Hypoparathyroidism: Pathophysiology and Diagnosis*

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ABSTRACT:

Calcium plays a vital role in nearly all cells in the body. As a result, calcium homeostasis is precisely regulated through the actions of parathyroid hormone (PTH), vitamin D, and calcitonin. Hypoparathyroidism is an endocrine disorder characterized by a deficiency in PTH, resulting in hypocalcemia and hyperphosphatemia. Causes include immune-mediated, surgical gland destruction and hypomagnesemia, among other conditions better defined in humans. Hypocalcemia results primarily in neurologic and neuromuscular abnormalities, including generalized seizures. A diagnosis can be made based on the presence of hypocalcemia, hyperphosphatemia, and inappropriately low PTH levels as well as exclusion of other causes of hypocalcemia, especially renal disease.

Primary hypoparathyroidism is an uncommon endocrine disorder that develops as the result of an absolute or relative deficiency in parathyroid hormone (PTH).1,2 PTH deficiency causes various physiologic abnormalities, including hypocalcemia, hyperphosphatemia, decreased levels of vitamin D (i.e., calcitriol), and clinical signs primarily involving neuromuscular disturbances.2–4

CALCIUM HOMEOSTASIS: THE ROLES OF PTH, VITAMIN D, AND CALCITONIN

Calcium circulates in three distinct fractions: ionized, protein bound, and complexed. About 50% of total calcium is ionized and serves as the biologically active portion.5,6 The protein-bound fraction is primarily bound to albumin and accounts for 40% of the total. Binding is affected by the pH of extracellular fluid. Acidemia decreases protein binding and thereby increases the amount of ionized calcium in serum. Alkalemia causes increased protein binding, resulting in less ionized calcium.5,6 About 10% of circulating calcium is complexed to anions such as lactate, bicarbonate,
The partitioning of calcium into these three fractions is influenced by the amount of calcium in the extracellular fluid, the quantity of protein and complexes available for binding, and the patient’s acid–base status.

Calcium concentration is regulated through the actions of three hormones: PTH, vitamin D, and calcitonin. PTH is synthesized and secreted by the chief cells of the parathyroid glands and is the principal hormone responsible for calcium homeostasis. It is secreted at a rate that is inversely proportional to the serum ionized calcium concentration. A high serum calcium concentration inhibits secretion of PTH by the parathyroid glands (i.e., negative feedback), whereas a low or falling calcium concentration prompts the release of PTH. This is achieved by means of a calcium-sensing receptor on the surface of the parathyroid cells. PTH performs its functions by three main actions: It increases osteoclastic bone resorption of calcium and phosphorus, it increases calcium and decreases phosphorus resorption from renal tubules, and it stimulates conversion of vitamin D to its active metabolite, which increases calcium absorption by the intestines. The net effect of PTH is to increase the serum calcium concentration and decrease the serum phosphorus concentration.

Vitamin D increases both serum calcium and phosphorus. Its primary action is to increase the absorption of calcium, phosphorus, and magnesium from the intestines. It also has a permissive effect on the action of PTH on bone and thereby stimulates bone resorption and calcium mobilization. It also acts at the level of the kidneys to increase renal tubular resorption of calcium and phosphorus, although this is likely a minor effect. In addition, vitamin D is absorbed in the intestine as an inactive prohormone and requires a two-step hydroxylation in the body to become active. The inactive hormone is first transported to the liver, where it is hydroxylated at the 25 position to 25-hydroxyvitamin D—a partially active metabolite. Then it is transported to the kidneys, where it is again hydroxylated at the 1 position via renal 1α-hydroxylase to produce the active metabolite 1,25-dihydroxyvitamin D. Both PTH and phosphorus play key roles in regulating the activity of renal 1α-hydroxylase. Elevated PTH and low phosphorus concentrations increase this enzyme’s activity, thus enhancing formation of active 1,25-dihydroxyvitamin D. Conversely, low PTH and high phosphorus levels decrease renal 1α-hydroxylase activity and therefore production of the active vitamin D metabolite.

Consequently, in patients with hypoparathyroidism (in which PTH is low and phosphorus is high), deficiency of active vitamin D also develops, contributing to the hypocalcemia already present (Figure 1). Calcitonin is a polypeptide secreted by the C cells of the thyroid gland. Its rate of secretion increases with increased calcium concentration. Calcitonin blocks bone resorption by inhibiting the release of calcium and phosphorus from bone. It also decreases resorption of calcium and phosphorus in the kidneys. The net effect of calcitonin is to decrease both calcium and phosphorus concentrations in the serum.

The precision of integrated control of PTH, vitamin D, and calcitonin is such that the ionized serum calcium concentration likely fluctuates by no more than 0.1 mg/dl from its “set” normal value in healthy animals. Bone resorption and distal renal tubular calcium resorption are the acute mechanisms that effect minute-to-minute serum calcium homeostasis, with the effect of the renal tubule being quantitatively more important. Conversely, changes in the rate of intestinal calcium absorption via the calcium–PTH–vitamin D axis require approximately 24 to 48 hours to become maximal.

**PATHOPHYSIOLOGY**

Various disease mechanisms have been described as causes of hypoparathyroidism. Iatrogenic, transient, or permanent hypoparathyroidism is a well-recognized but infrequent sequela to surgical treatment of the thyroid.
or parathyroid glands (such as in feline hyperthyroidism). This is the most common cause of hypoparathyroidism in cats and results not only from excised parathyroid tissue but also when tissue has been traumatized or its blood supply interrupted. In addition, in cases of prolonged hypercalcemia from hyperparathyroidism or other parathyroid-independent causes, treating hypercalcemia can result in transient hypocalcemia due to atrophy of normal parathyroid tissue. Given the associated patient history, such causes of hypoparathyroidism are easy to recognize and the pathophysiology is straightforward. Other causes include immune-mediated destruction, congenital hypoplasia or aplasia, end-organ resistance, and severe hypomagnesemia. The various disease mechanisms have been well defined in human medicine. However, in veterinary patients, when there is no evidence of trauma or surgical destruction, an underlying cause is rarely determined, and most cases in dogs are classified as idiopathic.

Detection of antibodies against parathyroid tissue in humans has led to the theory that hypoparathyroidism is an autoimmune process. Antibodies have been found against the calcium-sensing receptor of the parathyroid gland in humans with acquired hypoparathyroidism. The presence of concurrent immune-mediated diseases in humans, such as autoimmune polyendocrinopathy, provides further circumstantial evidence of an autoimmune cause. However, antiparathyroid antibodies in humans have been found in only a relatively low percentage of patients with hypoparathyroidism, suggesting that other mechanisms are likely involved.

In dogs, lymphocytic, plasmacytic infiltration of the parathyroid glands is a relatively common histologic finding. In dogs and cats in which surgical exploration is performed for histopathologic confirmation, the glands are often difficult to locate grossly and show microscopic evidence of atrophy. Histologic evaluation reveals fibrous connective tissue with diffuse lymphocytic, plasmacytic infiltration in approximately 60% to 80% of cases. This has been used as support for an immune-mediated cause of hypoparathyroidism, although circulating autoantibodies directed toward parathyroid tissue have not been demonstrated in dogs.

The cloning of the calcium-sensing receptor in 1993 and the subsequent discovery of mutations that make the receptor more or less sensitive to calcium have allowed a better understanding of several parathyroid hereditary disorders in humans. The calcium-sensing receptor is a low affinity, G protein-coupled receptor found in high concentrations on the surface of parathyroid cells, calcitonin-secreting C cells of the thyroid, and various sites along the nephron, brain, bone, and other tissues. Activation of the receptor stimulates phospholipase C, resulting in increased inositol 1,3,5-triphosphate, which mobilizes cytosolic calcium. Activation of the receptor also inhibits adenylate cyclase, thereby suppressing intracellular cAMP. The end result in the parathyroid gland is suppression of PTH secretion. The receptor is activated by minute changes in ionized calcium, which explains both the steep inverse relation-

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ship between PTH levels and small changes in calcium and the sharp rise in urinary calcium that occurs when serum calcium rises slightly above the “threshold” value. Mutations affecting the calcium-sensing receptor, making it more or less sensitive to calcium, are responsible for various clinical diseases in humans. More genetic research in veterinary patients is needed before such disease states can be appreciated.

Magnesium also plays an important role in calcium homeostasis. In humans, it is well-recognized that magnesium depletion can produce hypocalcemia and hyperphosphatemia by inducing a state of secondary hypoparathyroidism. This phenomenon has also been described in dogs, particularly those with protein-losing enteropathy (PLE). Several case reports have described severe hypomagnesemia, hypocalcemia, and inappropriately low PTH concentration in dogs with PLE.
Hypomagnesemia may be the result of renal loss, GI tract loss, decreased intake, or alterations in the distribution of magnesium. A low magnesium concentration allows increased calcium binding at the inhibitory site, exacerbating the inhibitory effect of calcium on adenylate cyclase. This causes decreased cAMP generation and blunted release of PTH. In addition to decreased production of PTH, decreased response to PTH in bone and the kidneys has been demonstrated in hypomagnesemic humans and suspected in dogs. Magnesium deficiency can also decrease serum 1,25-dihydroxyvitamin D concentration by lessening PTH release and impairing renal vitamin D activation. The effect of magnesium depletion on PTH and calcium is further supported by the fact that supplementation of magnesium rapidly normalizes the PTH concentration and ionized calcium concentration and alleviates clinical signs.

Regardless of the underlying cause, the absence of PTH in patients with hypoparathyroidism results in hypocalcemia secondary to increased urinary loss (i.e., hypercalcuria), decreased bone mobilization, and decreased intestinal absorption of calcium. Hyperphosphatemia occurs from decreased urinary loss, which overcomes decreased bone mobilization and decreased intestinal absorption of phosphorus. PTH is a potent stimulator and phosphorus a potent inhibitor of the 25(OH)-cholecalciferol–1α-hydroxylase system in the renal tubules; consequently, the absence of PTH and the presence of hyperphosphatemia work together to decrease renal synthesis of calcitriol. Decreased levels of calcitriol contribute to hypocalcemia through decreased intestinal calcium absorption.

**SIGNALMENT**

Primary hypoparathyroidism is most commonly seen in middle-aged dogs (mean age: 4.8 years); however, a wide age range of 6 weeks to 13 years of age has been reported. Females are predisposed (approximately 65% of cases). Breeds most frequently identified are the toy poodle, miniature schnauzer, Labrador retriever, German shepherd, dachshund, and terriers. However, this increased prevalence may merely reflect the popularity of these breeds. Fewer cases of primary hypoparathyroidism have been reported in cats compared with dogs; therefore, it is difficult to identify age, breed, and sex predisposition. Most reported cats have been young to middle aged (i.e., 6 months to 7 years of age).

**CLINICAL SIGNS**

The predominant clinical signs of hypoparathyroidism are directly attributable to the decreased concentration of ionized calcium in the blood. Calcium ions are integral to the function of nearly all cells in the body. Calcium is essential for muscle contraction and serves as a nerve cell membrane stabilizer by decreasing nerve cell permeability to sodium. When the extracellular concentration of calcium ions declines to subnormal levels, the nervous system becomes progressively more excitable because of increased neuronal membrane permeability. This increase in excitability occurs in both the peripheral system and central nervous system (CNS), although most clinical signs are manifested peripherally. Nerve fibers may become so excitable that they begin to discharge spontaneously, initiating impulses to peripheral skeletal muscles, where they elicit tetanic contraction. As a result, hypocalcemia causes tetany. The duration and magnitude of the calcium depression as well as the rate of calcium decline interact to determine the severity of clinical signs.

Clinical signs of hypocalcemia tend to occur intermittently. By the time of diagnosis, most patients have illustrated occasional signs anywhere from 1 day to 12...
Clinical tetany typically occurs when the total calcium concentration declines to 6 mg/dl or less. However, episodes of clinical tetany are interspersed with “normal” periods despite persistent hypocalcemia. It is not entirely understood why this occurs. It indicates adaptation to hypocalcemia and suggests that relatively minor changes in calcium concentrations in a state of hypocalcemia result in obvious clinical problems. For example, a serum calcium decline of 0.3 mg/dl with a serum concentration of 10 mg/dl has no effect, but the same decrease when the serum calcium concentration is 6 mg/dl could result in clinical tetany. A state of latent tetany likely exists in these hypocalcemic patients that appear “normal” between episodes of clinical tetany. This condition is described as one in which patients can progress from appearing clinically normal to becoming “tetanic” with minimal stimulation. The fact that owners frequently describe signs as occurring after exercise, excitement, or stress supports the notion of latent tetany. Such activity may induce respiratory alkalosis and therefore reduction in the ionized fraction of calcium.

A study examining plasma and cerebrospinal fluid (CSF) total and ionic calcium concentration in postthyroparathyroidecтомized dogs may help explain latent tetany and the episodic nature of this disease. It was shown that the calcium concentration within the CSF does not decrease as rapidly as the serum concentration. Thus the concentration of calcium ions in the CSF is relatively constant despite large fluctuations in plasma concentrations, suggesting a homeostatic protective function. However, when changes do occur, relatively small changes in CSF calcium concentration may also result in dramatic clinical signs.

The signs of hypocalcemia are similar regardless of the cause. Signs vary from hardly discernible lameness to severe, generalized seizures and can be abrupt or gradual in onset. As already discussed, clinical signs are typically intermittent and predominantly involve neurologic or neuromuscular disturbances. Common clinical signs include focal or generalized muscle tremors and seizures. Generalized convulsions, resembling those of an idiopathic seizure disorder, are the predominant CNS manifestation of hypoparathyroidism, occurring in 80% of dogs in one study. Unlike classic grand mal convulsions, however, hypocalcemic seizures are not reliably associated with loss of consciousness or incontinence. It is not uncommon for a dog to present with a prior presumptive diagnosis of a seizure disorder and to have been given anticonvulsant medication. Common muscular signs include cramping, tonic spasm or fasciculations of leg muscles, and a stiff, stilted, or rigid gait. Other clinical signs include nervousness, ataxia, disorientation, weakness and lethargy, facial rubbing, and excessive panting. Intense facial rubbing is thought to result from pain associated with masseter and temporal muscle cramping or from a “tingling” sensation around the mouth. Owners occasionally notice behavioral changes, including aggression, restlessness, irritability, decreased playfulness, slow movement, or painfulness. Aggressive behavior is assumed to be caused by pain associated with muscle cramping. Polydipsia and polyuria, vomiting, diarrhea, and inappetence are less commonly noted. Severe hypocalcemia with total calcium concentrations less than 4 mg/dl can cause death secondary to hypotension, decreased myocardial contractility, and paralysis of respiratory muscles.

The clinical features of cats with chronic hypocalcemia secondary to primary hypoparathyroidism are similar to those in dogs. In cats, however, seizure activity has not been noted to be induced by excitement. Anorexia and lethargy are also commonly seen and appear more frequently in cats than in dogs. Panting and raised nictitating membranes are also commonly noted.

**PHYSICAL EXAMINATION**

The most common physical examination abnormalities are attributed to tetany and include muscle rigidity and fasciculations, stiff gait, and a tense splinted abdomen. Fever, panting, nervousness, depression, weakness, and dehydration are also noted. Cardiac abnormalities include paroxysmal tachyarrhythmias and muffled heart sounds with weak pulses. Cataracts have been detected in both dogs and cats with primary hypoparathyroidism. It is also possible to find no physical examination abnormalities in patients with hypoparathyroidism; therefore, a normal physical examination does not rule out the disease.

**ELECTROCARDIOGRAM**

Hypocalcemia prolongs the duration of the action potential in cardiac cells. On an electrocardiogram, this is most consistently associated with deep, wide T waves, prolonged Q-T intervals, and bradycardia. These abnormalities rapidly return to normal after hypocalcemia has been corrected.
DIAGNOSIS

To diagnose primary hypoparathyroidism, clinicians should obtain a complete database, including history, physical examination, complete blood count, chemistry profile with ionized calcium and magnesium, and a PTH level. Through this information, the diagnosis can be made based on hypocalcemia and hyperphosphatemia, inappropriately low PTH, and exclusion of other causes of hypocalcemia.²,²⁵ (Table 1).

The ionized fraction of serum calcium is the biologically active form that regulates PTH production.⁸ Therefore, it is the preferred form to measure. Ionized calcium is measured in serum or heparinized plasma by an instrument using a calcium-specific electrode with a simultaneous measurement of pH.⁸ pH has an effect on the binding of calcium to protein in an inverse relationship.⁸ Serum samples collected in EDTA tubes are unsuitable because EDTA binds available ionized calcium.⁸

In general, nonhypoparathyroid-induced hypocalcemic conditions are associated with secondary hyperparathyroidism and a normal or high serum PTH level. In addition, as long as the glomerular filtration rate is not severely decreased, the serum phosphorus concentration will be normal or low in these disorders.¹² Both hypocalcemia and hyperphosphatemia occur only in hypoparathyroidism and renal insufficiency, and these conditions can usually be easily differentiated by routine evaluation of renal function via blood urea nitrogen, creatinine level, and urine specific gravity.¹² The exceptions to these disease trends are disorders causing severe hypomagnesemia; therefore, a magnesium concentration should be checked with a chemistry panel.¹³

A presumptive diagnosis of hypoparathyroidism can be made based on hypocalcemia, hyperphosphatemia, normal renal function, and the absence of an obvious alternative diagnosis.⁴,¹²,¹³ However, because primary hypoparathyroidism is a permanent condition requiring lifelong treatment, confirmation of the diagnosis with PTH measurement is highly recommended.⁴,¹² The PTH concentration may be in the low-normal range. However, this finding would not be normal in a hypocalcemic animal that has healthy parathyroid glands because hypocalcemia provides a strong stimulus to the normal parathyroid gland to secrete PTH at a high level.³,⁴,⁶ Therefore, the definitive diagnosis is made based on an inappropriately low rather than absolute PTH level.

The serum PTH concentration must be interpreted in conjunction with the serum calcium concentration while the patient is still hypocalcemic; therefore, blood samples for PTH determination should be obtained before initiating therapy.¹³ Serum or EDTA plasma may be used to measure the PTH concentration.⁸ Assays that detect the intact hormone are important.¹¹,¹³ The molecule is readily broken down into inactive fragments that are excreted by the kidneys.⁶ Therefore, with renal disease, elevations in inactive fragments in the bloodstream may overrepresent the amount of biologically active PTH if a different assay is used.⁶

CONCLUSION

Calcium plays a vital role in cell function, especially in the neuromuscular system. Essential to its role in the body is the precision of calcium homeostasis through PTH, vitamin D, and calcitonin. Primary hypoparathyroidism is a rare endocrine disease in which this homeostasis is altered, causing significant
Table 1. Differential Diagnosis of Hypocalcemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoalbuminemia</td>
<td>There is a decreased protein-bound fraction with normal ionized calcium. Correcting formula for dogs: Corrected total Ca(^{++}) = Serum Ca(^{++}) – Serum albumin + 3.5</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Acute renal failure resulting in hyperphosphatemia causes secondary hypocalcemia. Chronic renal failure can cause hypocalcemia or hypercalcemia.</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Mild hypocalcemia occurs. Coexisting acidosis increases ionized calcium. The mechanism is unknown. The theory is that it is caused by saponification of peripancreatic fat.</td>
</tr>
<tr>
<td>Puerperal tetany (eclampsia)</td>
<td>Lactating bitches and queens are affected. Small dogs are most often affected. The condition is acute and severe.</td>
</tr>
<tr>
<td>Ethylene glycol toxicosis</td>
<td>Ethylene glycol metabolites chelate calcium ions.</td>
</tr>
<tr>
<td>Phosphate enemas</td>
<td>Acute elevation in phosphorus causes reciprocal hypocalcemia.</td>
</tr>
<tr>
<td>Use of EDTA anticoagulant</td>
<td>EDTA chelates calcium.</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>There is decreased synthesis and secretion of PTH. There is increased PTH resistance. It occurs with PLE.</td>
</tr>
<tr>
<td>Nutritional secondary hyperparathyroidism</td>
<td>Transient hypocalcemia occurs. It induces PTH secretion. It occurs in animals fed diets with low calcium:phosphorus ratios.</td>
</tr>
<tr>
<td>Laboratory error</td>
<td>Always recheck the calcium concentration if it is unexpectedly high or low.</td>
</tr>
<tr>
<td>Malabsorption syndrome</td>
<td>It is uncommon in dogs. It occurs secondary to hypoalbuminemia with or without decreased absorption of dietary calcium, vitamin D, and magnesium.</td>
</tr>
<tr>
<td>Transfusion with citrated blood</td>
<td>Citrate chelates calcium.</td>
</tr>
<tr>
<td>Bone tumors</td>
<td>They most often cause hypercalcemia; however, hypocalcemia occurs in humans.</td>
</tr>
<tr>
<td>Soft tissue trauma</td>
<td>—</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>—</td>
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</tbody>
</table>
biochemical and clinical abnormalities. Clinicians should be readily able to identify primary hypoparathyroidism through clinical signs and laboratory abnormalities.

REFERENCES

ARTICLE #2 CE TEST
This article qualifies for 2 hours of continuing education credit from the Auburn University College of Veterinary Medicine. Subscribers may purchase individual CE tests or sign up for our annual CE program. Those who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. To participate, fill out the test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.

1. **Calcium circulates as ___% ionized, ___% protein bound, and ___% complexed.**
   a. 50, 40, 10
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   b. 60, 30, 10
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   c. 40, 50, 10
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   d. 10, 30, 60
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
2. **PTH**
   a. is secreted at a rate that is directly proportional to the serum ionized calcium concentration.
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   b. decreases osteoclastic bone resorption of calcium and phosphorus.
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   c. increases calcium and phosphorus resorption from the renal tubules.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   d. stimulates conversion of vitamin D to its active metabolite.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
3. **Calcitonin**
   a. is secreted by the C cells of the parathyroid gland.
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   b. is secreted when the calcium concentration decreases.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   c. inhibits the release of calcium and phosphorus from bone.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   d. increases resorption of calcium and phosphorus in the kidneys.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
4. **Which statement regarding vitamin D is incorrect?**
   a. It increases intestinal absorption of calcium and phosphorus.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   b. It increases renal resorption of calcium and phosphorus.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   c. Its activation is decreased by elevated PTH and low phosphorus levels.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   d. It requires two-step hydroxylation to become active.
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
5. **Clinical tetany typically occurs when the serum calcium concentration declines to ___ mg/dl.**
   a. 9
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   b. 8
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   c. 7
test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.
   d. 6
6. Which statement regarding ionized calcium is incorrect?
   a. It is the biologically active form of calcium.
   b. It regulates PTH production.
   c. It is the preferred form of calcium to measure.
   d. Blood should be collected in EDTA tubes to measure ionized calcium.

7. Which condition is most likely to result in tetany secondary to hypocalcemia?
   a. acute pancreatitis c. eclampsia
   b. hypoalbuminemia d. malabsorptive disease

8. Which statement regarding calcium and clinical signs in patients with hypoparathyroidism is true?
   a. Signs often occur after exercise, excitement, or stress.
   b. Calcium stabilizes nerve cell membranes by increasing cell permeability to sodium.
   c. Most clinical signs are manifested in the CNS.
   d. Calcium concentration within the CSF rapidly equilibrates with the plasma concentration.

9. Which clinical sign is commonly seen in patients with hypoparathyroidism?
   a. polydipsia and polyuria c. inappetence
   b. focal tremors d. vomiting

10. Which statement regarding hypoparathyroidism is true?
    a. The PTH level must be less than 0.5 pmol/L for a diagnosis of hypoparathyroidism.
    b. The main differentials for hypocalcemia and hyperphosphatemia are hypoparathyroidism and pancreatitis.
    c. The physical examination may be completely normal in a patient with hypoparathyroidism.
    d. Hypoparathyroidism has been diagnosed in cats only secondary to surgical trauma.