Update on Feline Ionized Hypercalcemia

Joao Felipe de Brito Galvão, MV, MS[a], Valerie Parker, DVM[b], Patricia A. Schenck, DVM, MS, PhD[c], Dennis J. Chew, DVM[b,*]

KEYWORDS

• Ionized calcium • Total calcium • Vitamin D • Parathyroid hormone • Calcitriol • Idiopathic hypercalcemia • Malignancy • Chronic kidney disease

KEY POINTS

- Serum ionized calcium should be measured when calcium disorders are suspected; there is substantial diagnostic discordance between ionized calcium and total calcium concentrations.
- If a point-of-care analyzer is used, a standardized technique should be used; separate reference ranges should be established for heparinized whole blood, anticoagulated plasma, whole blood without anticoagulants, and serum.
- Ionized calcium increases before serum total calcium in various disorders, and measurement of ionized calcium will allow earlier detection of hypercalcemia in idiopathic hypercalcemia; this is also likely to be true in other causes of hypercalcemia.
- Idiopathic hypercalcemia is the most common diagnosis associated with ionized hypercalcemia in cats, followed by chronic kidney disease, malignancy, and hyperparathyroidism.
- Orally administered alendronate is the treatment that most consistently lowers ionized calcium in cats with idiopathic hypercalcemia, but chronic treatment with bisphosphonates has recently been associated with bone toxicity.

INTRODUCTION

Ionized calcium (iCa) is the circulating fraction of total calcium (tCa) that exerts biologic functions, and its concentration is regulated within a tight range. Serum tCa includes iCa, protein-bound calcium, and complexed calcium. In most laboratories,

Disclosure Statement: Dr D.J. Chew is an Advisory Board Member for Nestle-Purina and provides continuing education lectures sponsored by Veterinary Centers of America (VCA Antech) and Abaxis, Inc. Dr J.F. de Brito Galvão is a VCA Antech employee and lecturer. Drs V. Parker and P.A. Schenck have nothing to disclose.

[a] VCA Arboretum View Animal Hospital, 2551 Warrenville Road, Downers Grove, IL 60515, USA; [b] Department of Veterinary Clinical Sciences, The Ohio State University, 601 Vernon L. Tharp Street, Columbus, OH 43210, USA; [c] Veterinary Consulting, 9897 South Airport Road, DeWitt, MI 48820, USA

* Corresponding author. 317 West 6th Avenue, Columbus, OH 43201.

E-mail address: dennischew@me.com

Vet Clin Small Anim 47 (2017) 273–292

http://dx.doi.org/10.1016/j.cvsm.2016.09.004 **vetsmall.theclinics.com**

hypercalcemia in cats is defined as tCa greater than 10.8 mg/dL, or iCa greater than 5.6 mg/dL (>1.4 mmol/L). Parathyroid hormone (PTH) and calcitriol (1,25 dihydroxyvitamin D) are the hormones largely responsible for maintenance of circulating iCa concentrations. In a normal physiologic response, as the concentration of iCa decreases, concentrations of PTH and calcitriol increase to help increase iCa back into the normal range. Conversely, as iCa concentration increases, concentrations of PTH and calcitriol decrease to help lower iCa. Calcitonin exerts a minor role in limiting postprandial increases in iCa. Fibroblast growth factor-23 (FGF-23) and Klotho have recently been recognized for the roles they may play in calcium metabolism in addition to their better known effects on phosphorus[1–4] and may be important the pathogenesis of some hypercalcemic disorders. In order for ionized hypercalcemia to develop and be maintained, there must be a disturbance in the normal balance of calcium accretion from bone, excessive intestinal absorption of calcium, reduced renal calcium excretion following decreased glomerular filtration rate, increased tubular reabsorption of calcium, or some combination of these factors.

LABORATORY ANALYSIS

Total Calcium

Concentration of tCa is usually measured by colorimetric methods on serum samples. No special handling is needed because exposure to air does not impact the tCa measurement (as it does for iCa measurement). Lipemia can interfere with measurement of tCa, falsely increasing tCa concentration.[5] If patient serum tCa concentration is increased, then it is important to determine if that sample was lipemic. If the sample was not lipemic, then iCa concentration should be determined.

The use of correction formulas to create a "new" value for tCa based on serum albumin or serum total protein concentrations should be abandoned despite its widespread use in veterinary medicine. Only about one-third of the variability in serum tCa can be accounted for by changes in circulating proteins. Diagnostic discordance between iCa and tCa was not improved in cats when "correction" formulas were applied to populations of sick cats.[6,7] A false feeling of security may be imparted to the clinician when tCa is "corrected," especially into the reference range, when, in fact, the corrected tCa is not an accurate representation of the actual iCa concentration. The authors do not support the use of correction formulas for tCa based on proteins. There is no substitute for the measurement of iCa when knowledge of true calcium status is necessary.

Ionized Calcium

Analyzers using ion-specific electrodes and anaerobically collected serum or plasma remain the gold standard for measurement of iCa concentration. Sample pH and ionized magnesium are often measured at the same time and may allow further analysis of the iCa result. iCa is rapidly and significantly impacted by exposure to air. Exposure to air results in the loss of CO_2 from serum or plasma, which increases pH (often greater than 8.0), promoting binding of calcium to proteins, thus substantially lowering the iCa concentration.[8] Anaerobically collected serum or plasma samples that arrive cool (refrigerator temperature) or frozen are most accurate for measurement of iCa when sent to a referral laboratory (as long as the referral laboratory handles the sample anaerobically). Anaerobic sample collection is time consuming, and thus, in many cases, samples that have been exposed to air are used for measurement. In these cases, the sample is acidified to lower the increased pH, and the iCa concentration is calculated based on an adjustment factor, reported as iCa concentration at a pH of 7.4. Most laboratory analyzers have a built-in correction factor to convert the result