypercalcemia due to PHPTH may not be associated with owner observed signs. In these dogs, hypercalcemia was identified serendipitously only after a standard biochemical panel had been obtained for unrelated reasons. This serendipitous finding of hypercalcemia is also true in a majority of people with PHPTH, in whom "occult PHPTH" is more prevalent than the symptomatic form (Heath, 1989; Potts, 1990; Consensus Development Conference Panel, 1991; Silverberg et al, 1999; Wysolmerski and Insogna, 2012). When present, initial clinical signs in dogs tend to be mild, insidious, and nonspecific. Many owners can only estimate duration of signs (Table 15-4). In some cases, it is not until the pet has been treated for PHPTH that owners realize in retrospect that their dog had signs. This concept promoted the suggestion that people with PHPTH be treated regardless of perceived symptoms (Utiger, 1999).

TABLE 15-4 **APPROXIMATE DURATION OF CLINICAL SIGNS IN 210 DOGS WITH NATURALLY OCCURRING PRIMARY HYPERPARATHYROIDISM**

DURATION (MONTHS)	PERCENTAGE OF DOGS
< 1	20
1–3	20
3–6	20
6–12	25
> 12	15

Data from Feldman EC et al.: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004), *J Am Vet Med Assoc* 227:756, 2005.

TABLE 15-5 **FREQUENCY OF CLINICAL SIGNS REPORTED PROSPECTIVELY OR RETROSPECTIVELY IN 210 DOGS WITH PRIMARY HYPERPARATHYROIDISM***

SIGN	PERCENTAGE OF DOGS
Urinary tract signs Straining (stranguria) Frequency (pollakiuria) Blood (hematuria)	50
Polyuria/polydipsia	48
Weakness	46
Exercise intolerance	46
Listlessness	43
"Incontinence" (polyuria?)	39
Inappetence	37
Weight loss	18
Muscle wasting	18
Vomiting	13
Shivering	10
Constipation	6
Stiff gait	5

Data from Feldman EC et al.: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004), *J Am Vet Med Assoc* 227:756, 2005.
*Sixty-nine out of 210 owners reported no abnormalities.

As many as half of dogs with PHPTH have had or have signs at the time of a diagnosis related to stones or a urinary tract infection (pollakiuria, stranguria, and/or hematuria). Additional common owner observations include polyuria/polydipsia "incontinence", decreased activity, lethargy, and muscle weakness; decreased appetite; weight loss; and muscle atrophy (Feldman et al, 2005; Gear et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). Less commonly, owners have noted shivering/trembling, vomiting, constipation, diarrhea, and stiff or painful gait. Although quite uncommon, some PHPTH dogs were extremely ill when first examined due to renal failure. Central nervous system (CNS) signs include mental dullness and, far less commonly, signs of obtundation, seizures, collapse, or coma

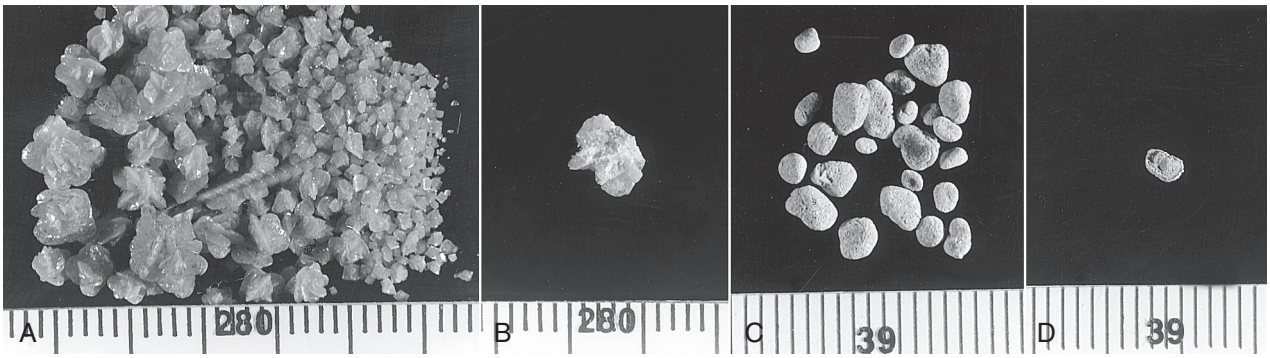


FIGURE 15-15 Calcium-containing cystic calculi from two dogs with primary hyperparathyroidism (PHPTH) **(A** and **C)** and individual cracked calculi from each dog **(B** and **D).**

(Table 15-5). In general, the more worrisome the clinical signs in a hypercalcemic dog, the greater the likelihood that the increase in calcium is not due to PHPTH. Extremely serious signs are usually the result of the underlying cause for the hypercalcemia (e.g., cancer, renal failure, hypoadrenocorticism, and/or toxin). However, in one report, about one third of 29 dogs with PHPTH were described as having renal failure (Gear et al, 2005).

Polydipsia and/or Polyuria

The most common clinical signs in dogs with PHPTH are polyuria, polydipsia, and/or urinary "incontinence." Polyuria develops as a result of impaired renal tubular response to antidiuretic hormone (ADH). In the normal state, ADH binds to V2 receptors located in the basolateral membrane of principal cells in the renal collecting tubules. Binding causes increased expression of aquaporin-2 water channels within apical cell membranes, increasing permeability to water and promoting water reabsorption (Shiel, 2012). Hypercalcemia interferes with ADH binding to V2 receptors. This acquired and reversible nephrogenic diabetes insipidus causes production of relatively dilute, solute-free urine (polyuria) and compensatory polydipsia.

Urinary Tract Calculi and Infections

Nephrocalcinosis, the diffuse deposition of calcium phosphate complexes in the renal parenchyma, and ureteroliths have not been commonly reported in dogs with PHPTH. Cystic calculi are common in dogs with PHPTH with the most common stone being calcium oxalate or mixed calcium oxalate and calcium phosphate (Fig. 15-15). The risk factors for stone formation in patients with PHPTH are hypercalciuria and a tendency to have renal losses of bicarbonate and phosphate. The loss of bicarbonate leads to relatively alkaline urine, favoring the precipitation of calcium phosphate. The incidence of urinary tract infection is increased with the presence of uroliths. Further, it is possible that the relatively dilute urine and, perhaps, some degree of decreased bladder tone following chronic excess urine production may also contribute to their incidence of infection. Both of these latter factors can lead to urine retention because of an inability to completely void.

Chronic Kidney Disease or Acute Kidney Injury

It is unclear in people whether PHPTH impairs renal function. In the majority of untreated human PHPTH patients followed over time, some for longer than a decade, renal function remains both normal and stable (Silverberg et al, 1999; Wysolmerski and Insogna, 2012). Why PHPTH seems to adversely affect kidney function in a few dogs and not the majority is not understood. Hydronephrosis and loss of function secondary to obstruction caused by nephroliths or ureteroliths is logical, but some dogs with severe kidney failure and PHPTH have not been described as having had obstructive disease. Dogs with PHPTH typically have decreases in serum phosphate concentrations and their calcium x phosphate products, usually similar or less than values in healthy dogs, have been considered a predictor of stable kidney function. In more than 300 dogs with PHPTH, renal failure was extremely uncommon (Feldman et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). However, in one report of 29 dogs with PHPTH, 13 had mild to severe kidney failure (Gear et al, 2005).

Lethargy, Weakness, Shivering, and Muscle Atrophy

Listlessness, decreases in activity and/or weakness are observed in one third to one half of dogs with PHPTH, whereas the signs of shivering, trembling, or stiff gait are less common (Feldman et al, 2005; Gear et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). Increased serum calcium concentrations tend to hyperpolarize membranes. This may cause a range of muscular, neuromuscular, and/or neurologic abnormalities in people with PHPTH—some of whom have been described as developing fatigue, weakness, and myopathies. Some, but not all affected individuals, comment on their weakness, fatigue, listlessness, and difficulty concentrating. However, the specificity and origin of these symptoms are debated (Wysolmerski and Insogna, 2012). Analogous abnormalities in dogs may explain the common observation of listlessness and/or "depression" associated with this disorder. Shivering and muscle twitching have uncommonly been observed in hypercalcemic dogs, as has the extremely unusual problems of circling or ataxia (Chew and Capen, 1980). Seizure activity has been reported in several dogs with PHPTH (Ihle et al, 1988; Gear et al, 2005; Arbaugh et al, 2012). The mechanism for these problems is not well understood but in rare cases may progress to stupor or coma. "Collapse" was described in two of 29 dogs in one report (Gear et al, 2005).

Inappetence, Weight Loss, and Abdominal or Nonspecific Pain

Hypercalcemia impairs gastrointestinal motility via decreases in excitability of smooth muscle. This may contribute to the signs of reduced appetite and subsequent weight loss observed in one-third to one half of PHPTH people (Wysolmerski and Insogna, 2012) and dogs. Abdominal pain, vomiting, and diarrhea are recognized but seem uncommon. Constipation, described in some people with PHPTH, is quite uncommon in dogs. The development of gastric or duodenal ulcers secondary to increases in gastrin

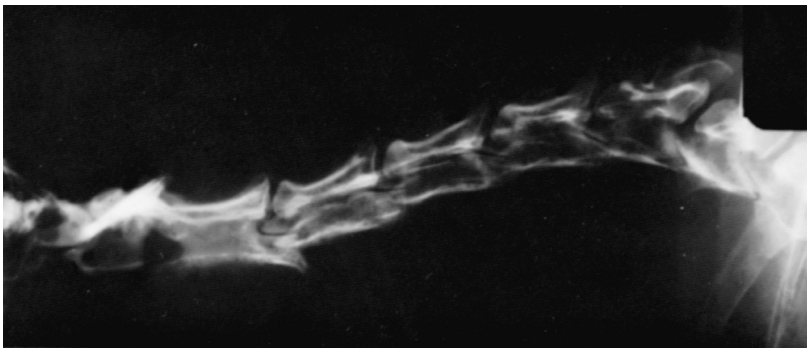


FIGURE 15-16 Lateral radiograph of the cervical spine from a dog with multiple myeloma and hypercalcemia. Note the severe osteolysis involving several vertebrae. These findings are consistent with a diagnosis of the hypercalcemia of malignancy syndrome.

secretion has been documented in hypercalcemic people but has not yet been reported in dogs (Aurbach et al, 1985a). Weight loss and decreases in appetite are far more common. Nonspecific arthralgias are complications recognized in humans with PHPTH (Arnaud and Kolb, 1991) and may account for the pain or stiff gait occasionally observed in dogs.

Stiff Gait, Fractures, and Skeletal Pain

Stiff gait and fractures are both uncommon but have been associated with PHPTH (see Table 15-5). Excessive subperiosteal bone resorption and osteoporosis induced by PHPTH can result in replacement of bone matrix with fibrous tissue (Fig. 15-16). This thinning and weakening is more likely in cortical bone, leading to fracture predisposition (Wysolmerski and Insogna, 2012). Lameness may be associated with pain as skeletal changes progress.

PHYSICAL EXAMINATION

General Observations

The physical examination was unremarkable in about 66% to 75% of dogs with PHPTH (Feldman et al, 2005). When abnormalities are found, they typically are related to the presence of uroliths, some concurrent and unrelated condition, or they are subtle and nonspecific. This concept is important, because the differential diagnoses for dogs with a serendipitous finding of hypercalcemia include lymphosarcoma, CKD, apocrine gland carcinoma of the anal sac, hypoadrenocorticism, multiple myeloma, vitamin D toxicosis, and granulomatous diseases. Dogs with any of these other conditions are usually ill or quite ill. In other words, a relatively stable or apparently healthy older dog with hypercalcemia is more likely to have PHPTH than one of the serious conditions that cause secondary hypercalcemia.

Common Abnormalities

Potential physical examination findings in dogs with PHPTH, other than those caused by uroliths, include thin body composition, generalized muscle atrophy, and/or weakness. Severity of these abnormalities is variable, but they are usually mild. Bone deformities involving the mandible or maxilla and fractures of long bones have been reported (Capen and Martin, 1983; Gear et al, 2005) but are extremely rare.

Ophthalmologic Changes

Infrequent ocular abnormalities in humans with PHPTH include "band keratopathy" and subconjunctival deposits of calcium (Aurbach et al, 1985a). Band keratopathy results from the deposition of calcium phosphate in the cornea. The condition is recognized as opaque material appearing as parallel lines in the limbus of the eye, best visualized on slit lamp examination.

Palpable Parathyroid Masses

It is extremely unusual to palpate an enlarged parathyroid gland in dogs. A palpable parathyroid mass has been reported in only one of more than 300 dogs with PHPTH (Feldman et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). Even with confirmed PHPTH, a nodule felt in the neck is much more likely to involve the thyroid or some other structure than a parathyroid. About 10% to 20% of dogs with PHPTH had an incidentally discovered thyroid mass on cervical ultrasonography in one study (Pollard et al, in press). Parathyroid masses are not palpable because they are located dorsolateral to the trachea, are usually 4 to 8 mm in diameter, and they are covered by several muscle layers. Although an enlarged parathyroid gland was not palpable in any of our dogs, palpable tumors have been identified in cats with PHPTH.

Importance of a Thorough Physical Examination

A thorough physical examination is imperative in any animal with documented hypercalcemia. Physical examination results are usually normal in dogs with PHPTH. Because the more common causes of hypercalcemia in dogs include malignant cancers, hypoadrenocorticism, toxicosis, CKD, and other worrisome conditions, the diagnostic approach to the dog with confirmed hypercalcemia is to rule out these differential diagnoses as completely as possible. Careful palpation of peripheral lymph nodes, mammary glands, perineal region, as well as digital rectal and vaginal examinations should be included. Lymphosarcoma, for example, can be extremely easy or extremely difficult to diagnose, and it is a condition not removed from a list of differential diagnoses until an alternative diagnosis has been confirmed. In addition to hypercalcemia of malignancy, other causes of hypercalcemia may be suspected after a thorough physical examination. Dogs with CKD or AKI may have palpably abnormal kidneys. Dogs with hypoadrenocorticism may have bradycardia, weak femoral pulses, melena, or a bloody rectal discharge.

CLINICAL PATHOLOGY

Hemogram

The hemogram is usually unremarkable in dogs, whereas people with PHPTH may have a nonregenerative anemia and elevation in erythrocyte sedimentation rates. In dogs with PHPTH,

TABLE 15-6 SERUM BLOOD UREA NITROGEN, CREATININE AND INORGANIC PHOSPHORUS (PHOSPHATE) CONCENTRATIONS, AND URINE SPECIFIC GRAVITIES AT TIME OF DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM IN 210 DOGS

	BLOOD UREA NITROGEN (mg/dL)	SERUM CREATININE (mg/dL)	SERUM PHOSPHATE (mg/dL)	URINE SPECIFIC GRAVITY
Reference range	18-28	0.5-1.6	3.0-6.2	—
Mean	16.9	0.8	2.8	1.012
Median	15	0.8	2.7	1.010
Ranges	5-92	0.4-4.1	1.3-6.1	1.008-1.037
Number / % ↑ reference range	9/4%	7/3%	0	—
Number / % ↓ reference range	132/63%	9/4%	136/65%	—

Data from Feldman EC et al.: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004), *J Am Vet Med Assoc* 227:756, 2005.

TABLE 15-7 DOGS WITH PRIMARY HYPERPARATHYROIDISM: SERUM TOTAL AND IONIZED CALCIUM CONCENTRACTIONS (210 DOGS), SERUM PARATHYROID HORMONE CONCENTRATIONS (185 DOGS), AND ULTRASONOGRAPHICALLY IDENTIFIED PARATHYROID MASSES (117 DOGS, EACH WITH A SOLITARY NODULE, AND 13 DOGS, EACH WITH TWO NODULES)

	TOTAL CALCIUM (mg/dL)	IONIZED CALCIUM (mmol/L)	PARATHYROID HORMONE (pmol/L)	ULTRASOUND MASS SIZE (mm)
Reference range	9.9-11.7	1.12-1.41	2-13	< 4
Mean	14.5	1.71	11.3	6
Median	14.3	1.77	11.3	5
Range	12.1-23.4	1.22-2.41	2.3-121	3-23
Number / % ↓ reference range	0	0	0	—
Number / % ↑ reference range	210/100%	191/91%	50/27%	—

Data from Feldman EC et al.: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004), *J Am Vet Med Assoc* 227:756, 2005.

no specific changes in bone marrow aspirates or peripheral blood smears are seen.

Biochemical Profile

Serum Total Calcium Concentration

Various factors can alter the reported serum TCa concentration and the differential diagnoses for hypercalcemia includes a number of possibilities. This increases the importance of many serum biochemistry parameters. Specifically, the serum calcium concentration should be assessed relative to serum albumin, phosphorus, BUN, and creatinine concentrations (Table 15-6).

Hypercalcemia is the hallmark abnormality of PHPTH (see Figs. 15-5 and 15-12). The mean serum calcium concentrations from four reports were 13.9, 14.3, 13.6, and 13.6 mg/dL, respectively, with an approximate range of 12.1 to 23.4 mg/dL (Feldman et al, 2005; Gear et al, 2005; Ham et al, 2009; Milovancev and Schmiedt, 2013; Table 15-7). These mean values could be slightly inflated because evaluation of hypercalcemia is often limited to animals with a serum TCa concentration greater than 12.0 mg/dL (the upper reference range limit is often about 11.5 to 11.8 mg/dL). After initial recognition of hypercalcemia and referral, 52% of dogs with PHPTH had an initial TCa concentration more than 12 but less than 14 mg/dL; about 30% had concentrations between 14 and 16 mg/dL, 12% had results of 16 to 18 mg/dL, and 6% had values in excess of 18 mg/dL (Feldman et al, 2005). One of eight dogs with serum TCa concentration more than18 mg/dL in that study had a mildly increased BUN concentration; the other seven had results within or below the reference range.

It seems logical that untreated PHPTH would result in progressively increasing serum calcium concentrations over time. This, however, has not been the experience in people. A group of 60 people with untreated PHPTH were evaluated periodically for 10 years. The mean total serum calcium concentration at the time of diagnosis was 10.5 mg/dL (reference range, 8.4 to 10.2 mg/dL); after 5 years it was 10.6 mg/dL and after a total of 10 years, it was 10.3 mg/dL (Silverberg et al, 1999). However, eight individuals developed uroliths during the decade, leaving 52 who remained asymptomatic. Two of 52 individuals (3.8%) developed "marked hypercalcemia" (defined as a serum calcium concentration greater than 12 mg/dL) during the study period, eight had significant hypercalciuria, and six had decreasing bone density. All 52, however, remained relatively asymptomatic. Dogs with PHPTH have persistent hypercalcemia and our subjective experience suggests that their hypercalcemia slowly increases with time.

Factors Affecting the Serum Calcium Concentration

Sample Error and Other Non-Pathologic Conditions. Marked lipemia can falsely increase serum TCa concentrations determined by some automated analyzers. Hemoconcentration (dehydration) and hyperproteinemia can produce mild increases in TCa. Hemolysis can also falsely increase the serum

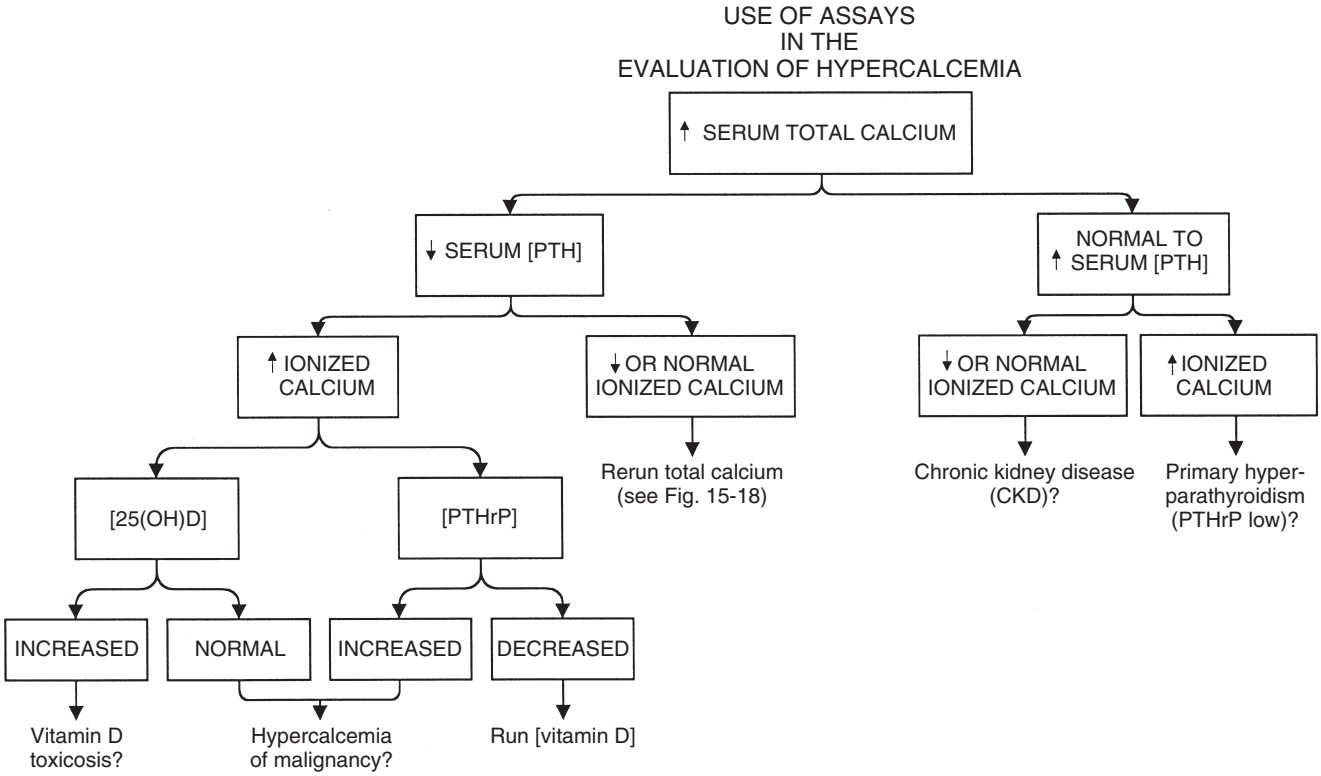


FIGURE 15-17 Algorithm showing the potential value and use of various assays in the evaluation of hypercalcemic dogs. *25(OH)D,* 25-hydroxyvitamin D; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone–related protein.

TCa concentration measured with some automated analyzers. Young growing animals may have mild increases in serum calcium concentration, and postprandial samples may, rarely, yield false increases. Excess use of oral phosphate binders may cause the serum calcium concentration to increase. Collection and storage of samples in glassware or plastic containers that have been washed with detergents may falsely increase or decrease calcium values. Simple prolonged storage may yield artifactual decreases in the calcium concentration, and contamination (chalk writing boards in the laboratory) may yield false increases. Confirmation of hypercalcemia with a fresh blood sample would help rule out any of these concerns (Schenck and Chew, 2012).

Acid-Base Status. Acidosis decreases plasma protein–binding affinity for calcium, increasing iCa concentrations and creating mild physiologic hypercalcemia. Alkalosis has the opposite effect, creating a physiologic hypocalcemia. The total serum calcium concentration appears to change with the acid-base status in a manner roughly parallel to the change in iCa concentration (Meuten, 1984).

Age. Age should be considered when serum concentrations of calcium, phosphorus, and alkaline phosphatase are evaluated. Young dogs have higher concentrations than adults (Meuten, 1984; Schenck and Chew, 2012). Reference values for TCa concentrations in young dogs were approximately 11.1 ± 0.4 mg/dL (10.5 to 11.5 mg/dL), higher than those observed in adults (8.8 to 11.0 mg/dL) (Meuten et al, 1982).

Serum Ionized Calcium Concentration

The iCa fraction of total circulating calcium concentrations is biologically active. Valid assays for iCa can be an integral component of determining the cause for a hypercalcemic condition (Figs. 15-17 and 15-18). The mean iCa concentration from more than 135 dogs with PHPTH reported in five studies was consistently above the reference range (Gear et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). In one study, 19 (9%) of 210 dogs with PHPTH had a serum iCa concentration within the reference range. These reference range results may have been affected by external factors (aerobic collection, pH) affecting the ionized result without altering serum TCa concentrations. In that latter study, about 25% had mildly increased serum iCa concentrations (1.42 to 1.65 mg/dL), about 50% had results of 1.66 to 1.90 mg/dL, and less than 20% had iCa concentrations more than1.9 mg/dL (Feldman et al, 2005).

Serum Phosphorus Concentration

Low or low-normal serum phosphorus concentrations (< 4.0 mg/dL) are typical of PHPTH (see Fig. 15-12). Hypophosphatemia develops after PTH-induced inhibition of renal tubular phosphorus resorption, resulting in excessive urinary losses. In three reports on more than 300 dogs with PHPTH, the mean serum PO_4 concentration was 2.9, 2.8, and 2.86 mg/dL (Feldman et al, 2005; Gear et al, 2005; Milovancev and Schmiedt, 2013). Reference ranges were similar in these reports (about 3.0 to 6.2 mg/dL). In one report, dogs with PHPTH had results that ranged from 1.3 to 6.1 mg/dL, with none above the reference range, and in another report, only two of 29 dogs had values above their reference range despite 13 of 29 dogs having increases in BUN and evidence of CKD and/or AKI (Feldman et al, 2005; Gear et al, 2005).

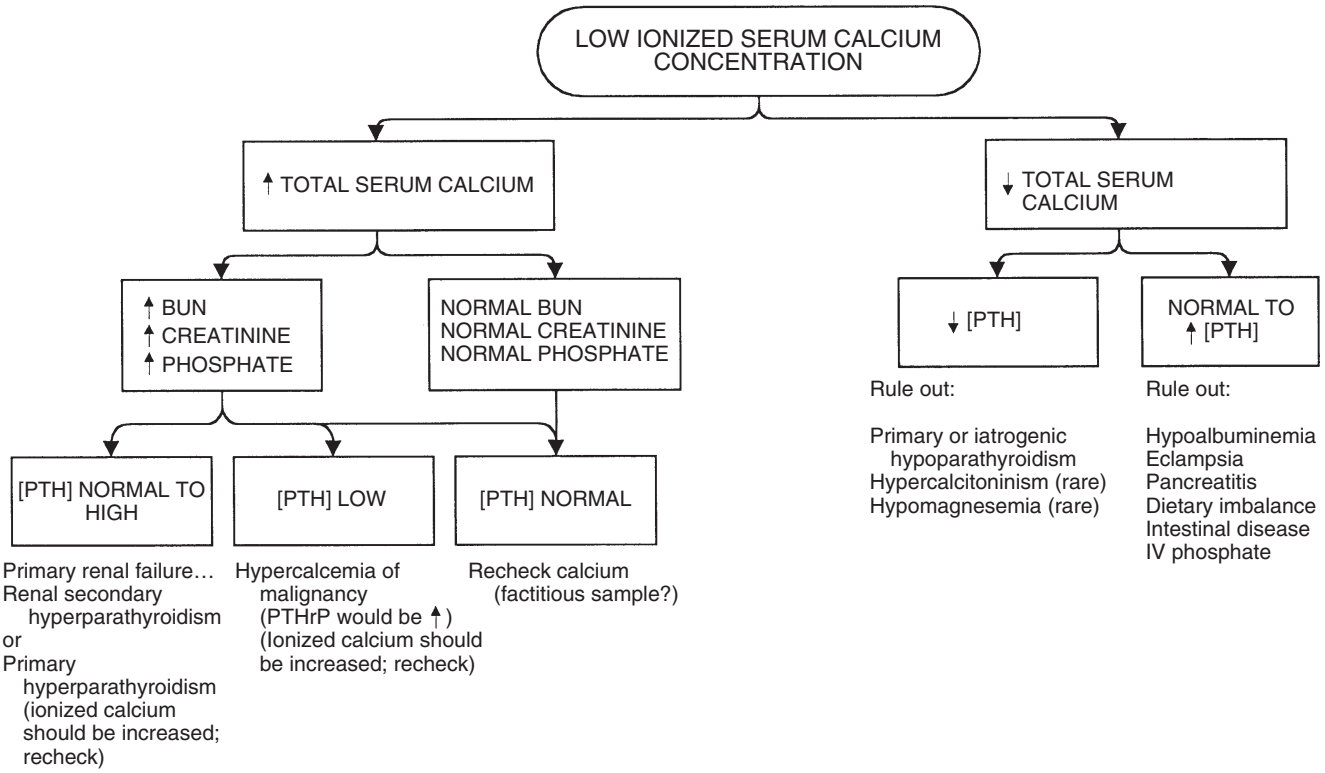


FIGURE 15-18 Algorithm for determining the cause of decreases in the ionized serum calcium concentration in dogs. *BUN,* Blood urea nitrogen; *IV,* intravenous; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone–related protein.

The serum phosphorus concentration should always be evaluated relative to the serum calcium concentration and renal parameters. Hypophosphatemia, when dietary phosphate is adequate and oral phosphate-binding agents are not being given, is consistent with either PHPTH or hypercalcemia of malignancy (see Fig. 15-12). Other causes of hypophosphatemia are less common (Box 15-2). Hyperphosphatemia in the absence of azotemia suggests a non-parathyroid cause of hypercalcemia. When both hyperphosphatemia and azotemia are present, the clinician must rely on the history, physical examination, and other parameters to determine the primary disorder. Differentiation remains a diagnostic dilemma. Dogs with CKD and an increased TCa concentration usually have iCa concentrations that are normal or mildly low, in contrast to dogs with PHPTH, in which both total and the ionized fractions are increased.

Age should also be considered when evaluating the serum phosphorus concentration. Young dogs (< 1 year old) tend to have a higher serum phosphorus concentrations than adults. Puppies may have similar serum phosphorus and calcium concentrations (i.e., both approximately 10 to 12 mg/dL). However, the serum phosphorus concentration gradually declines during puppyhood, reaching normal adult concentrations by 4 to 12 months of age.

Blood Urea Nitrogen and Serum Creatinine

Blood Urea Nitrogen. Almost all dogs with PHPTH have normal renal parameters (BUN, creatinine; see Table 15-6). Among about 320 dogs with PHPTH, the incidence of abnormally increased renal parameters was 4% or less. In one study of 210 dogs with PHPTH, their mean BUN of 16.9 mg/dL was below the reference

BOX 15-2 Potential Causes of Hypophosphatemia

Decreased Intestinal Absorption
Decreased dietary intake
Malabsorption/steatorrhea
Vomiting/diarrhea
Phosphate-binding antacids
Vitamin D deficiency

Increased Urinary Excretion
Primary hyperparathyroidism (PHPTH)
Diabetes mellitus ± ketoacidosis
Hyperadrenocorticism (naturally occurring/iatrogenic)
Fanconi syndrome (renal tubular defects)
Diuretic or bicarbonate administration
Hypothermia recovery
Hyperaldosteronism
Aggressive parenteral fluid administration
Hypercalcemia of malignancy (early stages)

Transcellular Shifts
Insulin administration
Parenteral glucose administration
Hyperalimentation
Respiratory alkalosis

range of 18 to 30 mg/dL. Three percent had a BUN less than 10, and 60% had concentrations of 10 to 17. Thus, almost two thirds of dogs with PHPTH had BUN concentrations less than the lower limit of the reference range. About 25% had results in the lower half of the reference range, and 10% had results in the upper half of the reference range. Nine of the 210 dogs had abnormally increased BUN concentrations, ranging from 31 to 92 mg/dL. The serum TCa concentrations from these nine dogs were not significantly different from the dogs whose BUN concentrations were within or below the reference range (Feldman et al, 2005). One report on 29 dogs with PHPTH, however, included 13 dogs with increases in BUN, 10 of which were "marked" (Gear et al, 2005). By contrast, renal failure was not mentioned or rare in the reports on about 110 dogs with PHPTH (Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013).

Creatinine. Mean serum creatinine concentrations for 210 dogs with PHPTH were 0.8 mg/dL. Sixty percent of the dogs had results less than 1.0, and 37% had values of 1.0 to 1.5 mg/dL. Thus, 97% had results within the reference range. Three percent (seven dogs) had results above 1.5 mg/dL. The highest serum creatinine concentration in any dog was 4.1 mg/dL, and six of the seven dogs had increases in both BUN and creatinine concentrations. Four dogs with increases in both BUN and creatinine concentrations had been diagnosed with CKD 3 to 24 months before becoming hypercalcemic.

Renal Values in Dogs Who Do Not Have Primary Hyperparathyroidism. In the study on 210 dogs with PHPTH, 200 control dogs that did not have PHPTH had significantly higher mean BUN and creatinine concentrations. It would appear that dogs with PHPTH are less likely to have abnormal renal parameters than dogs that do not have PHPTH. Whether this is the result of the low calcium x phosphate product or some other factor is not known. In one study, the TCa x phosphate product was not predictive of renal failure (Gear et al, 2005) and that study had far more dogs with renal failure than was seen in five studies on 320 dogs with PHPTH (Feldman et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013).

The uncommonly encountered combination of azotemia, hypercalcemia, hyperphosphatemia, and increases in serum PTH concentrations represents a diagnostic challenge. Such changes could lead to renal failure or develop as a consequence of renal failure. Increases in serum TCa concentration have been documented in as many as 10% to 15% of dogs with CKD, with hypercalcemia worsening severity of azotemia. However, the deleterious effects of hypercalcemia may only be associated with abnormally increased serum iCa concentrations. Fewer than 10% of all dogs with CKD have increases in iCa, most have normal or low concentrations. As discussed, the serum iCa is usually normal or low in CKD and almost always increased with PHPTH. Rarely, tertiary hyperparathyroidism occurs in dogs with CKD as an extremely unusual progression of renal secondary hyperparathyroidism. It is most likely due to an alteration in the set point for circulating iCa (Schenck and Chew, 2012). Use of both serum iCa and PTH concentrations are useful in determining cause (see Figs. 15-17 and 15-18). It is possible for PHPTH to predispose a small percentage of dogs to kidney injury, that some dogs with PHPTH may also have CKD, or that some dogs with CKD develop tertiary hyperparathyroidism, accounting for what might be autonomous secretion of PTH.

Serum Alkaline Phosphatase

In humans, an increase in serum alkaline phosphatase (SAP) is more common in hypercalcemia of malignancy than in PHPTH (Arnaud and Kolb, 1991). Increases in SAP activity are nonspecific in veterinary medicine; about 40% of dogs with PHPTH had an increased result. When present, increases were generally mild (twofold to sixfold) with a mean of 240 IU/L (range, 12 to more than 4,000 IU/L; reference range, 5 to 92 IU/L). The increased activity of this enzyme, when present, is thought to result from a compensatory increase in osteoblastic activity in bone trabeculae as a response to mechanical stress in bone weakened by excessive resorption (Capen and Martin, 1983).

Serum Alanine Aminotransferase

Serum alanine aminotransferase (ALT) concentrations are usually normal in dogs with PHPTH. Mild increases are nonspecific and not usually worrisome. The suggestion that mild increases may reflect hepatic ischemia due to systemic dehydration seems unlikely. Moderate to marked increases in ALT should raise concern that a separate and concurrent liver condition exists.

Serum Chloride Concentration

In people, excess PTH secretion decreases the proximal renal tubular resorption of bicarbonate, leading to increased resorption of chloride and the production of mild hyperchloremic renal tubular acidosis. Increased serum chloride concentrations in people with PHPTH often are associated with serum chloride-to-phosphate ratios greater than 33 (Arnaud and Kolb, 1991). With the availability of reliable PTH and PTHrP assays, the increases in the serum chloride concentration are less critical as a diagnostic tool but may aggravate existing hypercalcemia by impairing binding of calcium to albumin and by increasing the dissolution of bone mineral.

Urinalysis

Urine Specific Gravity

Many dogs with PHPTH have relatively dilute urine on randomly collected home-caught or in-hospital obtained samples. In 210 dogs with PHPTH, their mean urine specific gravity (USG) was 1.012. Fifty dogs (24%) had a USG less than 1.008 on randomly collected urine; 75 (36%) had a result of 1.008 to 1.012; 70 (33%) had a results ranging from 1.013 to 1.020; eight (4%) had a USG of 1.021 to 1.030; and seven had a result greater than 1.030 (see Table 15-6). These results reflect the effect of hypercalcemia interfering with the action of ADH action at the renal tubular level causing a reversible form of nephrogenic diabetes insipidus. Randomly obtained USG from 140 age-matched control dogs that did not have PHPTH had a significantly higher mean of 1.025 (Feldman et al, 2005).

Isosthenuria (or hyposthenuria) is a common consequence of hypercalcemia, regardless of its etiology. The combination of hypercalcemia and dilute urine is considered a cause and effect phenomenon, but it is not specific for any condition. Confusion regarding cause may arise because CKD is a differential diagnosis for isosthenuria. A thorough review of the serum chemistry profile and other parameters may be necessary to determine cause of isosthenuria or hyposthenuria.

Urine Sediment

Hematuria, pyuria, bacteriuria, and/or crystalluria are often identified in the urine sediment of dogs with PHPTH. Hypercalciuria, proximal renal tubular acidosis with impaired bicarbonate resorption, and the production of alkaline urine may predispose dogs to the development of bacterial cystitis and urolith formation. Urinary tract infection, at the time of PHPTH diagnosis, was identified in almost 30% of 210 dogs. One third of those dogs

had concurrent cystic calculi. Cystic calculi had been surgically removed from 42 of 210 dogs (20%) in the 6 month period preceding diagnosis of PHPTH. Fifty dogs (24%) had cystic calculi when seen at our hospital, but 27 of those 50 were among the 42 who had already had surgery, indicating recurrence. Thus, a total of 65 dogs (31%) with PHPTH had cystic calculi. All analyzed calculi were calcium oxalate, calcium phosphate, or both (Feldman et al, 2005; see Fig. 15-15).

Electrocardiography

Experimentally induced hypercalcemia may increase myocardial contractility, shorten mechanical ventricular systole, and decrease myocardial automaticity. Potential electrocardiographic changes caused by hypercalcemia include a prolongation of the P-R interval and a shortening of the QT interval as a result of a shortened ST segment (Feldman, 1989). Theoretically, the decrease in myocardial conduction velocity and the shortened refractory period could predispose to arrhythmias. Cardiac abnormalities are rare in dogs with PHPTH.

IMAGING

Radiography

General

Conventional radiography plays an integral role in the diagnostic evaluation of hypercalcemic dogs or cats. Thoracic radiographs should be obtained in order to screen for neoplasia. Abdominal ultrasonography may be preferred over radiographs, although these imaging modalities are complementary. Lack of thoracic or abdominal radiographic or ultrasonographic abnormalities in a dog with hypercalcemia is consistent with PHPTH.

Thoracic Radiographs

The anterior mediastinum, perihilar, and sternal lymph nodes should be evaluated for mass effect or lymphadenopathy. The classic finding in hypercalcemic dogs with lymphosarcoma is an anterior mediastinal mass (Fig. 15-19). The ribs, vertebrae, and any long bones included in the study should be evaluated for osteolytic areas arising from myeloma or other metastatic tumors. The lung fields should be carefully assessed for nodules that might represent primary or metastatic lesions.

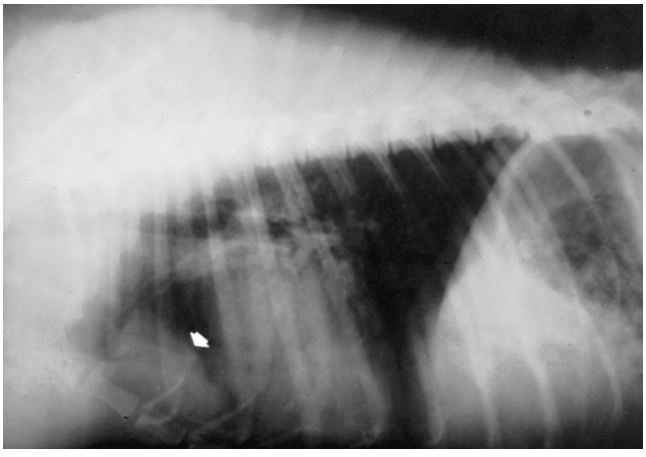


FIGURE 15-19 Lateral radiograph of the thorax of a dog with lymphosarcoma and hypercalcemia. Note the sternal lymphadenopathy *(arrow).*

Abdomen and Skeleton

Other than urinary tract calculi, radiographic alterations associated with PHPTH are rare. As previously discussed, cystic calculi are common and urethral calculi are always a concern, especially in male dogs. Uroliths have quite uncommonly been identified in the kidneys and ureters. The sublumbar area and mesenteric lymph nodes can be evaluated for any mass effect that might be indicative of metastatic apocrine gland carcinoma of the anal sac, lymphoma, or other neoplastic process (Fig. 15-20). The liver and spleen should be similarly evaluated for enlargement or irregularities associated with neoplasia.

Osteitis fibrosa cystica, the classic bony abnormality of primary and secondary hyperparathyroidism in humans, is rarely seen in dogs. It is manifested radiographically as generalized osteopenia due to increased bone resorption, especially at the subperiosteal surfaces, and the formation of cysts or cystlike areas in bone. In humans the phalanges and skull are usually involved. In severe cases, the long bones, patella, and ribs may become involved. The clinical manifestations of osteitis fibrosa cystica are bone pain, pathologic fractures, bone cysts, and localized swelling of bone (Hruska and Teitelbaum, 1995). Radiographic changes rarely associated with PHPTH in dogs include loss of the lamina dura, fractures of the long bones and vertebrae, and soft tissue calcification. Fractures have been described in only one of more than 340 dogs with PHPTH (Feldman et al, 2005; Gear et al, 2005; Ham et al, 2009; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013).

Ultrasonography

Neck

Background. Parathyroid ultrasonography has been used extensively in people as part of the diagnostic evaluation for hypercalcemia. Applications have included differentiation of primary and secondary hyperparathyroidism; confirmation of suspect lesions by ultrasound-guided, fine-needle aspiration biopsy; and presurgical localization of parathyroid adenomas (Attie et al, 1988; Krubsack et al, 1989; Lloyd et al, 1990). Reported sensitivity of ultrasonography in identifying one or more abnormal parathyroid glands in people is well over 90% (Wysolmerski and Insogna, 2012). In dogs, parathyroid glands as small as 1 to 2 mm

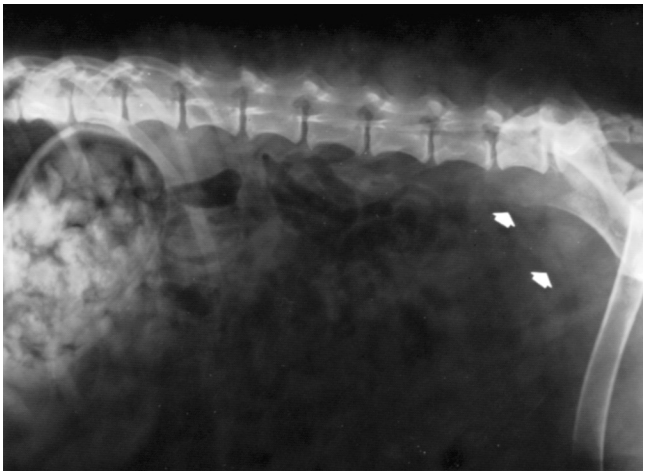


FIGURE 15-20 Lateral radiograph of the caudal abdomen of a dog with apocrine gland adenocarcinoma of the anal sac and hypercalcemia. Note the multiple masses in the sublumbar region and pelvic canal *(arrows),* which are suggestive of sublumbar lymph nodes that have been invaded by the neoplasia.

in diameter can be visualized. Accuracy of ultrasonographic evaluation is determined by facilities as well as the skill and experience of the ultrasonographer.

An "ectopic" location for parathyroid tumors is possible. Although reported in humans, ectopic parathyroid tumors have not been reported in dogs or cats. Localization of ectopic abnormal parathyroid tissue can be difficult. In humans, noninvasive procedures that can be used include esophagoscopy, computed tomography (CT), and radionuclide scans. Invasive procedures include thyroid arteriography, selective venous catheterization of the neck and mediastinal veins, and surgical exploration of the anterior mediastinum (Arnaud and Kolb, 1991). Although ectopic parathyroid tissue or tumor is rare, this condition may be considered in any dog whose testing is indicative of PHPTH but whose cervical ultrasonographic examination is negative. Visualization of "normal" parathyroid glands without seeing a "nodule" is not consistent with PHPTH. If the parathyroid glands seem small or not visualized, one may suspect an ectopic location. This would also be a concern should a surgeon be unable to see any abnormal thyroid-parathyroid tissue.

Dogs. The parathyroid glands in healthy dogs can be routinely visualized (Wisner et al, 1991; Reusch et al, 2000; Pollard et al, in press). Parathyroid masses are usually solitary, round or oval, well marginated, and hypoechoic to anechoic compared with surrounding thyroid gland parenchyma (Fig. 15-21). Occasionally two enlarged parathyroid glands may be identified in dogs with PHPTH. Seeing three or four enlarged glands is not typical. Not every nodule in the parathyroid anatomic region is obvious. Some masses have not been seen, whereas the cell type of others is sometimes questioned. The most common concern was whether an identified mass was thyroid or parathyroid (see Incidentally Discovered Thyroid Masses).

Parathyroid masses (usually adenomas) from dogs with PHPTH have been as small as 2 mm to as large as 23 mm in diameter. Most adenomas are 4 to 10 mm in diameter and easily visualized (Wisner et al, 1993; Wisner and Nyland, 1994). A statistically significant size difference was reported for solitary hyperplastic parathyroid glands (2 to 6 mm, mean 2.9 mm) as compared with solitary parathyroid adenomas or adenocarcinomas (4 to 20 mm, mean 7.5 mm) (Wisner et al, 1997).

Similar to reports in people, ultrasonography correctly identified parathyroid mass size and location (as determined by surgery) in 63% to 100% of dogs with PHPTH (Feldman et al, 2005; Gear et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). Although a reference range for parathyroid gland size on ultrasonographic examination has not been established for dogs, it has been suggested that most healthy dogs have glands 1 to 3 mm in greatest diameter. For the 142 masses correctly identified in one study, the mean abnormal parathyroid gland was 6 mm (range, 3 to 23 mm) in greatest diameter. Sixty percent of the nodules were 3 to 6 mm in greatest diameter, 24% were 7 to 10 mm, 10% were 11 to 15 mm, and 6% were greater than 15 mm in greatest diameter. In this study, 116 dogs had a solitary parathyroid mass and 13 dogs (10%) had 2 distinct masses. No dog had more than two masses identified (Feldman et al, 2005; see Table 15-7). In another study, 76% of the ultrasonographic assessments were correct as determined by the tissue identified and removed. However, in 19% of the dogs, ultrasonography results did not agree with surgical findings regarding laterality of the parathyroid mass location (Milovancev and Schmiedt, 2013). In another study, 12 ultrasonographic-identified parathyroid masses were confirmed at surgery, but five enlarged masses seen at surgery had not been identified via ultrasonography and two masses identified with ultrasonography were not seen at surgery (Ham et al, 2009). By contrast, all 17 parathyroid carcinomas in another study were correctly identified via ultrasonography (Sawyer et al, 2011).

Because results of cervical ultrasonography are often of use in establishing a diagnosis of PHPTH, we include and recommend cervical ultrasonography as a diagnostic aid for any hypercalcemic dog. Failure to identify a parathyroid mass in a dog suspected as having PHPTH is cause for reconsidering the differential diagnosis for hypercalcemia. Experience of the operator and equipment quality (including use of the correct transducer) must be considered (Wisner et al, 1993; Wisner and Nyland, 1994).

Abdomen

Ultrasonographic scanning of the abdomen, when possible, should be a component of the diagnostic evaluation of hypercalcemic dogs and cats. If the liver, spleen, mesenteric lymph nodes, or other abdominal structures appear abnormal, percutaneous fine needle aspiration or biopsy should be considered. Ultrasonography has proven to be an excellent tool for identifying uroliths as well. Most uroliths are found in the bladder, but renal, ureter, and urethral stones also have been identified.

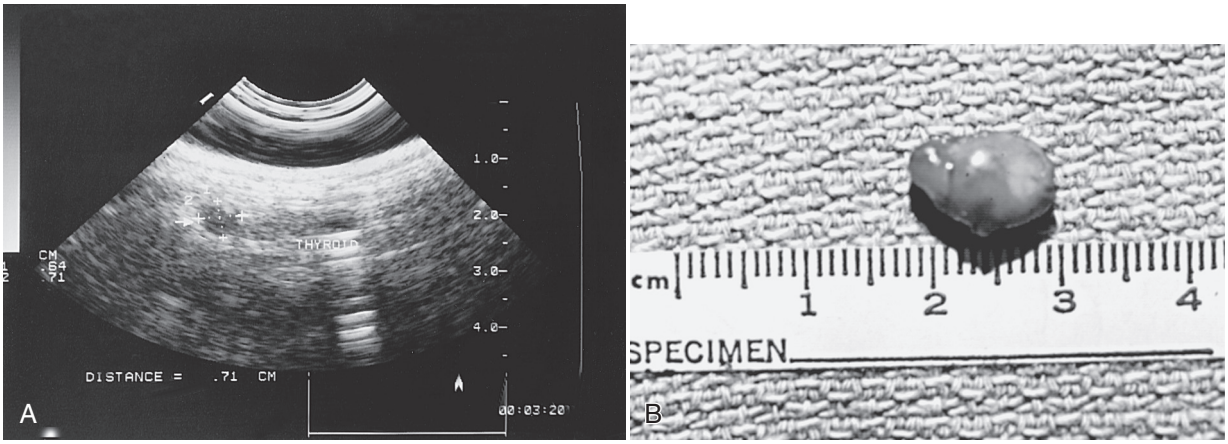


FIGURE 15-21 **A,** Cervical ultrasonogram of a dog with a functional parathyroid adenoma. Note the right thyroid lobe, in which a well-marginated, hypoechoic mass *(arrows)* is visible at the cranial pole of the thyroid. **B,** Solitary parathyroid adenoma removed from a dog with primary hyperparathyroidism (PHPTH; see Fig. 15-26, *C*). (**A,** Courtesy of Dr. Tom Nyland and Dr. Erik Wisner.)

Incidentally Discovered Thyroid Masses

One study has assessed the prevalence of subclinical thyroid nodules in dogs undergoing cervical ultrasonography as a component of evaluating hypercalcemia. No dog had a palpable mass, and in no dog was the thyroid believed responsible for hypercalcemia. At least one "incidentally discovered" thyroid nodule was identified in 14 of 91 PHPTH dogs. The thyroid gland masses had a mean length, width, and height of 1.5, 1.0, and 0.75 cm, respectively. Histologic diagnoses included thyroid cysts, adenomas, adenocarcinomas, and one dog with nodular hyperplasia. These results suggest that subclinical thyroid nodules are present in some hypercalcemic dogs that do not have a palpable neck mass (Pollard et al, in press). The clinical significance and management of incidentally identified thyroid nodules in dogs remains to be elucidated.

USE OF PARATHYROID HORMONE AND PARATHYROID HORMONE–RELATED PROTEIN ASSAYS

In dogs with PHPTH, serum PTH concentrations are typically mid/normal to increased (Figs. 15-5 and 15-22), serum PTHrP concentrations should be undetectable, and serum calcitriol concentrations would be expected to be normal to increased. Serum PTH concentration must always be evaluated relative to the serum calcium concentration. In normal animals, as the serum calcium concentration increases, the serum PTH concentration decreases. Therefore, a serum PTH concentration in the reference range from a hypercalcemic dog is not ***normal.*** Relative to their hypercalcemia (using TCa or iCa) dogs with PHPTH have excessive concentrations of serum PTH even though the result may be within the reference range. These results are consistent with a condition associated with autonomous secretion of PTH (Fig. 15-23).

The challenge for laboratories that offer serum PTH assays is that companies either go out of business or discontinue products. Therefore, assays utilized by laboratories invariably must change. Regarding PTH assays, quality of the results using newer products has either been similar or more reliable as compared with older products (see Fig. 15-5). Comparison of PTH assay results from different studies performed at various times and locations is difficult. Currently, the PTH assay that provides excellent correlation in dogs and cats is an intact-molecule assay, which has numerically lower test values as compared with previously reported results. The N-terminal antibody in previously utilized "intact sandwich" assay systems cross reacted with a biologically inactive PTH 7-83 amino acid fragment. The new intact-molecule PTH assay antibody requires the first four amino acids of the N-terminal be present for binding (Refsal, 2014). One study compared the "intact sandwich" PTH assay system that requires several days to complete with a rapid, 20-minute chemiluminescent assay. Within-run and day-to-day precisions were comparable, and there was a high correlation in results. Numerical results from the rapid chemiluminescent assay system were usually lower than the intact assay (Ham et al, 2009).

In one study, serum PTH concentrations were determined using an immunoradiometric "intact sandwich" assay for PTH in randomly obtained serum samples from 185 dogs with PHPTH. The mean serum PTH concentration of 11.3 pmol/L was within the reference range (2 to 13 pmol/L). Almost 75% of these dogs had a serum PTH concentration within the reference range, about 45% in the lower half and almost 30% in the upper half of the reference range. About 10% of the 185 dogs had "mildly increased" serum PTH concentration, and about 15% had moderate or extreme increases (see Table 15-7; Feldman et al, 2005). Other studies have reported similar results: a mean serum PTH concentration in dogs with PHPTH of 13.6 pmol/L

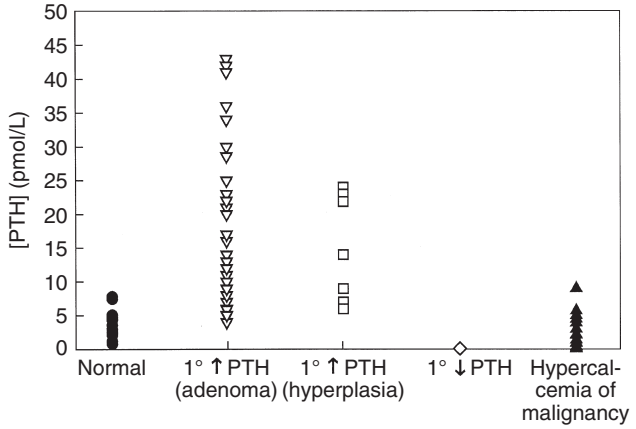


FIGURE 15-22 Serum parathyroid hormone *(PTH)* concentrations for normal dogs and those with various disorders of calcium homeostasis. Note that some overlap exists in test results and that the results shown in Fig. 15-23 are easier to interpret. *1° ↑ PTH,* primary hyperparathyroidism; *1° ↓ PTH,* primary hypoparathyroidism.

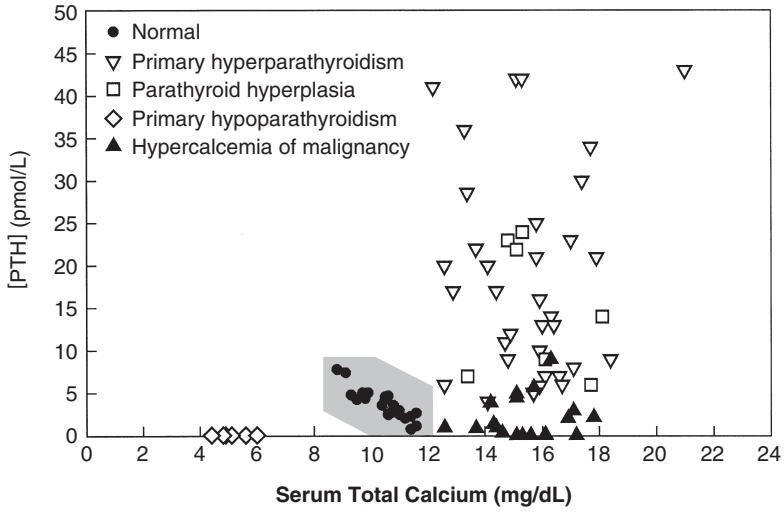


FIGURE 15-23 Serum parathyroid hormone *(PTH)* concentrations plotted against simultaneous serum calcium concentrations from normal dogs and those with abnormalities in calcium homeostasis. Note that the various groups are more distinguishable than would be the case if only the serum calcium or only the serum PTH concentrations were evaluated. The shaded area represents the approximate reference range.

BOX 15-3 Differential Diagnosis for Humoral Hypercalcemia of Malignancy

Hematologic Cancers
Lymphosarcoma
Lymphocytic leukemia
Myeloproliferative disease
Myeloma

Solid Tumors with Bone Metastasis
Mammary adenocarcinoma
Nasal adenocarcinoma
Epithelial-derived tumors
Pancreatic adenocarcinoma
Lung carcinoma

Solid Tumors without Bone Metastasis
Apocrine gland adenocarcinoma of the anal sac
Interstitial cell tumor
Squamous cell carcinoma
Thyroid adenocarcinoma
Lung carcinoma
Pancreatic adenocarcinoma
Fibrosarcoma

(reference range, 2 to 13 pmol/L) (Arbaugh et al, 2012); 8 out of 12 dogs (75%) with PHPTH had serum PTH concentrations within the reference range, and 4 out of 12 were increased (Ham et al, 2009); and a mean of 17.7 pmol/L in 19 dogs with PHPTH with a range of 4.7 to 156 pmol/L (reference range, 3 to 17 pmol/L) (Sawyer et al, 2011).

DIAGNOSTIC APPROACH TO THE HYPERCALCEMIC PATIENT

General Comments

The list of differential diagnoses for hypercalcemia is relatively short (see Boxes 15-1 and 15-3), allowing a logical approach to identification of its cause. At the same time, serum inorganic phosphorus should be assessed, and if low, that differential diagnosis can be considered as well (Box 15-2). The most common cause of hypercalcemia and hypophosphatemia in the dog is malignancy-associated hypercalcemia. In an attempt to be practical, logical, and cost-effective, the veterinarian should design the diagnostic approach to first identify or rule out an underlying malignancy. Diagnostic testing can proceed to assess each patient for PHPTH simultaneously as the testing is interwoven.

Review of the History and Physical Examination

First Steps

The diagnostic approach to the hypercalcemic patient is usually relatively straightforward (see Box 15-1; Fig. 15-24). One may wish to submit a second blood sample to recheck the calcium and phosphorus results, although the second sample is rarely different. Next, submit appropriate samples for a serum iCa concentration to confirm the presence of hypercalcemia. If the iCa concentration is within or below the reference range in a dog with confirmed increases in serum TCa concentration, CKD should be among the conditions considered (see Fig. 15-18). Rechecking an "illogical" iCa result is always wise.

Signalment

Review of breed is emphasized because of the genetic predisposition for developing PHPTH in the Keeshond. PHPTH typically occurs in dogs 7 years of age or older. CKD can occur at any age. Dogs of any age are at risk for malignancy (lymphosarcoma), toxin exposure, granulomatous disease, or hypoadrenocorticism, whereas apocrine gland carcinoma of the anal sac and some other malignancies occur in older dogs.

History

The owner should be asked about their pet's diet, travel history, vitamin-mineral supplementation, and exposure to rat or mouse poisons or houseplants that contain vitamin D analogs. An attempt can be made to determine whether the pet is in pain (lytic bone lesions). Response to questions about the presence of polydipsia, polyuria, appetite, activity, change in body weight, ability to exercise, vomiting, diarrhea, and any other pertinent information, may be important. Generally, as the pet appears more ill, PHPTH becomes less likely.

Physical Examination

After assessment of the dog's hydration status and severity of illness, the physical examination should include careful palpation of peripheral lymph nodes and the mammary glands (lymphoma and mammary cancer). A thorough rectal and perirectal examination is imperative to help rule in or out apocrine gland carcinoma of the anal sac. Anal sac tumors may be covered by haired skin and may not be identified unless rectal and perirectal examinations are performed. A digital vaginal examination should also be performed (vaginal tumor). The veterinarian should gently palpate as much of the skeleton as possible, searching for any area of focal bone pain, which then could be examined further with radiographs (multiple myeloma). The kidneys should be palpated in an attempt to assess size or irregularities.

Initial Database

Blood and Urine

The initial database should include a hemogram (complete blood count [CBC]), serum biochemical profile, serum iCa, urinalysis, and thoracic radiographs. The abdomen should be evaluated with ultrasonography, radiography, or both. If the serum phosphorus concentration is normal or low, CKD and rodenticide toxicosis are less likely (see Fig. 15-24). Dogs with hypoadrenocorticism usually have hyperphosphatemia in addition to their hyperkalemia and hyponatremia. Serum creatinine and BUN concentrations are also critically important. Evaluation of the sodium-to-potassium ratio should help identify hypoadrenocorticism. A sodium-to-potassium ratio less than 27:1 is consistent with but not necessarily diagnostic of adrenal insufficiency. An ACTH stimulation test should be performed if Addison's disease is considered likely, whereas a basal serum cortisol can be assessed if Addison's disease is considered a possibility. If the serum phosphorus concentration is increased and renal function is normal, bone osteolysis secondary to metastatic disease should be considered. Low, low-normal, or normal serum phosphate concentrations are consistent with PHPTH and malignancy-associated hypercalcemia (see Fig. 15-12). A striking increase in the total protein concentration, specifically due to a monoclonal spike, is classic for multiple myeloma.

Primary Parathyroid Disease Versus Primary Renal Disease

A diagnostic dilemma exists when hyperphosphatemia and hypercalcemia coexist with azotemia. The clinician must determine

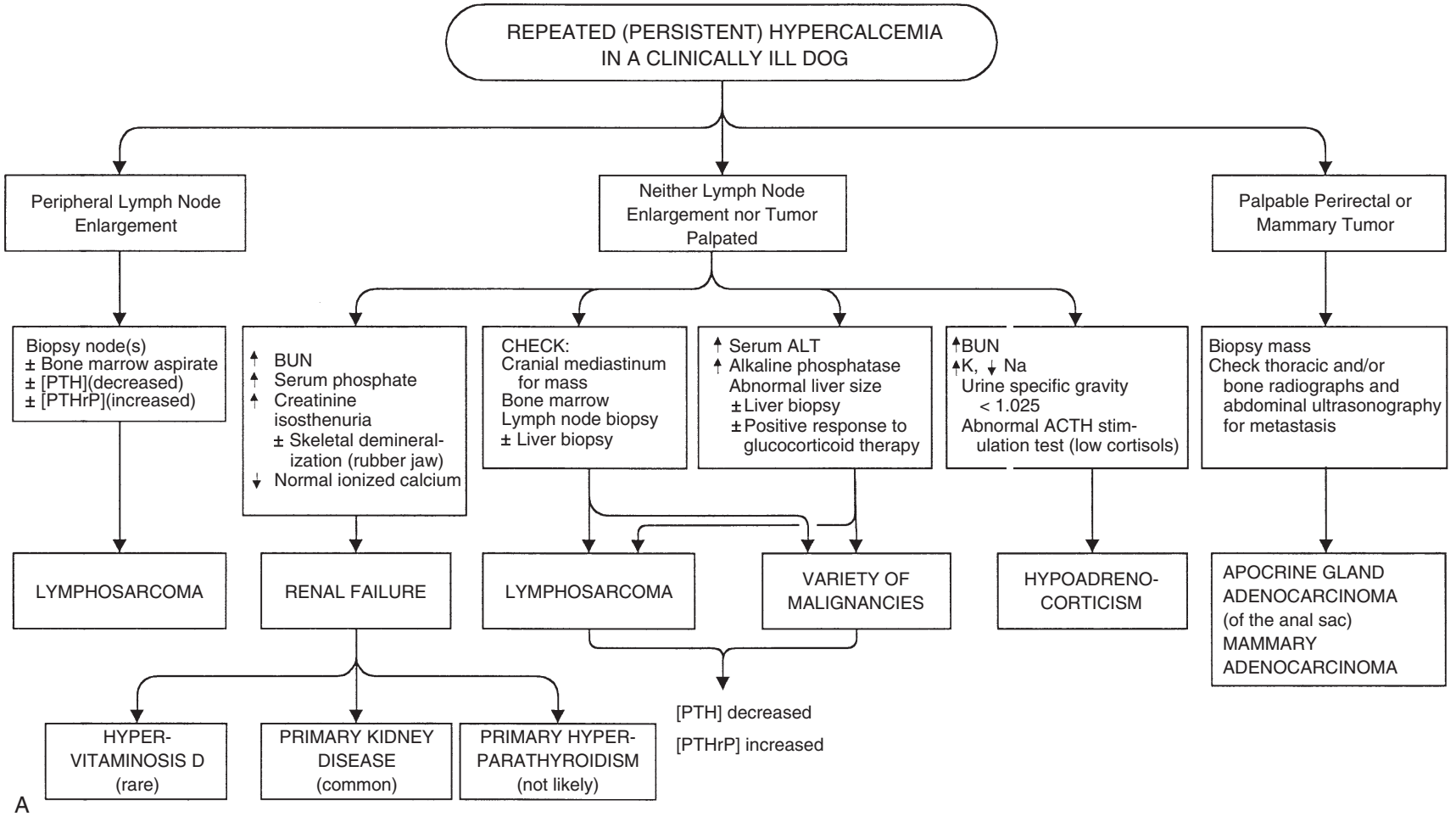
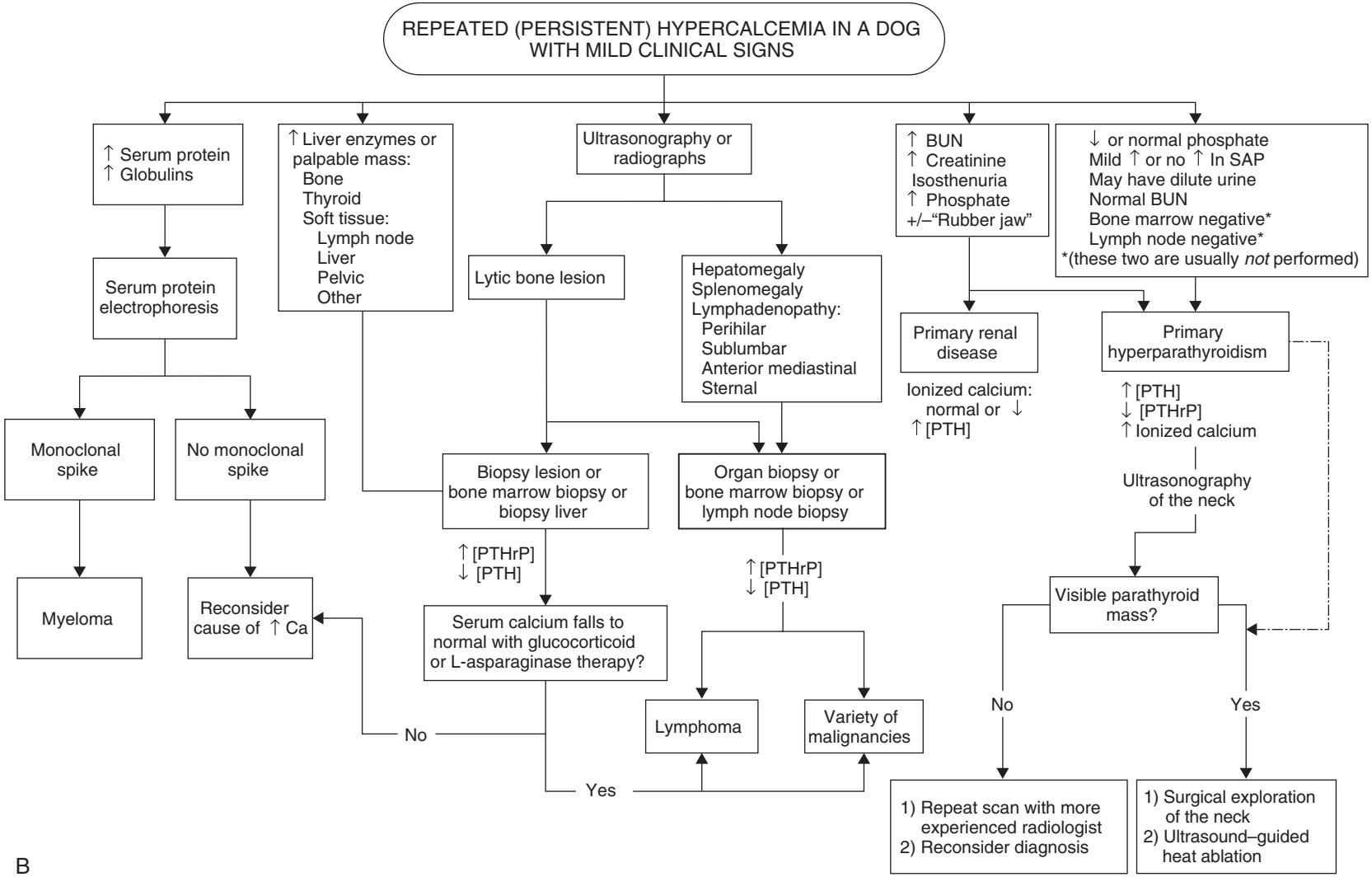


FIGURE 15-24 Algorithm for the clinical and diagnostic evaluation of dogs that are persistently hypercalcemic, including those that are ill **(A)** and those with mild clinical signs **(B).**

Continued



B

FIGURE 15-24, cont'd *ACTH,* Adrenocorticotropic hormone; *ALT,* alanine aminotransferase; *BUN,* blood urea nitrogen; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone–related protein, *SAP,* serum alkaline phosphatase.

whether the hypercalcemia is the cause or the consequence of renal disease. Other abnormalities in the initial database supportive of CKD as the primary problem include mild to marked increase in the serum phosphorus concentration, a normal to low serum iCa concentration, nonregenerative anemia, proteinuria, and/or palpably or radiographically small and irregular kidneys. The serum iCa fraction in dogs with PHPTH is increased. If hypercalcemia dissipates with aggressive fluid therapy and diuresis, PHPTH is less likely. Furthermore, dogs with renal failure usually have a TCa concentration less than 12.5 mg/dL. Dogs with PHPTH and secondary renal disease typically have a total serum calcium concentration greater than 13 mg/dL (see Figs. 15-5, 15-17, 15-18, and 15-24).

Radiography and Ultrasonography

Radiographs of the thorax and ultrasonographic examination of the abdomen should be evaluated for soft tissue masses, soft tissue calcification, evidence of fungal disease, organomegaly, osteolysis, and/or osteoporosis. The goal is to identify an abnormal area that could be biopsied in the hope of providing a definitive explanation for hypercalcemia. An anterior mediastinal mass is demonstrable radiographically in as many as 40% of hypercalcemic dogs with lymphosarcoma (see Fig. 15-19; Greenlee et al, 1990). If hepatomegaly or splenomegaly is identified, histologic evaluation of a fine needle aspirate or of a biopsy could be considered.

Adenocarcinomas derived from the apocrine glands of the anal sac may appear radiographically as a mass in the pelvic canal. Sublumbar lymphadenopathy caused by tumor metastasis is also common (see Fig. 15-20; Meuten et al, 1983b; Meuten, 1984). Soft tissue calcification is most frequently observed with hypervitaminosis D or CKD, although mineralization can be seen with any hypercalcemic disorder in association with hyperphosphatemia and a calcium x phosphorus product greater than 60 to 80.

Discrete lytic lesions in the vertebrae or long bones are suggestive of either myeloma or malignancy-associated hypercalcemia with bone metastasis (see Fig. 15-16). Radionuclide bone scans (Fig. 15-25) may identify or exclude focal bone lesions not detected with plain radiography (Chew et al, 1991). One dog with PHPTH had the uncommon finding of fractures at the time of presentation (Gear et al, 2005). Concurrent hyperproteinemia is supportive of myeloma. Solid tumors with metastasis to bone are more likely if lytic bone lesions and normoproteinemia (especially a normal serum globulin concentration) are present. A core biopsy of a lytic lesion may be necessary to establish a definitive diagnosis of neoplasia. Mild generalized osteoporosis is difficult to diagnose with plain survey radiographs. If present, however, it is suggestive of PHPTH or hypercalcemia of malignancy.

Ultrasonography of the cervical region has been reviewed. This tool is noninvasive and can be quite valuable (see Fig. 15-21). Identification of a solitary mass in or near one thyroid lobe supports the presence of an autonomously functioning parathyroid mass if the dog does not have CKD (Reusch et al, 2000).

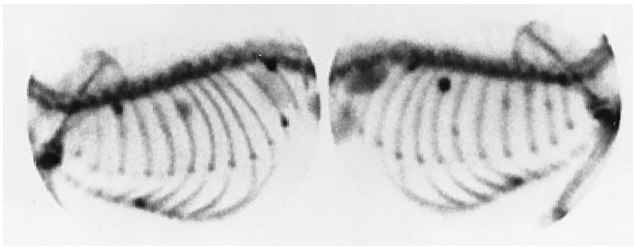


FIGURE 15-25 Bone scan from a dog with hypercalcemia caused by multiple myeloma. Note that the focal "black" areas are those of increased bone activity, as is typical for a metastatic lesion. (Courtesy of Dr. William Hornof, Davis, CA.)

Lymph Node and Bone Marrow Evaluations

If the initial database has not established a diagnosis, the clinician may consider histologic evaluation of lymph nodes, bone marrow, or both. Lymphosarcoma is the most common cancer associated with hypercalcemia in the dog and cat. Involvement of the peripheral lymph nodes in lymphosarcoma can be present without enlargement of those nodes, although such a finding would be unusual. Ideally, the largest lymph node (not the submandibular node) should be assessed for histologic evaluation. Needle aspirates for cytology are often diagnostic, but biopsy samples may be requested. These steps may be omitted in dogs that are relatively healthy according to their owners and veterinarians, who have unremarkable CBCs, and no abnormalities seen on thoracic radiographs.

A bone marrow aspirate may be considered in the hypercalcemic pet because the lymphosarcoma may invade the marrow (Meuten et al, 1983b). As with the peripheral lymph node evaluation, the presence of a normal bone marrow aspirate does not definitively rule out lymphosarcoma. As with the lymph node aspirate or biopsy, we usually omit this diagnostic tool when a dog is clinically well and when a CBC is unremarkable.

Specific Assays: Parathyroid Hormone, Parathyroid Hormone–Related Protein, and Calcitriol

See previous discussions.

Trial Therapy—Why This Approach Is *Strongly* Discouraged

If the diagnostic evaluation described fails to identify a cause for hypercalcemia, the clinician is faced with a diagnostic decision:

- Wait and retest?
- Trial medical therapy?
- Exploratory surgery of the neck?

If a hypercalcemic dog is stable, eating, and not significantly ill, we recommend rechecking any vague test result after a few days or weeks. The clinician should also consider referring the client and patient to a colleague more familiar with hypercalcemia and/or capable of performing high quality cervical ultrasonography, fine needle aspiration under ultrasonographic guidance, or some other diagnostic aid. Ill hypercalcemic dogs may also benefit from referral and a new opinion.

Most of the disorders that cause hypercalcemia are not "occult," but a diagnosis may occasionally be difficult. Diagnosis of PHPTH or malignancy-associated hypercalcemia (usually lymphosarcoma) can be straightforward (common) or problematic (uncommon). The veterinarian is reminded to complete a thorough history, bearing in mind the importance of diet, supplements, and potential exposure to toxins (Mellanby et al, 2005). The ability to utilize the combination of cervical and abdominal ultrasonography together with assessment of PTH and PTHrP assays usually leads to a correct diagnosis. Occasionally, the results of these tests are nebulous, and the clinician may consider one of two options: (1) surgical exploration of the neck to look for a parathyroid tumor, or (2) trial therapy with a chemotherapeutic drug effective against lymphosarcoma to see if the hypercalcemia can be alleviated.

Nonspecific Medical Treatment for Hypercalcemia

If hypercalcemia is caused by a lymphosarcoma (or other hematopoietic tumor), a rapid decline in the serum calcium concentration is common within 48 hours of glucocorticoid administration (Chew et al, 1991). The actions of glucocorticoids in inhibiting the growth of neoplastic lymphoid tissue and lymphocytolysis account for their rapid beneficial effect in most dogs with hematologic cancers, such as lymphoma or multiple myeloma (Goodwin et al, 1986). Glucocorticoids also counteract the effects of vitamin D, which accounts for their value, while limited, in animals with vitamin D toxicosis or granulomatous diseases (Sandler et al, 1984). In general, glucocorticoid therapy is ineffective in PHPTH or nonhematologic cancers (Bilezikian, 1992b). If the serum calcium concentration fails to decline after glucocorticoid administration, PHPTH may be considered as a possible explanation, but this represents a dangerous and inappropriate protocol for diagnosis. Unfortunately, glucocorticoids have nonspecific effects on calcium homeostasis and may cause transient declines in TCa or iCa. If the serum calcium concentration decreases into the reference range after administration of a chemotherapeutic agent, lymphosarcoma and other malignancies should be suspected and further diagnostic tests implemented to confirm this diagnosis. However, confirmation of lymphosarcoma in dogs who have received glucocorticoids may be challenging, and their response to adjunct therapy may be adversely affected.

Exploratory Surgery—No Longer Necessary?

Surgical exploration of the neck is an alternative approach for attempting to manage a dog with hypercalcemia of undetermined origin. The use of PTH, PTHrP, and iCa assays together with cervical and abdominal ultrasonography should negate the need for a true "exploratory" procedure. In other words, PHPTH can be confirmed in almost all dogs with PHPTH prior to surgery. Thus, surgery becomes a therapeutic regimen rather than a diagnostic tool. We again emphasize, *confidence in a diagnosis prior to surgery or medical therapy is preferred over "exploratory" or "trial" therapies.*

Spontaneous Resolution of Primary Hyperparathyroidism

Acute hypocalcemia has been described in two dogs with histories of chronic hypercalcemia. The acute hypocalcemia may have been the result of parathyroid gland tumor infarction and necrosis. Hypocalcemia may have resulted because the remaining parathyroid glands were atrophied and transiently unable to compensate for acute loss of PTH (Rosol et al, 1988).

ACUTE MEDICAL THERAPY FOR HYPERCALCEMIA (*NOT* PRIMARY HYPERPARATHYROIDISM)

Primary Hyperparathyroidism Versus Other Disorders

Dogs with Primary Hyperparathyroidism Do Not Require Immediate Therapy for Hypercalcemia

Treatment of dogs and cats with PHPTH involves ablation or surgical excision of abnormal tissue. Their hypercalcemia would rarely be "acute," and the calcium x phosphate product is usually normal or low. Although hypercalcemia can be theoretically cause mineralization of nephrons, this not a concern among most dogs with PHPTH. We have not employed any "acute" or other long-term medical therapy in dogs that we suspect as having PHPTH, other than strongly advising owners to provide their dog with ready access to water at all times. The following discussion on medical therapies is directed at ill or extremely ill dogs whose hypercalcemia is not caused by PHPTH. If a dog with PHPTH is ill, there should be concern of a concurrent problem. Despite a dramatic increase in the serum calcium concentration (mean serum TCa concentration > 14 mg/dL), dogs and cats with PHPTH are typically stable and not in need of emergency therapy (Table 15-8).

Therapy for Renal Failure or Vitamin D Toxicosis

Severity of clinical signs and degree of kidney injury depends, in part, on both serum calcium and phosphorus concentrations. Renal damage induced by metastatic mineralization is thought to correlate with the serum TCa x phosphate product. Products greater than 60 to 80 may be associated with nephrotoxicity. Thus hypercalcemia associated with PHPTH (low-normal or low serum phosphate concentrations) is less worrisome and dangerous than the hypercalcemia associated conditions like renal failure or hypervitaminosis D (high-normal to increased concentrations; see Table 15-8).

Indications and Alternatives for Acute Therapy in Hypercalcemia

Dogs with hypercalcemia of malignancy, vitamin D toxicosis, or other non-PHPTH causes of hypercalcemia often exhibit extremely worrisome clinical signs that are caused by their underlying malignancy as well as their hypercalcemia. Treatment for cancer may indirectly decrease serum calcium concentrations. Dogs that have mild hypercalcemia and CKD also have worrisome clinical signs, moderate to severe hyperphosphatemia, and are at risk for tissue mineralization. They may benefit from treatment directed at maintaining fluid homeostasis while decreasing the calcium x phosphorus product.

TABLE 15-8 **"CLASSIC" SERUM TOTAL CALCIUM AND INORGANIC PHOSPHORUS (PHOSPHATE) CONCENTRATIONS FOR VARIOUS CONDITIONS TO DEMONSTRATE THEIR TYPICAL NUMERICAL PRODUCTS**

	TYPICAL SERUM CALCIUM (mg/dL)	TYPICAL SERUM PHOSPHATE (mg/dL)	TYPICAL CALCIUM × PHOSPHATE PRODUCT
Normal dog	10	4.5	45
Primary hyperparathyroidism (PHPTH)	15	3.0	45
Lymphosarcoma	15	3.0	45
Apocrine cell carcinoma of the anal sac	15	3.0	45
Chronic kidney disease (CKD)	11.5	10	115
Vitamin D toxicosis	11.5	10	115

Note that therapy is likely indicated if the product of these two electrolytes exceeds 60 to 80.

There is no single treatment protocol consistently effective for all causes of hypercalcemia. Removal of the underlying cause is definitive, but this is not always possible. The goals of supportive treatment are to enhance renal excretion of calcium and to prevent calcium reabsorption from bone. Hemoconcentration contributes to increases in serum iCa concentration. Parenteral fluid therapy (saline is often the fluid of choice) is the single most important and potentially effective therapy. IV fluids should correct dehydration and, once fluid volume and blood pressure have been restored, induce diuresis. Renal calcium excretion is enhanced by sodium, thus the recommendation of saline. In the hydrated or rehydrated dog, furosemide should be the next therapy considered to further enhance renal calcium excretion.

Thiazide diuretics should be avoided as they may promote renal reabsorption of calcium (Schenck and Chew, 2008; 2012). Glucocorticoids are an effective therapy by inducing cytolysis (lymphosarcoma), as well as reducing bone resorption, decreasing intestinal absorption, and increasing renal excretion of calcium. Glucocorticoids have had demonstrable effect in dogs with hypercalcemia secondary to lymphosarcoma, multiple myeloma, hypoadrenocorticism, hypervitaminosis D, or granulomatous diseases, but have minimal effect on other causes.

Glucocorticoid therapy should be withheld if a definitive diagnosis has not been established. A bisphosphonate may be utilized for chronic control of hypercalcemia. Bisphosphonates lower calcium by reducing the number and action of osteoclasts. Several bisphosphonates have been employed in dogs (Box 15-4 and Table 15-9; Schenck and Chew, 2012; Skelly, 2012). Oral administration is not typically effective because of poor intestinal absorption. IV pamidronate, which is about 100 times more potent than etidronate, has been more reliable, is relatively well tolerated, lasts as long as 3 weeks, and repeat dosing can be considered if necessary (Hostutler et al, 2005).

BOX 15-4 General Treatment of Hypercalcemia

Definitive
Remove underlying cause

Supportive
Initial considerations
- Fluid (0.9% sodium chloride)
- Furosemide
- Sodium bicarbonate
- Glucocorticosteroids

Secondary considerations
- Bisphosphonates
- Calcitonin

Tertiary considerations
- Mithramycin
- Ethylenediaminetetraacetic acid (EDTA)
- Peritoneal dialysis
- Hemodialysis

Future considerations
- Calcium channel blockers
- Somatostatin congeners
- Calcium receptor agonists
- Non-hypercalcemic calcitriol analogues

SURGICAL THERAPY FOR PRIMARY HYPERPARATHYROIDISM

Introduction

Surgical techniques for the thyroid-parathyroid complex have been adequately described. Usually the surgery is not difficult; it is often described to owners as "easier than a spay and less time consuming than a dental prophylaxis." Recognition and surgical excision of autonomously functioning abnormal parathyroid tissue is the most commonly employed treatment for dogs with PHPTH (see Fig. 15-21, *B;* Fig. 15-26). The cure rate has been estimated at about 95% (Rasor et al, 2007; Ham et al, 2009). Failure to cure can be due to the presence of multiglandular disease known to occur in about 10% of dogs with PHPTH, incorrect intraoperative decisions that result in incomplete excision of all autonomously functioning tissue, ectopic autonomously functioning parathyroid tissue (extremely unlikely), or the presence of malignant disease with functioning distant metastases (extremely unlikely; Bilezikian et al, 2001; Ham et al, 2009). Correctly identifying all abnormal tissue can, uncommonly, be problematic because visible changes may be subtle or inapparent. Alternatively, after removing an abnormal nodule, another nodule may be present but not seen (Ham et al, 2009). An attempt must be made to ensure that at least one parathyroid gland remains intact to maintain calcium homeostasis and prevent permanent hypoparathyroidism. If none of the parathyroid glands appears abnormal, if all appear small, or if all are enlarged, the diagnosis of PHPTH must be questioned. The reader is reminded that 5% to 15% of dogs with PHPTH due to an abnormal parathyroid gland(s) may also have an incidentally identified thyroid mass.

Surgical Observations

In three studies describing 53 dogs with PHPTH, each had a solitary nodule successfully identified and removed (Gear et al, 2005; Sawyer et al, 2011; Arbaugh et al, 2012). In another study, seven of 12 dogs (58%) had a solitary nodule and five (42%) had two (Ham et al, 2009). One study included the only four dogs with three nodules excised (6% of 62 dogs). In that report, each of 16 dogs (26%) had two nodules and 42 dogs (68%) had a solitary nodule (Milovancev and Schmiedt, 2013). In our series, about 90% of dogs with PHPTH have had a solitary mass, and about 10% have had two. It is rare to diagnose PHPTH associated with more than two abnormal and autonomously secreting glands.

Cervical Imaging

Ultrasonography

The potential for excellence in sensitivity and specificity of cervical ultrasonography has been previously discussed. In three reports, ultrasonography results correctly identified the abnormal parathyroid tissue in 58 of 61 dogs (95%) (Gear et al, 2005; Sawyer et al, 2011; Arbaugh et al, 2012). However, in another study, ultrasonography correctly identified all abnormal tissue in only 44 of 55 dogs (80%) with PHPTH (Milovancev and Schmiedt, 2013). In a study of 12 dogs with PHPTH, ultrasonography correctly identified 12 abnormal nodules but also identified two nodules that were not seen at surgery and failed to identify five masses that were seen at surgery (Ham et al, 2009).

Cervical ultrasonography should be an integral component of evaluating hypercalcemic dogs and cats. We are reluctant to recommend surgery in any dog suspected to have PHPTH but that

TABLE 15-9 **TREATMENT OPTIONS FOR HYPERCALCEMIA NOT CAUSED BY PRIMARY HYPERPARATHYROIDISM**

TREATMENT	DOSE	INDICATIONS	COMMENTS
Volume Expansion			
SC saline (0.9%)	Small volumes		Rarely indicated or beneficial
IV saline (0.9%)*	100 to 125 mL/kg/day or "as needed"	Moderate to severe hypercalcemia	Careful in patients with congestive heart failure or hypertension (rarely indicated in dogs with PHPTH)
Diuretics			
Furosemide	2 to 4 mg/kg every 8 to 12 hours, IV, SC, or by mouth	Moderate to severe hypercalcemia	Volume expansion is necessary before use of this drug
Alkalinizing Agent			
Sodium bicarbonate	1 mEq/kg IV slow bolus; may continue at 0.3 × base deficit × weight in kg/day	Severe hypercalcemia	Requires close monitoring
Glucocorticoids			
Prednisone	1 to 2.2 mg/kg every 12 hours by mouth, SC, or IV	Moderate to severe hypercalcemia	Use of these drugs before identification of etiology may make definitive diagnosis difficult
Dexamethasone	0.1 to 0.22 mg/kg every 12 hours, IV or SC	Same	Same
Bone Resorption Inhibitors			
Calcitonin	4 to 6 IU/kg as IV infusion and then SC every 8 or 12 hours	Hypervitaminosis D	Response may be short-lived; vomiting and anorexia may occur
Bisphosphonates			
Etidronate	5 to 15 mg/kg every 12 to 24 hours	Moderate to severe hypercalcemia	Expensive and use in dogs is limited
Clodronate	20 to 25 mg/kg in a 4-hour IV infusion	Same	Same
Pamidronate	1.3 mg/kg in 150 mL 0.9% saline in a 2-hour IV infusion; can repeat in 1 week	Same	Same
Alendronate	5 to 20 mg orally every 7 days	Same	Must ensure complete passage of medication into stomach to avoid esophagitis
Miscellaneous			
Sodium EDTA	25 to 75 mg/kg/h	Severe hypercalcemia	Nephrotoxicity
Peritoneal dialysis	Low calcium dialysate	Severe hypercalcemia	Short duration of response; use in hypercalcemia not reported

EDTA, Ethylenediaminetetraacetic acid; *IHC,* idiopathic hypercalcemia of cats; *IV,* intravenous; *PHPTH,* primary hyperparathyroidism; *SC,* subcutaneous.
*Potassium supplementation may be necessary.

fails to demonstrate at least one abnormal parathyroid nodule on cervical ultrasonography. If a relatively inexperienced individual is performing the examination in which no abnormal nodules are seen or if more than one is seen, we recommend that the examination be repeated when one of our more experienced radiologists is available. Disagreement between ultrasonography and surgical observations are not common. Incidentally identified thyroid masses are encountered.

Radionuclide Scans

Radionuclide procedures have been used for the detection and localization of parathyroid adenomas in humans (Fine, 1987). The most commonly used radionuclide imaging technique is a dual radioisotope procedure combining thallous chloride (^{201}Tl) with either pertechnetate (^{99m}Tc) or radioactive iodine (^{123}I) (Picard et al, 1987). Various problems with this methodology led to the use of one radionuclide: technetium-99m-sestamibi (^{99m}Tc-sestamibi) (O'Dougherty et al, 1992; Taillefer et al, 1992). The procedure and hospitalization time for radionuclide scans using ^{99m}Tc-sestamibi in humans are similar to those for ^{99m}Tc scans in dogs. ^{99m}Tc-sestamibi radionuclide scans provide excellent results for localizing parathyroid adenomas in people (O'Dougherty et al, 1992; Taillefer et al, 1992).

Two reports suggested that this procedure might be helpful in localizing parathyroid adenomas in dogs with PHPTH (Wright et al, 1995; Matwichuk et al, 1996). In a subsequent study, double-phase parathyroid scintigraphy was evaluated in a group of PHPTH dogs with one of 10 having a scan that correlated with surgery. The poor sensitivity and specificity of parathyroid gland scintigraphy led the authors to conclude that use of this tool could not be recommended (Matwichuk et al, 2000).

Selective Venous Sampling

An attempt was made to determine the side on which an autonomously functioning parathyroid nodule was located by taking blood from both jugular veins and measuring PTH concentrations in each. The hypothesis was that the vein draining the side of the autonomously functioning tissue would have greater amounts of PTH than the opposite side. PTH concentrations were compared from the samples obtained from each jugular vein prior to surgery. Each dog had PHPTH caused by a solitary functioning adenoma.

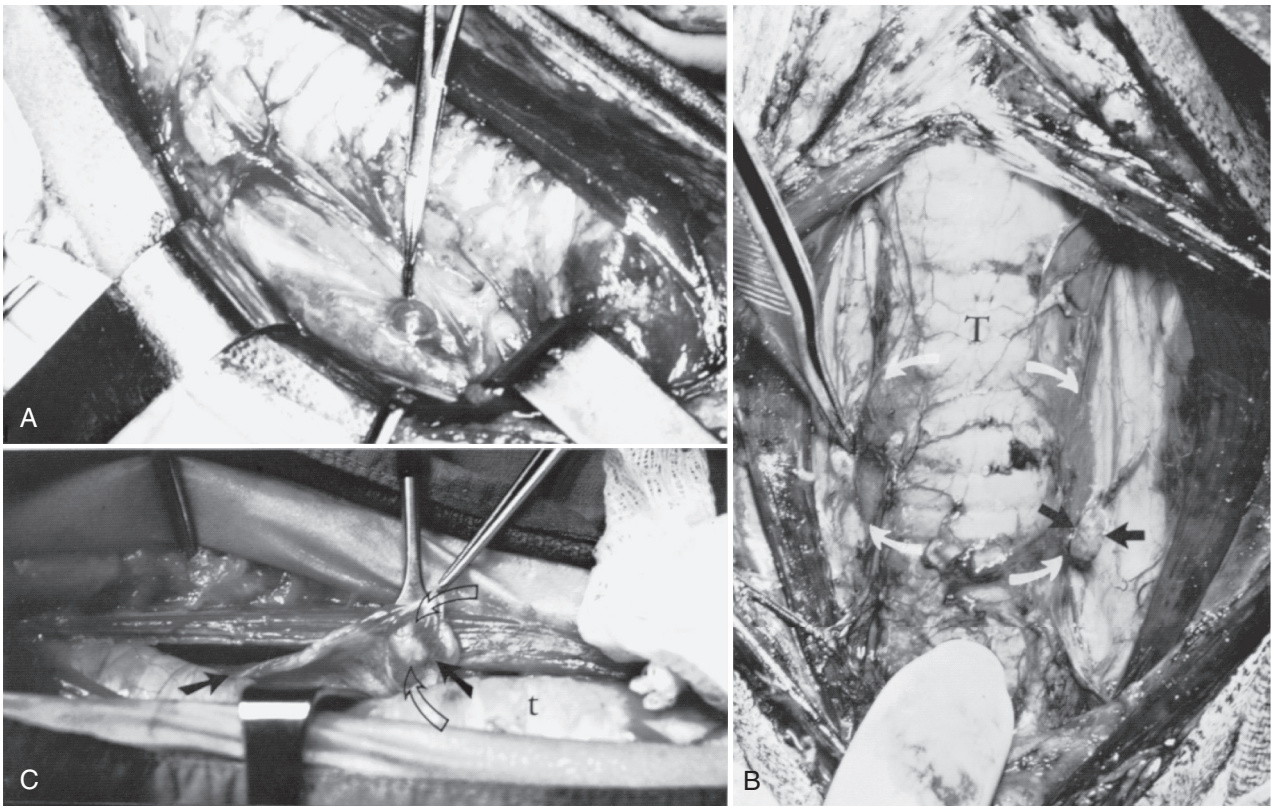


FIGURE 15-26 **A,** Surgical site during removal of a solitary parathyroid adenoma (tip of forceps). **B,** Surgical site during removal of a solitary parathyroid adenoma (*T,* trachea). *White arrows* delineate the cranial and caudal poles of the thyroid glands; *black arrows* point out the parathyroid adenoma. **C,** Surgical site during removal of an "internal" parathyroid adenoma (*t,* trachea). *Solid arrows* delineate the cranial and caudal poles of the thyroid, which is being retracted from the trachea to reveal the parathyroid adenoma *(open arrows)* on the dorsal surface of the thyroid.

Unfortunately, a gradient between samples was identified in only one of 11 dogs and this is not recommended (Feldman et al, 1997).

A rapid chemiluminescent PTH assay was employed on blood samples obtained during surgery from local veins to help identify laterality (left or right side) of autonomously functioning parathyroid tumors. In addition, plasma PTH concentrations were obtained from local veins to determine if all abnormal tissue had likely been removed. Systemic and local PTH concentrations decreased more than 50% from presurgical values in all dogs after complete excision of abnormal tissue. Mean preoperative systemic plasma PTH concentrations were significantly higher than mean postoperative concentrations. The mean local pre-excision PTH concentration from the affected side was significantly higher than mean pre-excision concentration taken from the unaffected side. Unfortunately, local PTH concentrations from the affected side were greatly increased in comparison to the opposite side in a minority of the dogs. Thus, the side on which an autonomously nodule was located and removed was not consistently detected with intraoperative PTH sampling. Results of this elegant study did not support intraoperative blood sampling for PTH to locate the side on which an autonomously functioning gland resided (Ham et al, 2009).

New Methylene Blue Infusions

IV infusion of new methylene blue (3 mg/kg) has been described as a means of improving the surgeon's ability to recognize abnormal glands. Three dogs with PHPTH were evaluated, and in each a tumor was identified after the infusion. However, two of three dogs developed Heinz body anemia and red blood cell "blistering" after the procedure (Fingeroth and Smeak, 1988).

Solitary Adenoma, Hyperplastic Nodule, or Carcinoma?

In surgery, a large majority of dogs with PHPTH have had a solitary nodule identified and removed. One cannot predict the histologic classification from gross appearance. About 50% of nodules are identified on the ventral surface of the thyroid glands. If the mass is not seen on the ventral surface, careful inspection of the dorsal surface of each thyroid lobe should be conducted. "External" parathyroid nodules are usually removed easily and without damage to surrounding tissue (see Figs. 15-4 and 15-26). In some dogs with an "internal" parathyroid adenoma, surgeons may choose to remove the entire thyroid-parathyroid complex from the affected side. In a small number of dogs, tissue removed was based on cervical ultrasonography identifying an intrathyroidal nodule.

Enlargement of Multiple Parathyroid Glands

Approximately 10% of dogs with PHPTH have enlargement of more than one gland in our experience. Others have identified more than one gland enlarged in more than 20% of dogs with PHPTH (Gear et al, 2005). Histologic classification of removed tissue may or may be similar. A dog may have more than one adenoma, carcinoma, or hyperplastic gland or have any

combination (DeVries et al, 1993). When more than one enlarged gland is identified, the concern is primary versus secondary hyperparathyroidism. The presurgical evaluation, as reviewed, should discriminate dogs with PHPTH from non-surgical causes of hypercalcemia. If the clinician is convinced that primary disease is present, the decision to remove two glands is straightforward. However, if three or four glands are involved, the decision regarding removal should be based on one's confidence in the presurgical diagnosis and, potentially, the owner's ability to treat permanent hypoparathyroidism.

Recurrence of Primary Hyperparathyroidism

About 8% to 10% of dogs with treated PHPTH have complete resolution of their condition for 6 months to longer than 5 years and then have had a recurrence (Ham et al, 2009). In each, their second diagnosis of PHPTH was caused by a solitary, autonomously functioning parathyroid nodule, in a gland not previously affected. Nodules surgically removed after recurrence have had the same range of histologic diagnoses; adenoma is the most common, whereas "carcinoma" or "hyperplasia" is each diagnosed in about 5% to 10% of the cases. Because recurrence of PHPTH has been documented, periodic rechecks are warranted.

Absence of a Parathyroid Mass at Surgery

If an abnormal parathyroid nodule is not seen at surgery (or with ultrasonography), one must first consider the confidence with which the diagnosis of PHPTH was established. If convinced of the condition, the most likely diagnoses include hypercalcemia due to PTH production by a parathyroid tumor in an aberrant location or the presence of a non-parathyroid tumor producing PTH (i.e., ectopic hyperparathyroidism). Either would be extremely rare. The ventral neck should be carefully explored and any suspicious mass excised. New methylene blue infusion, as previously described, can also be considered (Fingeroth and Smeak, 1988).

PERCUTANEOUS THERAPIES FOR PRIMARY HYPERPARATHYROIDISM IN DOGS

Percutaneous Ultrasound-Guided Ethanol Ablation

Based on experience using cervical ultrasonography as a diagnostic aid for dogs and on the use of chemical ablation for small nodules in people (Bennedbaek et al, 1997), the efficacy of ethanol ablation as a treatment for dogs with PHPTH was evaluated (Long et al, 1999). Ethanol causes coagulation necrosis and vascular thrombosis. PHPTH was diagnosed in twelve dogs whose clinical and biochemical evaluation was typical for the condition. Each dog had a solitary, hypoechoic, round or oval mass near a thyroid lobe on cervical ultrasonography. Parathyroid nodules were identified on the right side in eight and left side in four dogs. The nodules ranged from 4 to 10 mm in greatest diameter; they were located at the cranial aspect of a thyroid lobe in six, within the caudal pole of a thyroid lobe in three, and in the midbody of a thyroid lobe in three dogs. The calculated volume of the nodules ranged from 0.06 to 0.16 cm^3.

Each dog was placed under general anesthesia, and the ventral cervical region was clipped and aseptically prepared. The parathyroid nodule was identified and continuously monitored throughout the procedure via ultrasonography, using an appropriate transducer. The tip of a 27-gauge needle, with arterial tubing attached to a syringe containing about 50% more ethanol than the estimated nodular volume, was inserted into the nodule (Fig. 15-27). That volume was slowly injected, with a goal of having the entire parenchyma exposed to ethanol. Because parathyroid nodules are small, considerable experience with ultrasonographic-guided needle placement is necessary. Parathyroid nodules may also be in close proximity to the carotid artery and vagosympathetic trunk; therefore absolute certainty about needle placement is required prior to and during injection.

Because ethanol is hyperechoic, it is easily visualized with ultrasonography (see Fig. 15-27). The parathyroid nodules received different calculated volumes, as dictated by the monitored diffusion. The injected volumes ranged from 50% to 150% of the calculated nodular volume. No dog was under anesthesia for more than an hour, and the mean duration of anesthesia was 38 minutes. A single injection was administered to 11 of the 12 dogs. One dog was injected a second time 48 hours after the first dose failed to reduce the serum calcium concentration into the reference range. In all 12 dogs, the serum TCa concentrations decreased into the reference range. In 11 dogs this decrease was documented within 48 hours of injection (10 after the first injection and one after the second injection). One dog remained hypercalcemic for 4 days, but the serum calcium concentration decreased into the reference range 5 days after treatment (Fig. 15-28). One dog had a recurrence of hypercalcemia 30 days after injection and was treated surgically. Each of the other 11 dogs remained normocalcemic for more than 12 months. The only adverse side effect was a transient change in the bark of two dogs, both of whom were believed, retrospectively, to have suffered transient, unilateral laryngeal paralysis.

Ethanol ablation was an efficacious mode of therapy for PHPTH in dogs (Long et al, 1999). The cost of the procedure was considerably less than for surgery. Chemical ablation of parathyroid masses may be more effective in dogs than in humans because canine parathyroid nodules are considerably smaller, thus requiring a smaller volume of ethanol for complete ablation. One group treated five dogs utilizing this approach without success (Gear et al, 2005). A subsequent study concluded that ethanol ablation was an effective mode of therapy but not as effective as surgery or heat ablation. Control of hypercalcemia for a median of 540 days was achieved in 13 of 18 dogs (72%) (Rasor et al, 2007).

Percutaneous Ultrasound-Guided Radio Frequency Heat Ablation

Based on experience with cervical ultrasonography both as a diagnostic aid and for ethanol ablation, the efficacy of treatment with percutaneous ultrasonographic-guided radio frequency heat ablation was evaluated. Radio frequency waves are converted to heat at the needle tip causing thermal necrosis at the needle tip (Pollard et al, 2001). This treatment modality has several advantages over ethanol ablation. Radio frequency damages a discrete amount of tissue surrounding the uninsulated portion of the needle. (There is no potential for "leakage," as there is with ethanol.) Radio frequency offers the additional advantage of not damaging regional vasculature. Vascular blood flow disperses heat. In humans, this treatment modality has a higher success rate than ethanol for mass ablation and fewer retreatments required to achieve remission. Radio frequency heat ablation has been used in the treatment of multifocal hepatic, breast and nasal masses, as well as for prostatic hypertrophy (Jiao et al, 1999; Livraghi et al, 1999). One disadvantage of the radio frequency technique is equipment cost.

In the first report using this treatment modality for dogs with PHPTH, 27 dogs were treated, 22 with a solitary parathyroid nodule and five dogs each had two nodules. In three of the five

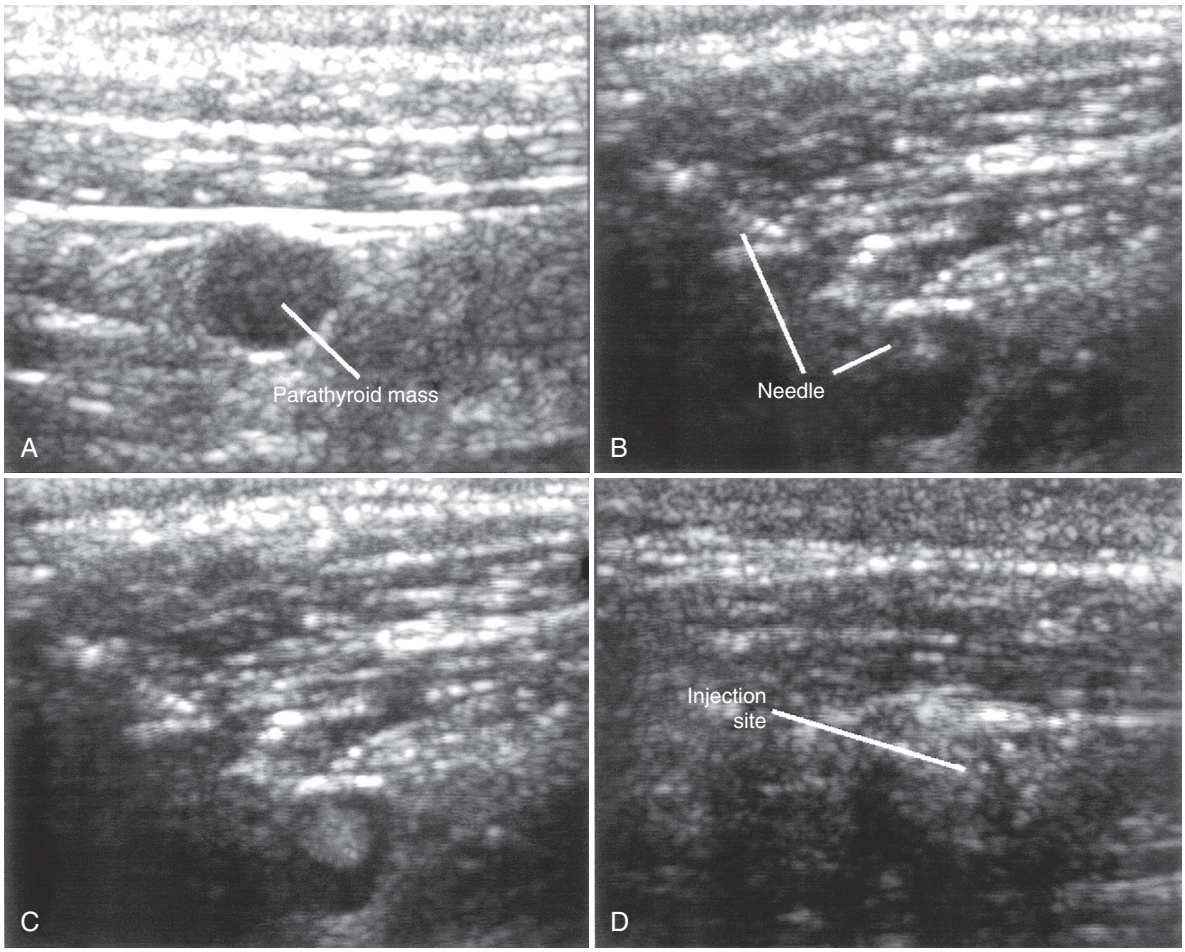


FIGURE 15-27 Ultrasonographic appearance of chemical ablation of a parathyroid mass in a dog. **A,** Sagittal view of the parathyroid mass prior to treatment. **B,** A 27-gauge needle is inserted into the mass. **C,** A test injection of 96% ethanol is used to confirm placement of the needle inside the mass. Note that the ethanol is hyperechoic in relation to the parenchyma of the mass. **D,** After injection of the target dose of ethanol, the entire mass has an echogenic appearance. (From Long CD, et al.: Percutaneous ultrasound–guided chemical parathyroid ablation for treatment of primary hyperparathyroidism in dogs, *J Am Vet Med Assoc* 215:217, 1999.)

dogs with two nodules, both were on the left side of the neck, and two dogs had one nodule on each side. Ultrasonographic appearance of each nodule was similar: spherical to ovoid and hypoechoic to the surrounding thyroid parenchyma. Length of the masses ranged from 3 to 15 mm. Each dog with a solitary parathyroid mass was treated once. When two parathyroid nodules were present and located on the same side, as in the three dogs, both were ablated during the first anesthesia. In the two dogs with one nodule on either side of the neck, each nodule was treated separately, 30 days apart. Preparation was the same as utilized for ethanol ablation. The parathyroid nodule was identified and continuously monitored with ultrasonography, including guiding the tip of a 20-gauge, over-the-needle (insulated) catheter into the mass. The needle hub was removed, allowing for an insulated wire to connect the needle to the radio frequency unit (Radiotherapeutics Inc., Redwood City, CA). Initially, 10 watts of energy were applied to the tissue for 10 to 20 seconds. If echogenic bubbles were not seen via ultrasonography at the needle tip, the wattage was increased by 2 watts every 5 to 10 seconds until echogenic foci became apparent (Fig. 15-29). Also, if a "popping sound" could be heard, the maximum heat application was assumed to have been reached and no additional increases in wattage were made. The needle tip was arbitrarily redirected multiple times, as necessary, in an attempt to expose all the parenchyma to heat. Mean anesthesia time was 41 minutes, but with experience it now averages about 15 minutes.

The procedure was successful in 26 of the 27 dogs with a dramatic reduction in the serum PTH concentration and normalization of both the TCa and iCa concentrations within 24 hours (Fig. 15-30). Serum calcium concentrations remained within the reference range for more than a year in each dog. One dog improved for only 1 month and was treated surgically after hypercalcemia recurred. Immediately after heat ablation, one dog with a unilateral parathyroid nodule developed a transient voice change, which resolved within 5 days. It is unclear whether this voice change occurred secondary to intubation or to the ablation procedure. Signs of pain, swelling, or respiratory distress were not detected in any dog. Eleven of the 26 successfully treated dogs required vitamin D therapy for postablation hypocalcemia (see next section). In a retrospective evaluation of ultrasonographic-guided heat ablation in dogs with PHPTH, success rates were comparable to those achieved with surgery. Forty-four of 49 dogs with PHPTH (90%) experienced rapid resolution (hours to days) of their condition following heat ablation, resulting in normal calcium concentrations for a median of 580 days (Rasor et al, 2007). Inclusion criteria for heat ablation include having a readily seen abnormal parathyroid nodule more than 2 mm but less than 16 mm in greatest diameter, not too close to the carotid or

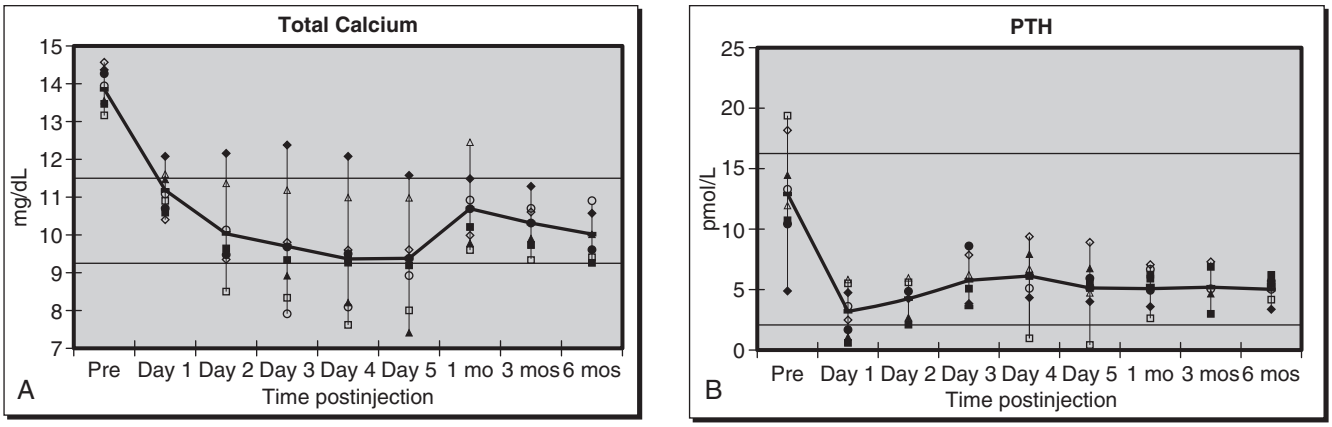


FIGURE 15-28 **A,** Serum total calcium (TCa) concentration in eight dogs before *(Pre)* and after chemical ablation of a parathyroid mass. The *horizontal black lines* indicate the reference range. Dog 6 developed clinical signs of hypocalcemia 4 days after the ablation procedure. Dog 8 received two injections of ethanol (the data given represent values obtained after the second injection). Dog 7 underwent surgical removal of a parathyroid mass after the 1-month reevaluation. Dog 5 died of unrelated causes after the 3-month reevaluation. **B,** Serum parathyroid hormone *(PTH)* concentrations in eight dogs before *(Pre)* and after chemical ablation of a parathyroid mass. The *horizontal black lines* indicate the reference range. (From Long CD, et al.: Percutaneous ultrasound–guided chemical parathyroid ablation for treatment of primary hyperparathyroidism in dogs, *J Am Vet Med Assoc* 215:217, 1999.)

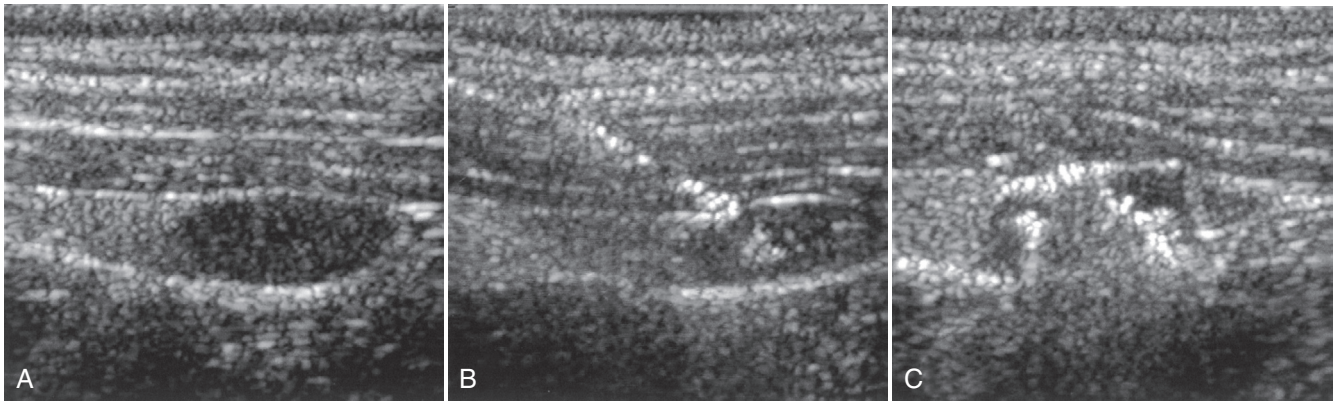


FIGURE 15-29 Left lateral sonographic images of an oval hypoechoic parathyroid nodule in a dog prior to heat ablation **(A),** with the insulated needle passing through the superficial soft tissues into the cranial aspect of the mass **(B),** and after heat ablation **(C).** Note the hyperechoic foci in the parenchyma of the gland in **C.** (From Pollard RE, et al.: Percutaneous ultrasonographically guided radio frequency heat ablation for treatment of primary hyperparathyroidism in dogs, *J Am Vet Med Assoc* 218:1106, 2001.)

any other vital structure, and no cystic calculi documented. It is recommended that dogs with PHPTH and cystic calculi have parathyroid and abdominal surgery performed during the same anesthesia.

POSTTREATMENT MANAGEMENT OF POTENTIAL HYPOCALCEMIA

A full discussion of vitamin D and calcium supplementation is presented in Chapter 16.

Background

Physiologically, the long-term response to autonomous secretion of PTH by an abnormal parathyroid nodule is atrophy of normal glands. Duration of hypercalcemia is apparent for some dogs but is unknown for most. Thus, the use of pretreatment serum calcium concentrations has been used in an attempt to predict dogs most likely to become seriously hypocalcemic after therapy. Surgical removal or percutaneous ablation of an autonomous source of PTH results in rapid disappearance of circulating PTH (see Fig. 15-30; Fig. 15-31) and decreases in serum calcium concentrations. Potential for serious decreases in serum calcium concentration (see Figs. 15-28 and 15-30; Fig. 15-32) exist for any dog treated successfully for PHPTH. After resolution of PHPTH, decreases in serum calcium concentrations usually continue for a period of 1 to 7 days but rarely longer. Our hypothesis and experience has been that posttreatment hypocalcemia correlates with severity of hypercalcemia prior to surgery. We compared 50 dogs with PHPTH who did not become seriously hypocalcemic (TCa < 7mg/dL; iCa < 0.8mmol/L) with 50 who did following treatment. The mean pretreatment serum TCa and iCa concentrations of those who did not become seriously hypoglycemic (13.88 mg/dL, 1.61 mmol/L,

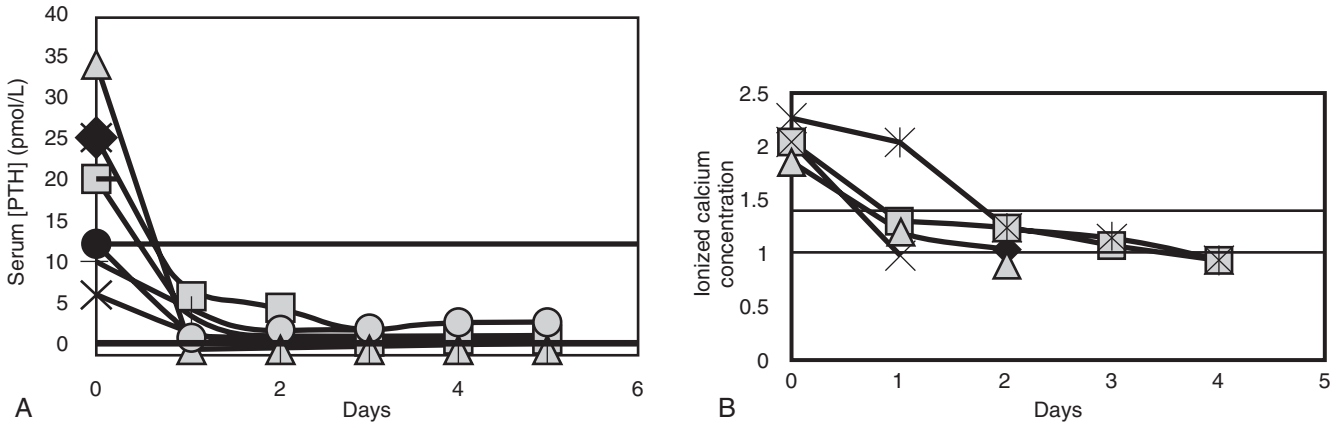


FIGURE 15-30 A, Serum parathyroid hormone *(PTH)* concentration (pmol/L: individual data points) of eight dogs that were successfully treated for primary hyperparathyroidism (PHPTH). The reference range is 2 to 13 pmol/L. **B,** Serum ionized calcium (iCa) concentrations (mmol/L; individual data points) in five dogs that were successfully treated for PHPTH on day 0 and eventually required vitamin D supplementation 1 to 4 days after treatment. The reference range is 1.1 to 1.4 (From Pollard RE, et al.: Percutaneous ultrasonographically guided radio frequency heat ablation for treatment of primary hyperparathyroidism in dogs, *J Am Vet Med Assoc* 218:1106, 2001.)

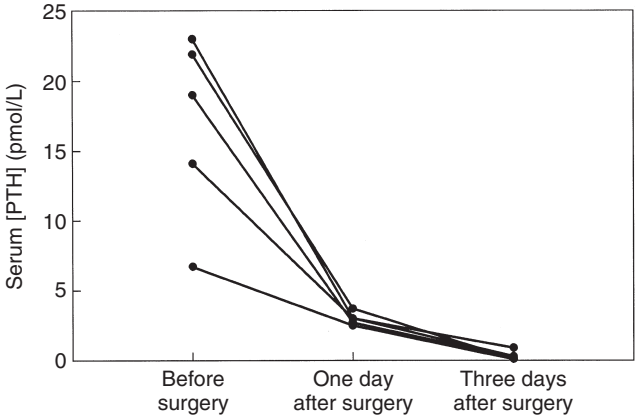


FIGURE 15-31 Serum parathyroid hormone *(PTH)* concentrations before and after surgery in eight dogs in which a solitary functional parathyroid adenoma was removed.

respectively) were significantly lower than results from those who did (16.12 mg/dL, 1.87 mmol/L). These unpublished data are comparable to those reported by another group: Mean pretreatment TCa concentration of those who did not develop posttreatment hypocalcemia (13.6 mg/dL) was significantly lower than the TCa pretreatment of those who did become seriously hypocalcemic (16.8 mg/dL) (Gear et al, 2005).

Although we and Gear and colleagues (2005) have noted correlation between presurgical TCa or iCa concentrations and development of posttreatment hypocalcemia, this has not been appreciated in other studies (Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). Size of unaffected parathyroid tissue is another consideration with dogs that have undetectable atrophied parathyroid glands being at greater risk for posttreatment hypocalcemia than dogs with small but visible parathyroid glands.

Some veterinarians have suggested that it is imperative to document a decline in the serum calcium concentration after surgery to subnormal levels before considering supportive therapy. Although such a protocol allows further confirmation that PHPTH existed and was corrected, it places a dog at risk for discomfort as well as life-threatening hypocalcemia. The next sections review dogs for which no therapy or immediate therapy (posttreatment) is suggested. Beginning therapy before or soon after surgery or ablation but before documented decreases in the serum calcium concentration has not prevented the serum calcium concentration to decline into or below the reference range, but it has prevented serious hypocalcemia and tetany.

Protocol Based on the Pretreatment Total Calcium Concentration

Pretreatment Total Calcium Less Than 14 mg/dL

If the serum calcium concentration prior to surgery is less than 14 mg/dL, the risk of postsurgical hypocalcemia is relatively small, *but we now recommend that all dogs with PHPTH receive prophylactic treatment to prevent posttreatment hypocalcemia*. If prophylactic treatment is withheld, the dog should be hospitalized for 3 to 5 days after treatment to monitor the TCa and/or iCa concentrations once or twice daily. Hospitalization also reduces activity levels of most dogs. Dogs sent home are likely to be more active and, if hypocalcemic, at much greater risk of clinical tetany than one kept quiet. If the serum TCa concentration remains above about 8.5 mg/dL (assuming a lower reference limit of about 9.5 mg/dL) and/or the serum iCa concentration remains above about 0.95 mmol/L (assuming a lower reference limit of 1.10 mmol/L), vitamin D treatment can be withheld. It should be noted, however, that these are general guidelines and prophylactic treatment of all PHPTH dogs to prevent hypocalcemia may be warranted (Box 15-5). Chapter 16 presents a complete discussion of the acute and chronic management of hypocalcemia in dogs and cats.

Chronicity of Primary Hyperparathyroidism

Experience indicates an association between posttreatment hypocalcemia and chronicity of PHPTH in dogs. Often, duration of hypercalcemia secondary to PHPTH is unknown. Occasionally, however, PHPTH has been documented for extended time periods. Dogs with protracted histories of confirmed disease often have not been treated because owners have not observed worrisome signs and they are monitoring the condition. Another cause

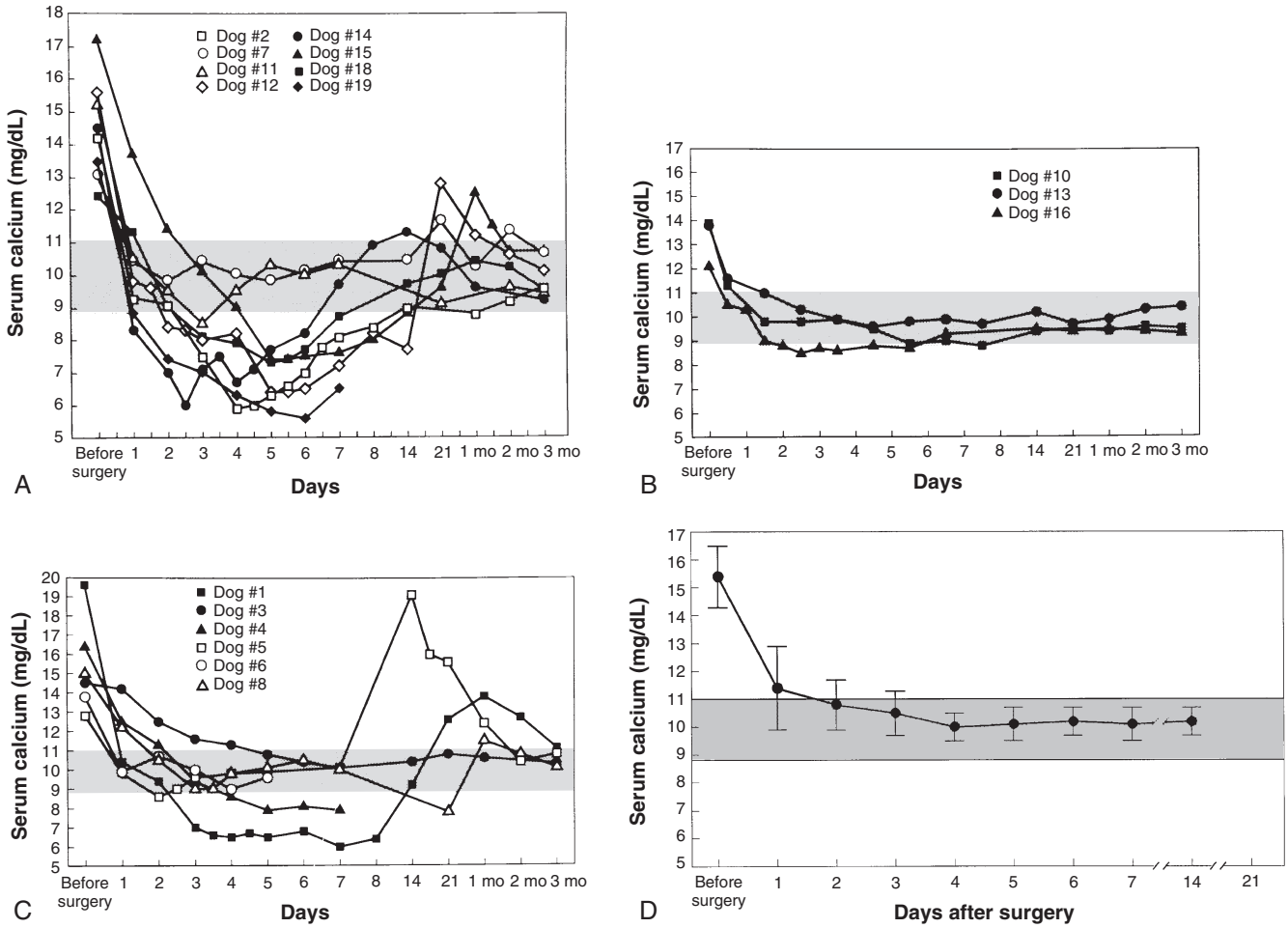


FIGURE 15-32 Serial calcium concentrations before and after removal of a parathyroid tumor from dogs with primary hyperparathyroidism (PHPTH). **A,** These eight dogs were placed on vitamin D_2 and calcium supplementation after hypocalcemia was identified. **B,** These three dogs had mild hypercalcemia prior to surgery, and they were not treated with vitamin D or calcium after surgery. **C,** These six dogs began receiving vitamin D_2 and calcium immediately after recovery from anesthesia. **D,** Serum calcium concentrations from 34 dogs that began receiving dihydrotachysterol immediately after recovery from anesthesia.

BOX 15-5 Clinical Signs Associated with the Acute Onset of Hypocalcemia

Panting
Nervousness
Anxiety
Muscle trembling, twitching
Leg cramping, pain (may be seen as "weakness")
Ataxia
Atypical aggressive behavior
Stiff gait
Facial rubbing
Biting at feet
Vocalizing
Hypersensitivity
Seizures: focal or generalized

for longer histories is the client/veterinarian team who choose a more deliberate approach. We now recommend prophylactic treatment with vitamin D in an attempt to prevent hypocalcemia or, at least, to reduce its severity clinically and biochemically.

Pretreatment Serum Calcium Concentration (More Than 15 mg/dL; Ionized Calcium More Than 1.75 mmol/L)

We assume that dogs with a serum TCa or iCa persistently greater than 15 mg/dL or 1.75 mmol/L, respectively, due to PHPTH have been hypercalcemic "chronically" or their level of negative feedback and resultant atrophy of normal glands greater. The recommendation is to prophylactically attempt to avoid hypocalcemia after PHPTH therapy by beginning vitamin D (calcitriol, 20 to 30 ng/kg/day, divided b.i.d. [twice a day]) that morning (see Chapter 16). In some cases we have begun calcitriol therapy 24 to 36 hours before surgery, but this may not be necessary. Initiation of calcitriol has not prevented decreases in the serum calcium concentration to or below reference ranges after surgery, but it has prevented or decreased the severity of clinical and biochemical hypocalcemia. Each dog should be kept quiet in a cage or run for at least 3 to 5 days after treatment.

Timing of Posttreatment Hypocalcemia and Recommendations Regarding Vitamin D

Postsurgical hypocalcemia has been observed as early as 12 hours to as late as 20 days after curative therapy. Most dogs that become hypocalcemic, usually do so between the second and sixth days posttreatment.

Tetany, when it has occurred, has usually been seen 4 to 7 days after treatment. The serum calcium concentration should be monitored once or twice daily. The goal of vitamin D therapy is to maintain serum calcium concentrations in the low to low-normal range (i.e., TCa, 8 to 9.5 mg/dL; iCa, 0.9 to 1.2 mmol/L). Such serum calcium concentrations are well above those associated with clinical signs, are not likely to be a cause of iatrogenic vitamin D toxicosis, and are low enough to stimulate functional recovery in atrophied parathyroid glands. Mid- to high-normal or greater serum calcium concentrations in dogs being given vitamin D should be avoided. Such concentrations may be associated with worrisome increases in serum phosphate concentration, and they predispose the dog to AKI.

The Tapering Process

In order to stimulate the remaining parathyroid glands to regain control of calcium homeostasis, vitamin D supplements must be gradually withdrawn. This process of returning parathyroid function in remaining glands is not completely predictable. Once serum calcium concentrations have stabilized and the dog has been returned to the owner, tapering vitamin D (calcitriol) begins. It is usually withdrawn by gradually extending the time between administration (e.g., twice daily to once daily for 2 weeks; to once every other day for 2 weeks; then once every third day for 2 weeks; then once every fourth day for 2 weeks; and finally, once weekly for 2 to 4 weeks). The serum calcium concentration should be checked prior to each adjustment in the dosing interval to prevent the development of occult hypo- or hypercalcemia. If the serum calcium concentration drops below 8 mg/dL, reduction of the vitamin D supplementation should be delayed or the dose increased. The serum calcium concentration should remain above 8 mg/dL to minimize the risk of tetany. However, if the serum calcium concentrations are high-normal or increased, vitamin D should be discontinued (permanently or transiently, as determined by the patient). Once the vitamin D supplementation has been reduced to once weekly for 2 to 4 weeks, it may be discontinued. Also, if serum calcium concentrations remain in reference ranges after the dose has been reduced to once weekly, any calcium supplements should then be withdrawn. Specific calcium supplementation should not be needed if the dog is being fed quality food. If calcium content of the diet is questionable, supplemental calcium can be given (see Chapter 16). Using this protocol, the withdrawal process for vitamin D and calcium usually takes 3 to 4 months. It is important to remember that there is considerable individual variation in response to therapy, and it is difficult, therefore, to check the serum calcium concentration too frequently.

Prophylactic Vitamin D (Calcitriol) Therapy in All Dogs Treated for Primary Hyperparathyroidism

Background

Prediction of posttreatment hypocalcemia in dogs with PHPTH has proven difficult and may depend on multiple factors, including but not limited to signalment, history, physical examination findings, clinicopathologic results, and imaging results (Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). Prophylactic vitamin D treatment strategies have been employed based on pretreatment factors used to identify dogs most likely to suffer serious hypocalcemia after being treated for PHPTH. Many dogs with PHPTH develop posttreatment subclinical hypocalcemia (Arbaugh et al, 2012). Further, some dogs with PHPTH develop posttreatment clinical tetany, and a few have had serious life-threatening hypocalcemia persist (Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013).

Current Recommended Protocol

We have embarked on a new, more aggressive protocol to avoid posttreatment hypocalcemia in dogs being treated for PHPTH. Results have been encouraging to date, and time will tell if this protocol is satisfactory. All dogs being treated for PHPTH should be given calcitriol the morning of the planned treatment at a dose of 20 to 30 ng/kg. That posttreatment night, the dog should be given 10 to 15 ng/kg, and that dose should be continued (20 to 30 ng/kg/day divided b.i.d.) for the first 2 days following treatment. The third day after therapy, and every 4 days thereafter, the dose of calcitriol should then be reduced by 10%, continuing for about 45 to 60 days. Twice daily monitoring of serum TCa and iCa concentrations are strongly recommended while in the hospital. Both parameters should be checked prior to every planned dose reduction. As described in the previous section, monitoring serum calcium concentrations are required in an attempt to avoid under or over dosage. If calcium concentrations are less than 8.5 mg/dL (TCa) or 0.95 mmol/L (iCa) at any time, the dose of vitamin D should be at least transiently increased to a previously used and safe dose. Monitoring of serum calcium concentrations is also required in an attempt to avoid iatrogenic vitamin D toxicosis. If calcium concentrations are within the upper portion of the reference range, the dose of calcitriol should be decreased by 50%. If the serum calcium concentrations are above reference ranges, the calcitriol should be stopped for 48 hours and the values again rechecked. If hypercalcemia and hyperphosphatemia are documented, IV saline therapy for 24 hours or longer should be considered.

Vitamin D Resistance/Time Until an Effect Is Documented

It is not common for calcitriol to begin to have an immediate effect. Rather, vitamin D gradually takes effect during the first several days of therapy and almost always within 4 to 7 days. Individual variation is typical.

PATHOLOGY

Subjectivity of Histologic Interpretation

Abnormal, autonomously functioning parathyroid glands from people, dogs, and cats have been characterized histologically as adenoma, carcinoma, and hyperplasia. Controlled studies reviewing histologic interpretations by pathologists have shown that classifying a parathyroid nodule as adenoma, hyperplasia, or carcinoma is not straightforward (Aurbach et al, 1985a; DeVries et al, 1993; Ham et al, 2009). Histologic classification of parathyroid tissue may be influenced to some degree by gross features observed during surgery. The surgeon determines the number, size, and appearance of normal and abnormal glands. The pathologist then determines whether removed tissue is parathyroid and further classifies the tissue, when possible, as benign or malignant.

As previously discussed, single-gland involvement (adenoma, carcinoma, or hyperplasia) occurs in about 80% to 90% of people and dogs with PHPTH. Multiple-gland involvement has been documented in 10% to 20% (Arnaud and Kolb, 1991; Gear et al, 2005; Ham et al, 2009; Sawyer et al, 2011; Arbaugh et al, 2012; Milovancev and Schmiedt, 2013). The diagnosis of carcinoma is based on gross appearance, histologic features, and ultimately the biologic behavior of the lesion. Fewer than 2% of autonomously secreting parathyroid nodules in people are malignant. Five percent to 10% of parathyroid tissue removed from dogs with PHPTH has been assigned the

diagnosis of carcinoma, but we are aware of only one dog being described as having "multicentric disease" not amenable to surgical extirpation (Ham et al, 2009).

Solitary Parathyroid Mass

Background

In people, dogs, and cats, the most common cause of PHPTH is a solitary functioning chief cell adenoma, resulting in the secretion of excessive amounts of PTH. A denomas are usually solitary (developing in an existing parathyroid gland), light brown-red in color, and located in close proximity to that thyroid lobe (see Figs. 15-21 and 15-26). Because of the difficulty involved in histologically classifying an enlarged parathyroid gland as an adenoma, carcinoma, or adenomatous hyperplasia, a "nodule" is tentatively diagnosed during surgery when a solitary abnormal parathyroid gland is identified and the remaining glands are normal, atrophied, or not seen. The term *adenoma* may also be arbitrary as applied to such tissue.

Adenoma

"Adenoma" is diagnosed when a single nodule is easily seen, well demarcated, and histologically compresses a rim of atrophied but otherwise normal parathyroid tissue (Capen and Martin, 1983; DeVries et al, 1993). Adenomas are generally composed of a diffuse pattern of parathyroid chief cells. About 75% to 85% of dogs with PHPTH have a solitary parathyroid adenoma identified and removed during surgical exploration of the neck. Multiple adenomas have been reported in people (Aurbach et al, 1985a) and are found in 3% to 5% of dogs with PHPTH (Pollard et al, 2001).

About 5% to 10% of dogs with PHPTH experience complete resolution of their condition after removal or ablation of a solitary parathyroid nodule but have a recurrence of the condition 6 months or more afterward. Each of those dogs then had this second nodule ablated or removed. In most cases the second mass was also an adenoma, but carcinoma and hyperplasia have been diagnosed. In none of these dogs were two masses present initially, demonstrated in part by resolution of hypercalcemia for an extended period. Thorough exploration of the neck, initially, also failed to demonstrate two masses.

Carcinoma

Chief cell carcinomas are identified in fewer than 3% to 4% of people with PHPTH (Shane and Bilezikian, 1982). In as many as 50% of these people, the malignant lesion may be palpable in the neck, and at surgery the mass is often firm and densely adherent to local structures (Aurbach et al, 1985a). Capsular and vascular invasion are characteristic histologic findings. Parathyroid carcinomas in people tend to be locally invasive with the potential to spread to regional lymph nodes, lung, liver, and bone. Parathyroid gland carcinomas in dogs behave as an adenoma (Berger and Feldman, 1987; DeVries et al, 1993: Sawyer et al, 2011). In one study, each of 19 dogs with PHPTH caused by a parathyroid carcinoma had a solitary nodule identified at surgery. Each nodule was described as having a benign gross appearance. Hypercalcemia resolved in 18 of 19 after surgery, and no dog was confirmed to develop recurrent or metastatic PHPTH (Sawyer et al, 2011).

Primary Hyperplasia

Hyperplasia implies an abnormality involving all parathyroid tissue and is frequently diagnosed when more than one parathyroid gland is grossly and microscopically abnormal. Gross enlargement of all four glands is not a prerequisite for a diagnosis of hyperplasia because microscopic alterations may be present in a normal-sized gland (Aurbach et al, 1985a). An accurate histologic diagnosis requires clear criteria for distinguishing adenoma from hyperplasia and for distinguishing either of these from normal. A tentative differentiation often is based on the number of glands involved (i.e., one gland supports a diagnosis of adenoma and multiple glands a diagnosis of hyperplasia) (Verdonk and Edis, 1981).

We reported a group of six dogs with PHPTH (8% of the 72 in our series at the time) that had hyperplasia as determined by board certified pathologists (DeVries et al, 1993). That percentage approximates the experience in the literature since. The terms *nodular hyperplasia* and *adenomatous hyperplasia* may be applied to parathyroids that contain multiple nodules less than 5 mm in diameter as opposed to adenomas, which are often defined as parathyroid tumors consisting of a solitary nodule greater than 5 mm in diameter.

Differentiation of hyperplasia and adenoma has important implications regarding surgery, medical therapy, and long-term prognosis. A dog or cat with PHPTH may be cured after complete surgical removal of a solitary adenoma with three normal parathyroid glands (albeit atrophied in the immediate postsurgical period) remaining to prevent permanent hypoparathyroidism. In contrast, parathyroid hyperplasia implies that if all abnormal parathyroid tissue is not removed, the chance for persistent or recurrent hyperparathyroidism is high. However, this has not consistently been observed in dogs with PHPTH. Most PHPTH dogs diagnosed as having a solitary hyperplastic parathyroid nodule removed at surgery have complete resolution of the condition. Their PHPTH seems no different than for dogs diagnosed as having a parathyroid adenoma or carcinoma (DeVries et al, 1993).

Summary

In our series of dogs with PHPTH that have had surgery and that had a solitary mass, about 87% had a solitary parathyroid adenoma, about 8% had a diagnosis of solitary primary parathyroid hyperplasia, and 5% had a diagnosis of carcinoma. In general, long-term response to therapy was similar regardless of histologic classification. Recurrences occur regardless of the initial histologic diagnosis. When recurrences occur (approximately 10% of our dogs), the histologic diagnosis of tissue removed at second surgery is just as likely to be different from the initial diagnosis as it is to be similar. Distant metastasis from a parathyroid carcinoma and/or local invasion has been described, but is extremely uncommon (Ham et al, 2009). It is also worth repeating that about 10% of dogs with PHPTH have two parathyroid nodules at the time of initial diagnosis. Again, the histologic classification of these masses is as likely to be different (e.g., one adenoma and one carcinoma or one hyperplasia and one adenoma) as they are to be the same. The recurrence rate in dogs with two masses at the time of diagnosis is less than the recurrence rate of dogs with a single solitary mass.

Mediastinal Parathyroid Tissue

Parathyroid tissue, displaced into the anterior mediastinum during the embryologic expansion of the thymus and often referred to as "ectopic" because its location is not associated with the thyroid, may become autonomously functioning. In humans, this is an uncommon but recognized location for a solitary adenoma (Heath, 1989). Mediastinal parathyroid tissue that results in PHPTH has been reported in a dog, and a mediastinal parathyroid cyst was diagnosed in a normocalcemic cat (Swainson et al, 2000; Ham et al, 2009).

Multiple Endocrine Neoplasia and Adrenal Secondary Hyperparathyroidism

Multiple Endocrine Neoplasia

Multiple endocrine neoplasia (MEN) refers to a group of syndromes in humans (often familial) consisting of hyperplasia or neoplasia in two or more endocrine glands. Two patterns of MEN involve the parathyroid gland: (1) MEN type I, parathyroid hyperplasia with pancreatic islet cell adenoma/carcinoma or adenoma/hyperplasia of the anterior pituitary; and (2) MEN type IIa, medullary carcinoma of the thyroid with pheochromocytoma and/or parathyroid hyperplasia (see Chapter 5). In both conditions, hyperplasia, not neoplasia, is the most common parathyroid abnormality. Although the clinical expression of the MEN components is variable, hyperparathyroidism usually predominates in MEN type I, whereas medullary thyroid carcinoma predominates in MEN type IIa (Leshin, 1985). Sporadic cases of dogs and cats with multiple endocrine disorders are occasionally reported. Our experience of multiple endocrine conditions involving PHPTH would include the common combination with Cushing's syndrome. It remains elucidated if dogs with these concurrent conditions have pituitary dependent Cushing's and parathyroid hyperplasia. Further, as we recognize more thyroid tumors incidentally on cervical ultrasonography, this may add to the combinations seen (Pollard et al, in press).

Adrenal Secondary Hyperparathyroidism

Hypercortisolism is associated with dysregulation of calcium homeostasis as illustrated by dogs with calcinosis cutis and/or bronchial tree calcification. A majority of dogs with hypercortisolism were demonstrated to have increases in circulating PTH concentrations, although not associated with changes in TCa or iCa (Ramsey et al, 2005). With successful treatment of hypercortisolism, serum PTH concentrations returned to reference range concentrations (Tebb et al, 2005).

Hereditary Neonatal Primary Hyperparathyroidism

A rare form of hereditary neonatal PHPTH has been described in humans, which is associated with diffuse hyperplasia of the parathyroid chief cells. Primary parathyroid hyperplasia has also been reported in two German Shepherd pups from a litter of four females (Thompson et al, 1984). Clinical signs were apparent in these dogs by 2 weeks of age, including stunted growth, muscular weakness, and polyuria/polydipsia. An autosomal recessive mode of inheritance for the PHPTH was suggested, and an analogous condition is recognized in children.

PROGNOSIS: DOGS WITH PRIMARY HYPERPARATHYROIDISM

The prognosis for most dogs with PHPTH is excellent. Hypocalcemia may occur after therapy, but clinical hypocalcemia should not be common with use of posttreatment calcitriol. Care must be taken not to overdose vitamin D.

HYPERCALCEMIA IN CATS

BACKGROUND

In general, the same differential diagnoses for hypercalcemia in dogs can be used in cats. In a study of 71 hypercalcemic cats, their mean age was about 9 years and their mean serum TCa concentration was 12.2 mg/dL. Anorexia and lethargy were their most common clinical signs (70%). Vomiting, diarrhea, and/or constipation were observed in 27%, polyuria and/or polydipsia were observed in 24%, urinary signs were seen in 23%, and neurologic signs were observed in 14% (Savary et al, 2000). Hypercalcemia secondary to malignancy was diagnosed in 30% of these cats. The most common cancers diagnosed included lymphoma and squamous cell carcinoma. Less common neoplasms included leukemia, osteosarcoma, fibrosarcoma, undifferentiated sarcoma, and bronchogenic carcinoma (Anderson et al, 2000; Bollinger et al, 2002; Geddes, 2013). CKD was diagnosed in 25% of the cats, and half of those had urolithiasis. In a separate study, CKD in cats was usually associated with a serum TCa concentration in the reference range and a low-normal to low serum iCa concentration (Barber and Elliott, 1998). Of cats with hypercalcemia, several had urolithiasis without renal injury. Four cats (6%) had PHPTH. One cat had hypoadrenocorticism. Several cats had hyperthyroidism or diabetes mellitus, but it would not seem likely that either of these endocrine conditions would contribute to hypercalcemia. However, four cats (6%) had infectious or granulomatous disease (e.g., feline infectious peritonitis [FIP], toxoplasmosis, actinomycosis, or cryptococcosis). Thus the differential diagnosis for hypercalcemia in cats is not dramatically different from that in dogs (Mealey et al, 1999; Savary et al, 2000; Pineda et al, 2012).

IDIOPATHIC HYPERCALCEMIA OF CATS

Idiopathic hypercalcemia of cats (IHC) may be their most common cause of hypercalcemia. In contrast to hypercalcemic dogs, in which a diagnosis can usually be made, this condition remains frustrating to understand and treat. IHC has been recognized in North America and in other areas (Schenck and Chew, 2012). There is no age or gender predisposition. Long-haired cats may be over represented (Barsanti, 1997; Refsal et al, 1998; Midkiff et al, 2000; Rosol et al, 2000; Schenck and Chew, 2005a). About 50% of cats with IHC have no apparent clinical signs. When present, signs include any combination of weight loss, weakness, diarrhea, constipation, vomiting, and decreases in appetite. Calcium containing uroliths have been documented in about 10% to 15% of cats with IHC. Increases in their serum iCa concentrations are similar to or higher than expected from the increases noted in TCa. Serum PTH concentrations have been within or below reference intervals, and PTHrP is not increased. Serum magnesium and 25(OH)D concentrations have usually been within reference intervals, and concentrations of $1,25(OH)_2D_3$ are decreased (Schenck and Chew, 2012). Some cats with IHC have developed CKD.

The pathogenesis of IHC is not understood, making therapies nonspecific. Increasing dietary fiber has been advocated to decrease intestinal absorption of calcium. Increasing dietary fiber has not been uniformly helpful, probably related to the many forms of fiber used. Use of diets formulated for cats with CKD have also been helpful in some but not all IHC cats. These diets are usually low in calcium and phosphorus and may have an alkalinizing effect. A positive dietary response with normalization of serum calcium concentrations, however, does not usually persist.

Prednisolone has been beneficial in some cats with IHC. Doses of 5 to 20 mg/cat/day often reduce serum calcium concentrations and in some cats contribute to long-term control. Prednisolone has also improved appetite and body weight in some cats. When diet and prednisolone fail to resolve IHC, the use of a bisphosphonate has been recommended. IV administration is not recommended because of the chronic nature of IHC. Rather, oral alendronate is recommended, 10 mg weekly after a 12 hour fast, with special note made of the medication causing esophagitis if not completely passed into the stomach. To

TABLE 15-10 **CLINICAL, LABORATORY, AND HISTOLOGIC FINDINGS IN 10 CATS WITH PRIMARY, NATURALLY OCCURRING, HYPERPARATHYROIDISM IN THE UC DAVIS SERIES**

SIGNALMENT	CLINICAL SIGNS	SERUM Ca (mg/dL)	SERUM PO_4 (mg/dL)	BLOOD UREA NITROGEN (mg/dL)	SERUM CREATININE (mg/dL)	URINE SPECIFIC GRAVITY	PARATHYROID HISTOLOGY
15 y.o. M/N, DLH	Anorexia, vomiting	14.6	3.4	35	1.8	1.011	Solitary adenoma
14 y.o. F/S, Siamese	Anorexia, vomiting, muscle fasciculation	22.8	6.6	70	3.2	1.013	Solitary adenoma
15 y.o. M/N, Siamese	None	13.5	3.3	21	2.2	1.031	Solitary adenoma
15 y.o. F/S, Siamese	Polydipsia, polyuria	13.3	2.2	31	2.7	1.010	Solitary adenoma
8 y.o. F/S, DSH	Anorexia, weight loss	13.8	1.8	15	1.0	1.015	Solitary adenoma
14 y.o. F/S, DSH	Polydipsia, polyuria, lethargy	15.4	2.5	30	1.2	1.010	Solitary adenoma
9 y.o. F/S, Siamese	Anorexia	17.1	6.2	63	2.6	1.026	Bilateral cystadenoma
9 y.o. M/N, DSH	Anorexia, vomiting, lethargy, dysuria	15.2	2.6	59	3.6	1.015	Solitary carcinoma
14 y.o. M/N, DSH	Constipation	13.4	3.7	41	2.2	1.022	Solitary adenoma
12 y.o. M/N, DSH	Weight loss, lethargy, constipation	14.1	3.2	27	1.4	1.018	Bilateral carcinomas
Reference values		8.8-11.4	2.4-6.1	10-30	0.8-2.0	—	—

DLH, Domestic Long-Haired; *DSH,* Domestic Short-Haired; *F,* female; *M,* male; *N,* neutered; *S,* spay/ovariohysterectomy; serum Ca, serum total calcium; serum PO_4, serum phosphate concentration; *y.o.,* years old.

avoid esophageal irritation and to enhance passage into the stomach, water should be given (Schenck and Chew, 2012).

PRIMARY HYPERPARATHYROIDISM IN CATS

A relatively small number of cats with PHPTH have been reported (Kallet et al, 1991; Marquez et al, 1995; den Hertog et al, 1997; Savary et al, 2000; Sueda and Stefanacci, 2000). Their mean age was approximately 13 years (range, 8 to 20 years) and various breeds were represented. The most common clinical signs were anorexia, lethargy, and vomiting. Owners also observed constipation, polyuria, polydipsia, and weight loss. Other signs were uncommon. A parathyroid mass was palpable in 11 of the 19 cats. The presence of a palpable mass and the owners' observations contrast with our experience in dogs with PHPTH. A palpable parathyroid mass in dogs with PHPTH is quite uncommon (Sawyer et al, 2011).

The only consistent abnormality on CBC and serum biochemical profiles is hypercalcemia (Table 15-10). Afflicted cats have persistent increases in both the serum TCa and iCa concentrations. Several cats had cystic calculi and a large percentage had abnormalities in their BUN and serum creatinine concentrations, in contrast to dogs. Cervical ultrasonography was described as normal in several cats, but others had visible masses that would be considered huge in a dog. On cervical ultrasonography, two cats each had a single parathyroid mass, one mass measuring 4.5 × 2 × 1 cm and the other measuring 1.7 × 1.1 × 1 cm (Sueda and Stefanacci, 2000). Serum PTH concentrations, when measured, ranged from within the reference range (0 to 4 pmol/L) to increased. In one cat, seven separate serum PTH samples were assayed; five results were in the reference range and two were increased.

Most of the 19 cats had surgical nodule removal followed by resolution of their PHPTH. Tetany has not been described in any cat treated with surgery, although several cats became subclinically hypocalcemic and were treated with vitamin D and calcium. Of the nine cats we followed after surgery, all lived well beyond 1 year, although at 1½ years, one had recurrence of hypercalcemia and at necropsy was demonstrated to have had both a parathyroid adenoma and a parathyroid carcinoma. Histologic evaluation of tissue removed showed that 13 cats had had a parathyroid adenoma, three had had parathyroid carcinomas, two had had parathyroid hyperplasia (involving all four glands), and one had had bilateral cystadenomas.

REFERENCES

Anderson TE, et al.: Probable hypercalcemia of malignancy in a cat with bronchogenic adenocarcinoma, *J Am Anim Hosp Assoc* 36:52, 2000.

Arbaugh M, et al.: Evaluation of preoperative serum concentrations of ionized calcium and parathyroid hormone as predictors of hypocalcemia following parathyroidectomy in dogs with primary hyperparathyroidism: 17 cases (2001-2009), *J Am Vet Med Assoc* 241:233, 2012.

Arnaud CD, Kolb FO: The calciotropic hormones and metabolic bone disease. In Greenspan FS, editor: *Basic and clinical endocrinology*, Los Altos, CA, 1991, Lange Medical Publications, p 247.

Attie JN, et al.: Preoperative localization of parathyroid adenomas, *Am J Surg* 156:323, 1988.

Attie MF: Treatment of hypercalcemia, *Endocrinol Metab Clin North Am* 18:807, 1989.

Aurbach GD, et al.: Parathyroid hormone, calcitonin, and the calciferols. In Wilson JD, Foster DW, editors: *Williams textbook of endocrinology*, ed 7, Philadelphia, 1985a, WB Saunders, p 1137.

Bahri LE: Poisoning in dogs by vitamin D3 containing rodenticides, *Compend Continu Ed Pract Vet* 12:1414, 1990.

Barber PJ, Elliott J: Feline chronic renal failure: calcium homeostasis in 80 cases diagnosed between 1992 and 1995, *J Small Anim Pract* 39:108, 1998.

Barber PJ, et al.: Measurement of feline intact parathyroid hormone: assay validation and sample handling studies, *J Small Anim Pract* 34:614, 1993.

Barsanti JA: Hypercalcemia and urolithiasis in cats, *Proc Am Coll Vet Intern Med Ann Forum* 15:327, 1997.

Bennedbaek FN, et al.: Percutaneous ethanol injection therapy in the treatment of thyroid and parathyroid diseases, *Eur J Endocrinol* 136:240, 1997.

Bennett PF, et al.: Canine anal sac adenocarcinomas: clinical presentation and response to therapy, *J Vet Intern Med* 16:100, 2002.

Berger B, Feldman EC: Primary hyperparathyroidism in dogs, *J Vet Med Assoc* 191:350, 1987.

Bilezikian JP: Hypercalcemic states. In Coe FL, et al.: editors: *Disorders of bone and mineral metabolism*, New York, 1992a, Raven Press, p 493.

Bilezikian JP: Management of acute hypercalcemia, *N Engl J Med* 326:1196, 1992b.

Bilezikian JP, et al.: *The parathyroids: basic and clinical concepts*, ed 2, San Diego, CA, 2001, Academic Press.

Black KS, Mundy GR: Other causes of hypercalcemia: local and ectopic secretion syndromes. In Bilezikian JP, et al.: editors: *The parathyroids*, New York, 1994, Raven Press, p 341.

Bollinger AP, et al.: Detection of parathyroid hormone-related protein in cats with humoral hypercalcemia of malignancy, *Vet Clin Pathol* 31:3, 2002.

Boyce RA, Weisbrode SE: Effect of dietary calcium on the response of bone to 1,25(OH)2D3, *Lab Invest* 48:683, 1983.

Broadus AE, Stewart AF: Parathyroid hormone–related protein: structure, processing, and physiologic actions. In Bilezikian JP, editor: *The parathyroids: basic and clinical concepts*, New York, 1994, Raven Press, pp 259–294.

Brown EM, et al.: Calcium ion–sensing cell surface receptors, *N Engl J Med* 333:234, 1995.

Brown EM, et al.: G-protein–coupled, extracellular Ca^{2+}–sensing receptor: a versatile regulator of diverse cellular functions, *Vitam Horm* 55:1, 1999.

Brown RC, et al.: Circulating intact parathyroid hormone measured by a two-site immunochemiluminometric assay, *J Clin Endocrinol Metab* 65:407, 1987.

Budayr AA, et al.: Increased serum levels of parathyroid hormone–like protein in malignancy-associated hypercalcemia, *Ann Intern Med* 111:807, 1989.

Burtis WJ: Parathyroid hormone-related protein: structure, function, and measurement, *Clin Chem* 38:2171, 1992.

Capen CC, Martin SL: Calcium-regulating hormones and diseases of the parathyroid glands. In Ettinger SJ, editor: *Textbook of veterinary internal medicine*, ed 2, Philadelphia, 1983, WB Saunders, p 1550.

Carothers MA, et al.: 25-OH-cholecalciferol intoxication in dogs, *Proc Am Coll Vet Intern Med Forum* 12:822, 1994.

Chew DJ, Capen CC: Hypercalcemic nephropathy and associated disorders. In Kirk RW, editor: *Current veterinary therapy VII*, Philadelphia, 1980, WB Saunders, p 1067.

Chew DJ, Meuten DJ: Disorders of calcium and phosphorus metabolism, *Vet Clin North Am* 12:411, 1982.

Chew DJ, et al.: Effect of sodium bicarbonate infusions on ionized calcium and total calcium concentrations in serum of clinically normal cats, *Am J Vet Res* 50:145, 1989.

Chew DJ, et al.: Hypercalcemia in dogs and cats: overview of etiology, diagnostic approach, and therapy, *Proceedings of the Waltham/OSU Symposium* 1991, p 35.

Consensus Development Conference Panel: NIH conference; diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement, *Ann Intern Med* 114:593, 1991.

Cortadellas O, et al.: Calcium and phosphorus homeostasis in dogs with spontaneous chronic kidney disease at different stages of severity, *J Vet Intern Med* 24:73, 2010.

Crager CS, Nachreiner RF: Increased parathyroid hormone concentration in a Siamese kitten with nutritional secondary hyperparathyroidism, *J Am Anim Hosp Assoc* 29:331, 1993.

den Hertog E, et al.: Primary hyperparathyroidism in two cats, *Vet Q* 19:81, 1997.

DeVries SE, et al.: Primary parathyroid gland hyperplasia in dogs: six cases (1982-1991), *J Am Vet Med Assoc* 202:1132, 1993.

Dougherty SA, et al.: Salmon calcitonin as adjunct treatment for vitamin D toxicosis in a dog, *J Am Vet Med Assoc* 196:1269, 1990.

Dow SW, et al.: Hypercalcemia associated with blastomycosis in dogs, *J Am Vet Med Assoc* 188:706, 1986.

Durie BG, et al.: Relation of osteoclast activating factor production to the extent of bone disease in multiple myeloma, *Br J Haematol* 47:21, 1981.

Estepa JC, et al.: Dynamics of secretion and metabolism of PTH during hypo- and hypercalcemia in the dog as determined by the "intact" and "whole" PTH assays, *Nephrology Dialysis Transplantation* 18:1101, 2003.

Eubig PA, et al.: Acute renal failure in dogs after the ingestion of grapes or raisins: a retrospective evaluation of 43 dogs (1992-2002), *J Vet Intern Med* 19:663, 2005.

Feldman EC: Canine primary hyperparathyroidism. In Kirk RW, Bonagura JD, editors: *Current veterinary therapy X*, Philadelphia, 1989, WB Saunders, p 985.

Feldman EC, et al.: Comparison of results of hormonal analysis of samples obtained from selected venous sites versus cervical ultrasonography for localizing parathyroid masses in dogs, *J Am Vet Med Assoc* 211:54, 1997.

Feldman EC, et al.: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004), *J Am Vet Med Assoc* 227:756, 2005.

Fine EJ: Parathyroid imaging: its current status and future role, *Semin Nucl Med* 17:350, 1987.

Fingeroth JM, Smeak DD: Intravenous methylene blue infusion for intraoperative identification of parathyroid gland tumors in dogs: III. clinical trials and results in three dogs, *J Am Anim Hosp Assoc* 24:673, 1988.

Flanders JA, Reimers TJ: Radioimmunoassay of parathyroid hormone in cats, *Am J Vet Res* 52:422, 1991.

Foley P, et al.: Serum parathyroid hormone–related protein concentration in a dog with a thymoma and persistent hypercalcemia, *Can Vet J* 41:867, 2000.

Fooshee SK, Forrester SD: Hypercalcemia secondary to cholecalciferol rodenticide toxicosis in two dogs, *J Am Vet Med Assoc* 196:1265, 1990.

Fradkin JM, et al.: Elevated parathyroid hormone–related protein and hypercalcemia in two dogs with schistosomiasis, *J Am Anim Hosp Assoc* 37:349, 2001.

Gao P, et al.: Development of a novel immunoradiometric assay exclusively for biologically active whole parathyroid hormone 1-84: implications for improvement of accurate assessment of parathyroid function, *J Bone and Mineral Research* 16:605, 2001.

Garrett IR: Bone destruction in cancer, *Semin Oncol* 20:4, 1993.

Gear RN, et al.: Primary hyperparathyroidism in 29 dogs: diagnosis, treatment, outcome and associated renal failure, *J Small Animal Prac* 46:10, 2005.

Geddes, et al.: Eight novel polymorphisms identified in the feline calcium sensing receptor in cats with varying plasma ionized calcium concentrations, *J Am Vet Med Assoc* 687, 2013.

Goldschmidt MH, Shofer FS: *Skin tumors of the dog and cat*, Oxford, England, 1992, Pergamon Press, pp 103–108.

Goldstein RE, et al.: Inheritance, mode of inheritance and candidate genes for primary hyperparathyroidism in Keeshonden, *J Vet Intern Med* 21:199, 2007.

Goodwin JS, et al.: Mechanism of action of glucocorticoids: inhibition of T cell proliferation and interleukin-2 production by hydrocortisone is reversed by leukotriene B_4, *J Clin Invest* 77:1244, 1986.

Grain E, Walder EJ: Hypercalcemia associated with squamous cell carcinoma in a dog, *J Am Vet Med Assoc* 181:165, 1982.

Greenlee PG, et al.: Lymphomas in dogs: a morphologic, immunologic and clinical study, *Cancer* 66:480, 1990.

Grone A, et al.: Dependence of humoral hypercalcemia of malignancy on parathyroid hormone–related protein expression in the canine anal sac apocrine gland adenocarcinoma (CAC-8) nude mouse model, *Vet Pathol* 35:344, 1998.

Gross KL, et al.: Nutrients. In Hand MS, et al.: editors: *Small animal clinical nutrition*, ed 4, Kansas, 2000, Mark Morris Institute, p 84.

Gunther R, et al.: Toxicity of a vitamin D_3 rodenticide to dogs, *J Am Vet Med Assoc* 193:211, 1988.

Gwaltney-Brant S, et al.: Renal failure associated with ingestion of grapes or raisins in dogs, *J Am Vet Med Assoc* 218:1555, 2001.

Ham K, et al.: Validation of rapid parathyroid hormone assay and intraoperative measurement of parathyroid hormone in dogs with benign naturally occurring primary hyperparathyroidism, *Vet Surg* 38:122, 2009.

Harrington DD, Page EH: Acute vitamin D_2 (ergocalciferol) toxicosis in horses: case report and experimental studies, *J Am Vet Med Assoc* 182:1358, 1983.

Harris NL, et al.: Case records of the Massachusetts General Hospital, *N Engl J Med* 347:1952, 2002.

Heath DA: Primary hyperparathyroidism: clinical presentation and factors influencing clinical management, *Endocrinol Metab Clin North Am* 18:631, 1989.

Henderson JE, et al.: Circulating concentrations of parathyroid hormone–like peptide in malignancy and in hyperparathyroidism, *J Bone Miner Res* 5:105, 1990.

Henry CJ: Paraneoplastic syndromes. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine: diseases of the dog and cat*, St Louis, 2010, Elsevier, p 2213.

Hirt RA, et al.: Severe hypercalcemia in a dog with a retained fetus and endometritis, *J Am Vet Med Assoc* 216:1423, 2000.

Hollis BW, et al.: Quantification of circulating 1,25-dihydroxyvitamin D by radioimmunoassay with an ^{125}I-labeled tracer, *Clin Chem* 42:586, 1996.

Hostutler RA, et al.: Uses and effectiveness of pamidronate disodium for treatment of dogs and cats with hypercalcemia, *J Vet Intern Med* 19:29, 2005.

Hruska KA, Teitelbaum SL: Renal osteodystrophy, *N Engl J Med* 333:166, 1995.

Ihle SL, et al.: Seizures as a manifestation of primary hyperparathyroidism in a dog, *J Am Vet Med Assoc* 192:71, 1988.

Jiao LR, et al.: Clinical short-term results of radio frequency ablation in primary and secondary liver tumors, *Am J Surg* 177:303, 1999.

Johnessee JS, et al.: Primary hypoadrenocorticism in a cat, *J Am Vet Med Assoc* 183:881, 1982.

Kallet AJ, et al.: Primary hyperparathyroidism in cats: seven cases (1984-1989), *J Am Vet Med Assoc* 199:1767, 1991.

Klausner JS, et al.: Calcium urolithiasis in two dogs with parathyroid adenomas, *J Am Vet Med Assoc* 191:1423, 1987.

Krubsack AJ, et al.: Prospective comparison of radionuclide, computed tomography, and sonographic and magnetic resonance localization of parathyroid tumors, *Surgery* 106:639, 1989.

Legendre AM, et al.: Canine blastomycosis: a review of 47 clinical cases, *J Am Vet Med Assoc* 178:1163, 1981.

Lemann J, Gray RW: Calcitriol, calcium, and granulomatous disease, *N Engl J Med* 311:1115, 1984.

Leshin M: Multiple endocrine neoplasia. In Wilson JC, Foster DW, editors: *Williams textbook of endocrinology*, ed 7, Philadelphia, 1985, WB Saunders, p 1274.

Livraghi T, et al.: Small hepatocellular carcinoma: treatment with radio frequency ablation versus ethanol ablation, *Radiology* 210:655, 1999.

Llach F, et al.: The pathophysiology of altered calcium metabolism in rhabdomyolysis-induced acute renal failure, *N Engl J Med* 305:117, 1981.

Lloyd MN, et al.: Preoperative localization in primary hyperparathyroidism, *Clin Radiol* 41:239, 1990.

Long CD, et al.: Percutaneous ultrasound–guided chemical parathyroid ablation for treatment of primary hyperparathyroidism in dogs, *J Am Vet Med Assoc* 215:217, 1999.

Marquez GA, et al.: Calcium oxalate urolithiasis in a cat with a functional parathyroid adenocarcinoma, *J Am Vet Med Assoc* 206:817, 1995.

Marx SJ: Hyperparathyroid and hypoparathyroid disorders, *N Engl J Med* 343:1863, 2000.

Matus RE, Weir EC: Hypercalcemia of malignancy. In Kirk RW, Bonagura JD, editors: *Current veterinary therapy X*, Philadelphia, 1989, WB Saunders, p 988.

Matus RE, et al.: Prognostic factors for multiple myeloma in the dog, *J Am Vet Med Assoc* 188:1288, 1986.

Matwichuk C, et al.: Use of ^{99m}Tc-sestamibi for detection of a parathyroid adenoma in a dog with primary hyperparathyroidism, *J Am Vet Med Assoc* 209:1733, 1996.

Matwichuk C, et al.: Double-phase parathyroid scintigraphy in dogs using ^{99m}Tc-sestamibi, *Vet Radiol Ultrasound* 41:461, 2000.

McArthur W, et al.: Bone solubilization by mononuclear cells, *Lab Invest* 42:452, 1980.

McCauley LK, et al.: In vivo and in vitro effects of interleukin-1a and cyclosporin A on bone and lymphoid tissues in mice, *Toxicol Pathol* 19:1, 1991.

Mealey KL, et al.: Hypercalcemia associated with granulomatous disease in a cat, *J Am Vet Med Assoc* 215:959, 1999.

Mellanby RJ, et al.: Hypercalcaemia in two dogs caused by excessive dietary supplementation of vitamin D, *J Small Animal Prac* 46:334, 2005.

Messinger JS, et al.: Ionized hypercalcemia in dogs: a retrospective study of 109 cases (1998-2003), *J Vet Intern med* 23:514, 2009.

Meuten DJ: Hypercalcemia, *Vet Clin North Am (Small Anim Pract)* 14:891, 1984.

Meuten DJ, Armstrong PJ: Parathyroid disease and calcium metabolism. In Ettinger SJ, editor: *Textbook of veterinary internal medicine: diseases of the dog and cat*, ed 3, Philadelphia, 1989, WB Saunders, p 1610.

Meuten DJ, et al.: Relationship of calcium to albumin and total proteins in dogs, *J Am Vet Med Assoc* 180:63, 1982.

Meuten DJ, et al.: Hypercalcemia in dogs with lymphosarcoma: biochemical, ultrastructural, and histomorphometric investigation, *Lab Invest* 49:553, 1983a.

Meuten DJ, et al.: Hypercalcemia in dogs with adenocarcinoma derived from apocrine glands of the anal sacs: biochemical and histomorphometric investigations, *Lab Invest* 48:428, 1983b.

Michelangeli VP, et al.: Evaluation of a new, rapid, and automated immunochemiluminometric assay for the measurement of serum intact parathyroid hormone, *Ann Clin Biochem* 34:97, 1997.

Midkiff AM, et al.: Idiopathic hypercalcemia in cats, *J Vet Intern Med* 14:619, 2000.

Milovancev M, Schmiedt CW: Preoperative factors associated with postoperative hypocalcemia in dogs that underwent parathyroidectomy: 62 cases (2004-2009), *J Am Vet Med Assoc* 242:507, 2013.

Mischke R, et al.: The effect of the albumin concentration on the relation between the concentration of ionized calcium and total calcium in the blood of dogs, *Dtsch Tierarztl Wochenschr* 103:199, 1996.

Mol JA, et al.: Elucidation of the sequence of canine (pro)-calcitonin: a molecular biological and protein chemical approach, *Regul Pept* 35:189, 1991.

Moore FM, et al.: Hypercalcemia associated with rodenticide poisoning in three cats, *J Am Vet Med Assoc* 193:1099, 1988.

Morrow C: Cholecalciferol poisoning, *Vet Med* 2001, p 905.

Mundy GR: Hypercalcemia of malignancy revisited, *J Clin Invest* 82:1, 1988.

Mundy GR, et al.: The hypercalcemia of cancer: clinical implications and pathogenic mechanisms,, *N Engl J Med* 310:1718, 1984.

Murphy MJ: Rodenticides, *Vet Clinics N Amer: Small Anim Pract* 32:469, 2002.

Nicholson SS: Toxicology. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine: diseases of the cat and dog*, ed 5, Philadelphia, 2000, WB Saunders, p 357.

O'Dougherty MJ, et al.: Parathyroid imaging with technetium-^{99m}-sestamibi: preoperative localization and tissue uptake studies, *J Nucl Med* 33:313, 1992.

Orloff JJ, Stewart AF: The carboxy-terminus of parathyroid hormone: inert or invaluable, *Endocrinology* 136:4729, 1995.

Parker M: *Personal communication*, 2001.
Peterson ME: *Hypercalcemia in dogs and cats: differential diagnosis and treatment*, Proceedings: 84th Annual Western Veterinary Conference, Las Vegas, NV, 2012.
Peterson ME, Feinman JM: Hypercalcemia associated with hypoadrenocorticism in sixteen dogs, *J Am Vet Med Assoc* 181:804, 1982.
Peterson ME, et al.: Primary hypoadrenocorticism in ten cats, *J Vet Intern Med* 3:55, 1989.
Peterson ME, et al.: Pretreatment clinical and laboratory findings in dogs with hypoadrenocorticism: 225 cases (1979-1993), *J Am Vet Med Assoc* 208:85, 1996.
Philbrick WM, et al.: Defining the roles of parathyroid hormone–related protein in normal physiology, *Physiol Rev* 76:127, 1996.
Picard D, et al.: Localization of abnormal parathyroid glands using ^{201}thallium/^{123}iodine subtraction scintigraphy in patients with primary hyperparathyroidism, *Clin Nucl Med* 12:61, 1987.
Pineda C, et al.: Feline parathyroid hormone: validation of hormonal assays and dynamics of secretion, *Domest Anim Endocrinol* 42:256, 2012.
Pollard RE, et al.: Percutaneous ultrasonographically guided radio frequency heat ablation for treatment of primary hyperparathyroidism in dogs, *J Am Vet Med Assoc* 218:1106, 2001.
Pollard RE, et al.: Prevalence of subclinical thyroid nodules in dogs with hypercalcemia, *J Vet Radiol Ultrasonography, (2008–2013)* in press
Potts JT Jr: Management of asymptomatic hyperparathyroidism, *J Clin Endocrinol Metab* 70:1489, 1990.
Pressler BM, et al.: Hypercalcemia and high parathyroid hormone–related protein concentration associated with malignant melanoma in a dog, *J Am Vet Med Assoc* 221:263, 2002.
Quigley PJ, Leedale AH: Tumors involving bone in domestic cats: a review of fifty-eight cases, *Vet Pathol* 20:670, 1983.
Ramsey I, et al.: Hyperparathyroidism in dogs with hyperadrenocorticism, *J Small Animal Prac* 46:531, 2005.
Rasmussen H: The cycling of calcium as an intracellular messenger, *Sci Am* 261:66, 1989.
Rasor L, et al.: Retrospective evaluation of three treatment methods for primary hyperparathyroidism in dogs, *J Am Anim Hosp Assoc* 43:70, 2007.
Refsal KR: *Personal communication*, 2014.
Refsal KR, Nachreiner RF: Hormone assays and collection of samples. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology*, ed 4, British Small Animal Assoc, 2012, p 1.
Refsal KR, et al.: Laboratory assessment of hypercalcemia, *Proc Am Coll Vet Intern Med Forum* 16:646, 1998.
Reusch CE, et al.: Ultrasonography of the parathyroid glands as an aid in differentiation of acute and chronic renal failure in dogs, *J Am Vet Med Assoc* 217:1849, 2000.
Rohrer CR, et al.: Hypercalcemia in a dog: a challenging case, *J Am Anim Hosp Assoc* 36:20, 2000.
Rosol TJ, et al.: Acute hypocalcemia associated with infarction of parathyroid gland adenomas in two dogs, *J Am Vet Med Assoc* 192:212, 1988.
Rosol TJ, et al.: Parathyroid hormone (PTH)–related protein, PTH, and 1,25-dihydroxyvitamin D in dogs with cancer-associated hypercalcemia, *Endocrinology* 131:1157, 1992a.
Rosol TJ, et al.: Effects of mithramycin on calcium metabolism and bone in dogs, *Vet Pathol* 29:223, 1992b.
Rosol TJ, et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice*, ed 2, Philadelphia, 2000, WB Saunders, pp 108–162.
Ross JT, et al.: Adenocarcinoma of the apocrine glands of the anal sac in dogs: a review of 32 cases, *J Am Anim Hosp Assoc* 27:349, 1991.
Ross LA, Goldstein M: *Biochemical abnormalities associated with accidental hypothermia in a dog and in a cat*, Proceedings of the Annual American College of Veterinary Internal Medicine Meeting, St Louis, 1981, p 66.
Rumbeiha WK: Nephrotoxins. In Bonagura JD, editor: *Kirk's current veterinary therapy XIII*, Philadelphia, 2000, WB Saunders, pp 212–214.
Rumbeiha WK, et al.: Use of pamidronate to reverse vitamin D_3–induced toxicosis in dogs, *Am J Vet Res* 60:1092, 1999.
Sandler LM, et al.: Studies of the hypercalcemia of sarcoidosis: effect of steroids and exogenous vitamin D_3 on the circulating concentration of 1,25-dihydroxy vitamin D_3, *O J Med* 53:165, 1984.
Savary KC, et al.: Hypercalcemia in cats: a retrospective study of 71 cases (1991-1997), *J Vet Intern Med* 14:184, 2000.
Sawyer ES, et al.: Outcome of 19 dogs with parathyroid carcinoma after surgical excision, *Vet Comp Oncol* 10:57, 2011.
Schenck PA, Chew DJ: Idiopathic hypercalcemia in cats, *Waltham Focus* 15:20, 2005a.
Schenck PA, Chew DJ: Prediction of serum ionized calcium concentration by use of serum total calcium concentration in dogs, *Am J Vet Res* 66:1330, 2005b.
Schenck PA, Chew DJ: Calcium: total or ionized? *Vet Clin North Amer: Small Anim Pract* 38:497, 2008.
Schenck PA, Chew DJ: Investigation of hypercalcaemia and hypocalcaemia. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology*, ed 4, Gloucester, England, 2012, British Small Animal Veterinary Association, p 221.
Scott-Moncrieff CR: Hypoadrenocorticism. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine: diseases of the dog and cat*, ed 7, St Louis, 2010, Elsevier, p 1847.
Seymour JF, Gagel RF: Calcitriol: the major humoral mediator of hypercalcemia in Hodgkin's and non-Hodgkin's lymphomas, *Blood* 82:1383, 1993.
Shane E, Bilezikian JP: Parathyroid carcinoma: a review of 62 patients, *Endocrinol Rev* 3:218, 1982.
Shiel RE: Disorders of vasopressin production. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology*, ed 4, Gloucester, England, 2012, British Small Animal Veterinary Association, p 15.
Skelly BJ: Hyperparathyroidism. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology*, ed 4, Gloucester, England, 2012, British Small Animal Veterinary Association, p 43.
Skelly BJ, Franklin RJM: Mutations in genes causing human familial isolated hyperparathyroidism do not account for hyperparathyroidism in Keeshond dogs, *Vet J* 174:652, 2006.
Silverberg SJ, et al.: A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery, *N Engl J Med* 341:1249, 1999.
Stewart AF: Translational implications of the parathyroid calcium receptor, *N Engl J Med* 351:324, 2004.
Stewart AF: Hypercalcemia associated with cancer, *N Engl J Med* 352:373, 2005.
Strewler GL: The physiology of parathyroid hormone–related protein, *N Engl J Med* 342:177, 2000.
Sueda MT, Stefanacci JD: Ultrasound evaluation of the parathyroid glands in two hypercalcemic cats, *Vet Radiol Ultrasound* 41:448, 2000.
Swainson SW, et al.: Radiographic diagnosis: mediastinal parathyroid cyst in a cat, *Vet Radiol Ultrasound* 41:41, 2000.
Taillefer R, et al.: Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study), *J Nucl Med* 33:1801, 1992.
Tebb AJ, et al.: Canine HAC effects of trilostane on parathyroid hormone, calcium and phosphate concentrations, *J Small Animal Prac* 46:537, 2005.
Thompson KG, et al.: Primary hyperparathyroidism in German Shepherd dogs: a disorder of probable genetic origin, *Vet Pathol* 21:370, 1984.
Toribio RE, et al.: Cloning and sequence analysis of the complementary DNA for feline preproparathyroid hormone, *Am J Vet Res* 63:194, 2002.
Torrance AG, Nachreiner R: Human parathormone assay for use in dogs: validation, sample handling studies, and parathyroid function testing, *Am J Vet Res* 50:1123, 1989a.

Torrance AG, Nachreiner R: Intact parathyroid hormone assay and total calcium concentration in the diagnosis of disorders of calcium metabolism in dogs, *J Vet Intern Med* 3:86, 1989b.

Troy GC, et al.: Heterobilharzia americana infection and hypercalcemia in a dog: a case report, *J Am Anim Hosp Assoc* 23:35, 1987.

Uehlinger P, et al.: Differential diagnosis of hypercalcemia: a retrospective study of 46 dogs, *Schweiz Arch Tierheilkd* 140:188, 1998.

Utiger RD: Treatment of primary hyperparathyroidism, *N Engl J Med* 341:1301, 1999.

Verdonk CA, Edis AJ: Parathyroid "double adenomas": fact or fiction? *Surgery* 90:523, 1981.

Weir EC, et al.: Primary hyperparathyroidism in a dog: biochemical, bone histomorphometric, and pathologic findings, *J Am Vet Med Assoc* 189:1471, 1986.

Weir EC, et al.: Humoral hypercalcemia of malignancy in canine lymphosarcoma, *Endocrinology* 122:602, 1988a.

Weir EC, et al.: Adenyl cyclase stimulating, bone resorbing and b-TGF–like activities in canine apocrine cell adenocarcinoma of the anal sac, *Calcif Tissue Int* 43:359, 1988b.

Weir EC, et al.: Isolation of 16,000-dalton parathyroid hormone–like proteins from two animal tumors causing humoral hypercalcemia of malignancy, *Endocrinology* 123:2744, 1988c.

Weller RE, et al.: Chemotherapeutic responses in dogs with lymphosarcoma and hypercalcemia, *J Am Vet Med Assoc* 181:891, 1982.

Williams LE, et al.: Carcinoma of the apocrine glands of the anal sac in dogs: 113 cases (1985-1995), *J Am Vet Med Assoc* 223:825, 2003.

Wisner ER, Nyland TG: Clinical vignette, *J Vet Intern Med* 8:244, 1994.

Wisner ER, et al.: Normal ultrasonographic anatomy of the canine neck, *Vet Radiol* 32:185, 1991.

Wisner ER, et al.: Ultrasonographic evaluation of the parathyroid glands in hypercalcemic dogs, *Vet Radiol Ultrasound* 34:108, 1993.

Wisner ER, et al.: High-resolution parathyroid sonography, *Vet Radiol Ultrasound* 38:462, 1997.

Wright KN, et al.: Diagnostic and therapeutic considerations in a hypercalcemic dog with multiple endocrine neoplasia, *J Am Anim Hosp Assoc* 31:156, 1995.

Wysolmerski JJ, Insogna KL: The parathyroid glands, hypercalcemia and hypocalcemia. In Goldman L, Schafer AI, editors: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Elsevier Saunders, p 1591.