Calcium, Phosphorus, and Vitamin D in Dogs and Cats

Beyond the Bones

Jonathan Stockman, DVM[a], Cecilia Villaverde, BVSc, PhD[b], Ronald Jan Corbee, DVM, PhD[c,*]

KEYWORDS

• Metabolism • Renal • Urinary tract • Gastrointestinal • Cancer

KEY POINTS

- Calcium, phosphorus, and vitamin D have a key role in skeletal development and health as well as other important metabolic functions.
- Insufficient or unbalanced dietary provision of these nutrients can have multiple negative health impacts.
- Excess vitamin D intake may cause hypercalcemia and negative health effects in dogs and cats, and the health-related effects of high calcium and phosphorus intake are being studied.
- The dietary provision of calcium, phosphorus, and vitamin D and their interactions must be considered in patients with renal-urinary diseases.
- The role of vitamin D in chronic conditions, such as enteropathies and neoplasia, is receiving considerable attention, but research is still inconclusive, and no clinical recommendations can be made at this time.

INTRODUCTION

Calcium, phosphorus, and vitamin D are important essential nutrients in the dog and the cat. As such, these nutrients are required as a part of a complete and balanced diet. Most commercial diets for dogs and cats provide sufficient amounts of calcium, phosphorus, and vitamin D,[1–3] but homemade diets may be deficient or unbalanced in

J. Stockman is a consultant for Petco Animal Supplies, Inc. C. Villaverde has received honoraria for consulting and speaking engagements from pet food manufacturers. R.J. Corbee declares no conflict of interest regarding this article.

[a] Department of Clinical Veterinary Sciences, LIU College of Veterinary Medicine, Long Island University, 720 Northern Boulevard, Brookville, NY 11548, USA; [b] Expert Pet Nutrition, Fermoy, Cork P61KX38, Ireland; [c] Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 108, Utrecht 3584 CM, The Netherlands
* Corresponding author.
E-mail address: R.J.Corbee@uu.nl

Vet Clin Small Anim 51 (2021) 623–634
https://doi.org/10.1016/j.cvsm.2021.01.003 **vetsmall.theclinics.com**

these nutrients, which may lead to negative outcomes.[4] Calcium and phosphorus are stored mostly in skeletal tissue, although they are present throughout the body. Bone metabolism and calcium and phosphorus absorption and retention are influenced by vitamin D as well as the relative dietary concentrations of these and other minerals. Although bone health is closely impacted by the nutrition and metabolism of these nutrients, these nutrients also impact animal physiology in many additional ways and have health impacts that transcend skeletal health alone. The following summary is aimed to explore and explain the various ways calcium, phosphorus, and vitamin D all play complex roles in canine and feline health.

The Nutritional Requirements for Calcium, Phosphorus, and Vitamin D in Dogs and Cats

Calcium and phosphorus are essential nutrients in dogs and cats, and therefore, they need to be provided in the diet in adequate amounts and in bioavailable forms. Calcium and phosphorus are the first and second most abundant minerals in the body, respectively, where they play both structural (such as of bone and teeth) and functional roles. For example, calcium is involved in blood coagulation and nerve impulse transmission, and phosphorus has a major role in energy metabolism as a component of adenosine triphosphate. The National Research Council gives a recommended allowance for calcium and phosphorus for different life stages (**Table 1**).[5] It also defines a safe upper limit for calcium of 4.5 g/1000 kcal of metabolizable energy for puppies, specifically those of large and giant breeds, where excess can result in skeletal abnormalities.[6,7] Adult dogs seem able to adequately handle high dietary calcium intakes.[8]

Vitamin D is also an essential nutrient in dogs and cats, because synthesis from sunlight exposure seems to be limited.[9,10] Therefore, it must be included in complete and balanced diets for dogs and cats in all life stages. Vitamin D plays an important role in calcium and phosphorus homeostasis and, consequently, its deficiency is associated with skeletal abnormalities. There is a lack of research on vitamin D requirements, especially in adult animals,[11] and the dietary recommendations[5,12,13] are educated estimates based on intakes that appear to support skeletal health. There is a growing body of research that supports the importance of vitamin D in other areas, as the vitamin D receptor is present in multiple tissues, which could result in changes in dietary recommendations in the future.[14–17]

Dietary Sources of Calcium, Phosphorus, and Vitamin D and Their Absorption and Bioavailability

Calcium and phosphorus in pet food can be provided by bony raw materials (from meat and fish). Phosphorus is also provided by meat and vegetable ingredients, such as cereals, although phosphorus in grains can be present as phytate, which has a reduced bioavailability compared with other forms in monogastric animals.[18]

Table 1
Recommended allowances (grams per 1000 kcal of metabolizable energy) for calcium and phosphorus for growth, maintenance, and reproduction in dogs and cats[5]

		Growth	Maintenance	Reproduction
Calcium	Dog	3	1	1.9
	Cat	2	0.72	2.7
Phosphorus	Dog	2.5	0.75	1.2
	Cat	1.8	0.64	1.9

Both minerals can also be provided as purified salts, together (as calcium phosphate salts) or separately.

Calcium and phosphorus availability is affected by several dietary factors, such as total amount and relative proportion to each other. Because of the close relationship of calcium and phosphorus, the Association of American Feed Control Officials (AAFCO) guidelines[12] recommend that commercial dog food not only meets the individual requirements but also provides a minimum calcium-to-phosphorus ratio of 1:1 and a maximum ratio of 2:1. Bioavailability is also affected by form and source. Data in cats have shown that highly soluble phosphate salts can result in increased absorption and postprandial serum levels compared with diets whereby it is provided by the bony raw materials,[19] which could affect phosphorus homeostasis negatively and contribute to renal damage.[20,21]

Dietary vitamin D is provided as cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2), from animal and vegetable ingredients, respectively; it can also be added as a purified additive. Cats discriminate between vitamin D forms and use cholecalciferol more efficiently than ergocalciferol.[22] There is a lack of controlled, well-powered studies in dogs,[5,11] but vitamins D2 and D3 appear to have a similar potency in this species.[23]

Skeletal Development and Skeletal Health

Because the bone is the major reservoir of calcium and phosphorus, its metabolism is impacted by their relative homeostasis. During growth, imbalances of these nutrients have the most detrimental consequences, resulting in factures and limb deformities, such as valgus or varus stance, and incongruence of the elbow joint.[24–28] Vitamin D plays a key role in bone remodeling and bone growth by activating osteoblasts and osteoclasts. It is important for clinicians to distinguish between causes of limb deformities by nutritional evaluation, orthopedic examination, evaluation of radiographs, and determining plasma levels of calcium, phosphorus, parathyroid hormone (PTH), calcitonin (CT), and vitamin D metabolites.[29]

A common pitfall is to rule out insufficient calcium intake when plasma calcium levels are within the normal range. Even in cases of dietary calcium insufficiency, plasma calcium levels are usually kept within normal limits, unless the regulatory compensatory mechanisms fall short. Plasma calcium levels are strongly regulated because low calcium has immediate detrimental effects, such as cardiac arrhythmias, that can be fatal. Typically, with a low dietary calcium intake, radiographs will show decreased mineralization of bone, enlarged medullar areas, and thinner cortices that easily break (eg, green stick fractures). PTH levels will be increased as well as active vitamin D levels. Sometimes, deficient intake in both calcium and vitamin D occurs, which is often referred to as “all-meat syndrome.” These cases may show signs of low vitamin D, such as enlarged growth plates and decreased mineralization of bone and cartilage. In adult animals, the bone will be gradually demineralized and replaced by connective tissue under the influence of fibroblast growth factor-23 (FGF-23).[30] Many times, these diets also lead to a high phosphorus intake, which exacerbates the pathologic condition by increasing PTH activity, resulting in more osteoclastic activity. In contrast, low phosphorus intake results in decreased levels of PTH.[31] In cases of adequate calcium and phosphorus but deficient vitamin D intake, enlarged growth plates can be seen radiographically as well as decreased mineralization of bone. PTH levels are expected to be high, and active vitamin D levels will be low. To prevent hypercalcemia, CT levels will be increased. In growing animals, this will result in decreased osteoclastic activity, as osteoclasts can no longer make contact to the matrix with their ruffled borders. Prolonged decrease of osteoclastic activity

may result in enostosis, which can be visible on radiographs as an opaque cloud within the medullar area, and by painful reaction on deep palpation of the long bones during orthopedic examination. Treatment of these dietary imbalances is largely dependent on normalizing dietary intake, combined with pain medication and exercise instructions.[32]

The Importance of These Nutrients for Urinary Health

Urolithiasis is among the most common urinary diseases in companion animals. Uroliths and urinary crystals may occur as a result of multiple causes, including hereditary disease, infections, toxicity, and nutritional deficiency or excess. There are multiple uroliths and urinary crystals of varying compositions in dogs and cats, including organic and inorganic compounds. Some of the most common compounds are mineral salts, which include calcium and phosphorus. In fact, it is estimated that at least 90% of the uroliths in dogs and cats are composed of either calcium oxalate monohydrate or dehydrate compounds or struvite (magnesium-ammonium-phosphate hexahydrate).[33] Although crystalluria can be benign (with the exception of urethral plugs in male cats), crystal aggregation and nucleation may lead to the formation of uroliths.

The risk for urolith formation depends on the urinary saturation with minerals or organic compounds that precipitate into crystals[34]; however, this process also depends on the involvement of inhibitors of urolithiasis, including urinary proteins (nephrocalcin, uropontin, Tamm-Horsfall mucoprotein), urinary pH, and the presence and saturation of ions in the solution.[35,36]

Calcium oxalate urolithiasis

Hypercalcemia (of any cause) is a risk factor for the formation of calcium oxalate uroliths in both dogs and cats, as it may result in hypercalciuria.[37,38] Dietary phosphorus restriction below the established requirements may increase the risk for hypercalcemia, as a high calcium-to-phosphorus ratio may result in increased calcium absorption. When phosphorus intake is low, a decrease in FGF-23, which is a regulator of calcium and phosphorus excretion, results in increased activity of 1-alpha hydroxylase,[39] resulting in more active vitamin D, which increases intestinal calcium absorption and exacerbates hypercalciuria.

Normally, dogs and cats do not excrete much calcium in the urine even when the calcium intake is increased, as calcium homeostasis is regulated primarily via fecal excretion, presumably because dietary calcium absorption is reduced.[8,21] Increased dietary calcium was also found not to significantly change the urinary relative supersaturation for calcium oxalate.[8] However, in cases of hypercalcemia, the fractional excretion of calcium is increased, resulting in hypercalciuria.[33,40] Although hypercalciuria may not be a finding in all cases of canine and feline calcium oxalate urolithiasis,[41] it is a prominent risk factor.

Dogs with a medical history of calcium oxalate urolithiasis from highly predisposed breeds (miniature schnauzers, bichon frise, and shih tzu) were found to have greater urinary calcium excretion than control dogs of the same breed but not increased urinary oxalate excretion or overt hypercalcemia (although the ionized calcium was higher in case dogs).[42] The same researchers also found no increase in bone turnover markers in these dogs, possibly suggesting that the observed hypercalciuria is the result of increased intestinal calcium absorption or renal calcium leakage.[43]

Diets that are formulated to promote urine acidity may contain acidifiers, such as ammonium chloride, that have been shown to increase urinary calcium excretion.[44] Acidic urine may negatively impact urolith inhibitors, such as citrate or urinary mucoproteins, that prevent the formation of calcium oxalate crystals. It is thought that

metabolic acidosis promotes osteoclast activity and inhibits osteoblasts for a net bone resorption and release of a strong calcium-containing alkaline buffer, hydroxyapatite.[45] The increase in bone turnover and the release of calcium increase the ionized calcium concentrations and can result in hypercalciuria and possibly increased risk for calcium oxalate urolithiasis.

Feeding a high-fiber diet has been suggested as a nutritional strategy for the management of hypercalcemia in both dogs and cats; however, conflicting evidence indicates that further research is needed as far as the clinical benefit of this approach, particularly because evidence suggests that soluble fiber may increase intestinal calcium absorption.[32,40,46–48] Because some fiber sources are high in oxalates, this should also be taken into account when formulating a diet plan.

Struvite urolithiasis

Urinary phosphorus excretion is influenced by its intake (amount and bioavailability) as well as the intake of sodium, calcium, and magnesium.[21,49] Increased dietary phosphorus is not sufficient to increase the relative supersaturation for struvite in cats or dogs to values that are considered supportive of crystallization.[8,21] As a result of hyperphosphatemia, increased PTH promotes urinary phosphorous excretion in the kidneys by reducing expression of sodium phosphate cotransporter on the apical membrane of the proximal tubule. The active form of vitamin D, calcitriol, increases urinary phosphorus excretion indirectly as it increases the sodium phosphorus transporters (NaPi-2b transporters) in the intestines.[50] There are no reports to the authors' knowledge of a higher incidence of struvite urolithiasis in dogs or cats with hyperphosphatemia, presumably because hyperphosphatemia most often occurs in cats who suffer from renal disease and may have other related metabolic complications, such as dilute urine and metabolic acidosis.

Sterile struvite urinary calculi in cats and dogs may be dissolved with a diet that is reduced in phosphorous, magnesium, and protein, which contribute the components of struvite urolithiasis, and with an acidic urinary pH (6.0 or lower).[51–53] Nonsterile struvite uroliths may be dissolved with use of targeted antimicrobial treatment primarily and complementary nutritional therapy.[52] Urine pH may be influenced by the dietary anion-to-cation balance. Therefore, a diet that is aiming to reduce urine pH may be lower in cations, such as calcium, sodium, or potassium, and higher in phosphate, sulfate, and chloride.[5] There are also acidifying compounds that may be added to the diet to achieve low urine pH, including phosphoric acid, methionine, and ammonium chloride. Base excess and urine pH appear to be more important than the relative mineral intake for struvite prevention.[54] Dietary prevention of recurrence of sterile struvite urolithiasis is possible with a diet that promotes urine dilution, targets an acidic pH, and provides reduced amounts of phosphorus and magnesium, although recurrence rates are unknown.[33] Addressing predisposing factors for infection, such as anatomic features and obesity, can help prevent the recurrence of nonsterile struvite.

Calcium phosphate and calcium carbonate urolithiasis

Calcium phosphate and calcium carbonate are often a small component of complex uroliths precipitated with struvite or calcium oxalate. Pure calcium phosphate or carbonate uroliths are uncommon in dogs and cats. Several calcium phosphate compounds include hydroxyapatite, brushite, whitlockite, and octacalcium phosphate, of which hydroxyapatite and calcium carbonate compounds are most common.[55] In dogs, many times these result from bacterial cystitis, as is struvite, and are formed under alkaline conditions.[33] Other conditions, such as hyperparathyroidism, that lead to hypercalciuria and hyperphosphaturia are also possible risk factors. Physical removal

of these uroliths is usually necessary, although they may dissolve when the primary cause is addressed (for example, hyperparathyroidism).[56] Nutritionally, high dietary phosphorus in a bioavailable form may increase the relative supersaturation for brushite in cats.[21] Otherwise, there are no nutritional prevention strategies for these uroliths aside from addressing the primary cause (ie, bacterial cystitis) if possible.

In summary, calcium and phosphorus compounds are most common among those that are involved in precipitation in the canine and feline urinary system; however, the pathogenesis for these urinary calculi is complex, and simple dietary excess of these minerals is not the sole cause. As more data regarding the physiology and nutritional requirements and tolerance for calcium and phosphorus are accumulated, there will be a greater understanding of how best to nutritionally prevent and manage these in dogs and cats.

The Importance of These Nutrients for Renal Health

Calcium and phosphorus metabolism is commonly dysregulated in dogs and cats with chronic kidney disease (CKD), which has a major impact on the progression of disease and the associated clinical signs.

As discussed above, hypercalcemia may increase the risk of calcium oxalate urolithiasis as well as lead to soft tissue mineralization and possibly to kidney injury and impaired function. Hypercalcemia can be the result of dietary, metabolic, neoplastic, renal, and idiopathic causes in dogs and cats. The degree of hypercalcemia and its chronicity impacts prognosis. In cats, clinical signs of hypercalcemia are usually most severe when the increase in calcium is rapid.[40] Most often, clinical signs are noted when serum total calcium is higher than 14.0 mg/dL and ionized calcium is greater than 6.5 mg/dL (1.6 mmol/L). If serum total calcium increases to 16.0 mg/dL or if ionized calcium increases to above 7.5 mg/dL (1.9 mmol/L), clinical signs are severe and require hospitalization and immediate care.[40] A reduction in dietary vitamin D, which is one of the most important regulators of calcium absorption, is recommended when the cause of hypercalcemia is vitamin D toxicity. Some anecdotally recommend feeding a diet with moderately reduced calcium and vitamin D in addition to added insoluble fiber for all-cause hypercalcemia.[40] High dietary calcium on its own does not appear to be a cause of hypercalcemia or renal disease in dogs, such as Labrador retrievers and beagles.[8] It is unknown if dietary calcium reduction would benefit dogs with existing hypercalcemia.

Although regulatory mechanisms are aimed to maintain serum ionized calcium and inorganic phosphorus, shifts may occur and worsen with CKD progression and are associated with increased mortality.[57–59] A reduction of functioning nephrons, as occurs in advanced CKD, leads to lower glomerular filtration rate and a reduced phosphorus excretion, ultimately resulting in increased serum inorganic phosphorus. The result of this would be a compensatory increase in filtration, but with a gradual increase in the serum inorganic phosphorus set point, as compensation fails to keep up unless phosphorus intake is reduced. The retention of phosphorus can lead to soft tissue mineralization, which may further damage the renal tissue and lead to reduced renal function.[60]

The function of 1-α-hydroxylase enzyme is necessary to form calcitriol from calcidiol; this is reduced in CKD patients because of the decrease in renal mass and as a result of the activity of secreted FGF-23. Decreased calcitriol results in reduces calcium absorption from the intestines, decreased ionized calcium, and an increase in PTH.[39] PTH increase may lead to additional negative health implications, including osteodystrophy, pathologic fractures, and “rubber jaw.”[60]

Serum phosphorus may remain in normal reference ranges thanks to compensatory mechanisms despite pathologic shifts in renal glomerular filtration, urine concentration, creatinine, PTH, and FGF-23.[39] Therefore, relying on increased serum phosphorus as a marker of CKD or as a primary indication to limit dietary phosphorus has important limitations. PTH and FGF-23 are not typically included in routine biochemistry panels; therefore, clinicians may not be aware of early dysregulation that occurs in CKD patients. Increases in FGF-23 and symmetric dimethylarginine, a biomarker for decreased glomerular filtration in early CKD, are intercorrelated in geriatric preazotemic cats.[61] The timing of these increases indicates that alterations in normal phosphorus metabolism occur in early CKD or even before CKD in cats.[62,63] Evidence regarding the potential benefits of early phosphorous intake reduction is lacking; however, the shifts in normal phosphorous metabolism may be nutritionally managed with dietary phosphorus restriction in advanced CKD (approximating or under the minimum accepted dietary requirements), as this may slow CKD progression and reduce related health complications.[60,64–67]

Recent data suggest that dietary phosphorus greater than 3.0 or 3.6 g/1000 kcal may lead to kidney damage and CKD in healthy cats when it is provided in a highly available form of soluble inorganic salts and when the ratio between calcium and phosphorus is low.[20,21] The relevance of this is highlighted by recent surveys that evaluated the total calcium and phosphorus in feline diets and found that approximately 33% of the tested products had a higher total phosphorus than 3.6 g/1000 kcal and highly variable calcium-to-phosphorus ratio (0.5–1.7).[2] Although the ratio between organic and inorganic phosphorus in those diets was not evaluated, several diets had a low calcium-to-phosphorus ratio in addition to high total phosphorus. However, there is no evidence that commercial cat foods indeed cause renal disease in healthy cats, as the aforementioned studies included experimental diets with a high proportion of soluble phosphorus salts possibly exceeding that of most commercial diets. There is no current maximum for dietary phosphorus for adult cats in the guidelines by AAFCO, nor is there a guidance regarding calcium-to-phosphorus ratio or the use of inorganic phosphorus salt additives.[12] Although more research is required to establish safety maximums, the authors believe that interim limits should be considered as well as a recommended calcium-to-phosphorous ratio greater than 1. In dogs, there is currently no evidence that high dietary phosphorus (up to 4.0 g/1000 kcal) in organic or inorganic form leads to renal injury when the calcium-to-phosphorus ratio is greater than 1[8]; however, further research to determine the tolerability of high dietary phosphorus in dogs is needed.

Vitamin D and Its Importance for Other Conditions Such as Gastrointestinal Disease and Cancer

The vitamin D receptor is present in multiple organs, such as the small intestine and colon. Apart from the traditional role of increasing calcium absorption by active transcellular transportation in the small intestine in the case of low plasma calcium levels,[68] calcitriol (active vitamin D) has additional important functions within the gastrointestinal tract. Calcitriol is needed to maintain the gastrointestinal barrier function by upregulation of tight junction protein expression,[69] the production of brush border enzymes,[70] as well as the formation of microvilli.[71] An intact gastrointestinal barrier prevents pathogen invasion and bacterial translocation; therefore, vitamin D is regarded as protective for chronic gastrointestinal diseases. Calcitriol further protects against damage to the gastrointestinal tract by suppressing tumor necrosis factor-alpha and nuclear factor kappa-beta pathways. These proinflammatory pathways play a key role in the first line of defense against pathogens; however, when

overexpression occurs, this can contribute to chronic gastrointestinal diseases. The inhibition of these proinflammatory pathways makes calcitriol an interesting therapeutic option for multiple chronic inflammatory conditions (eg, osteoarthritis, atopic dermatitis), but so far, clinical studies in dogs and cats are lacking.

Vitamin D has several immune-modulating effects, demonstrated by in vitro studies, whereas the clinical effects are largely not yet elucidated.[72] Vitamin D–deficient mice are more prone to infection and support overgrowth by pathogenic bacteria because of inadequate response of the immune system.[71] Supplementation of vitamin D metabolites as a possible effective treatment or prevention of chronic gastrointestinal diseases in dogs and cats requires further investigation. Vitamin D also affects tissue fibrosis by suppressing the transforming growth factor-beta pathway, as was demonstrated in colon cell lines from people,[73] in gastrointestinal cells of mice,[74] and in the feline liver (hepatic stellate cells).[75] These studies suggest a possible preventative role for vitamin D in the progression of chronic inflammatory diseases to cancer (which has high relevance for prevention of colorectal cancer in people).

Together with the antifibrotic effects, vitamin D has antiproliferative effects. Calcitriol inhibits cyclins and enhances expression of inhibitors of cyclin-dependent kinases; however, clinical studies are scarce. Currently, the strongest clinical evidence is based on epidemiologic studies in people demonstrating lower odds ratios for colorectal cancer (0.88) and breast cancer (0.72) associated with increased vitamin D intake compared with a typical Western-type diet.[73] In people, deficient intake of vitamin D, combined with insufficient exposure to sunlight, is common, whereas most dogs and cats consume sufficient dietary vitamin D thanks to complete and balanced diets. Clinical studies in dogs and cats on the effects of vitamin D on different types of cancer have not been conducted thus far to the authors' knowledge.

CLINICS CARE POINTS

- Vitamin D might be protective for several inflammatory and proliferative diseases, like gastrointestinal disease and cancer, which are subjects for future research.

REFERENCES

1. Summers SC, Stockman J, Larsen JA, et al. Evaluation of nutrient content and caloric density in commercially available foods formulated for senior cats. J Vet Int Med 2020;34:2029–35.
2. Summers SC, Stockman J, Larsen JA, et al. Evaluation of phosphorus, calcium, and magnesium content in commercially available foods formulated for healthy cats. J Vet Int Med 2020;34(1):266–73.
3. Kritikos G, Weidner N, Atkinson JL, et al. Quantification of vitamin D3 in commercial dog foods and comparison with Association of American Feed Control Officials recommendations and manufacturer-reported concentrations. J Am Vet Med Assoc 2018;252:1521–6.
4. Hutchinson D, Freeman LM, McCarthy R, et al. Seizures and severe nutrient deficiencies in a puppy fed a homemade diet. J Am Vet Med Assoc 2012;241:477–83.
5. NRC. Nutrient requirements of dogs and cats. Washington, DC: National Academies Press; 2006.
6. Nap RC, Hazewinkel HA. Growth and skeletal development in the dog in relation to nutrition; a review. Vet Q 1994;16:50–9.

7. Dobenecker B, Kasbeitzer N, Flinspach S, et al. Calcium-excess causes subclinical changes of bone growth in beagles but not in foxhound-crossbred dogs, as measured in X-rays. J Anim Physiol Anim Nutr (Berl) 2006;90:394–401.
8. Stockman J, Watson P, Gilham M, et al. Adult dogs are capable of regulating calcium balance, with no adverse effects on health, when fed a high-calcium diet. Br J Nutr 2017;117:1235–43, 31.
9. Morris JG. Ineffective vitamin D synthesis in cats is reversed by an inhibitor of 7-dehydrocholestrol-delta7-reductase. J Nutr 1999;129:903–8.
10. How KL, Hazewinkel HA, Mol JA. Photosynthesis of vitamin D in the skin of dogs cats and rats. Vet Q 1995;17(Suppl 1):S29.
11. Weidner N, Verbrugghe A. Current knowledge of vitamin D in dogs. Crit Rev Food Sci Nutr 2017;57:3850–9.
12. AAFCO. Official Publication. Atlanta (GA): Association of American Feed Control Officials; 2018.
13. FEDIAF. Nutritional guidelines for complete and complementary pet food for cats and dogs 2020. Available at: www.fediaf.org. Accessed October 8, 2020.
14. Allison LN, Jaffey JA, Bradley-Siemens N, et al. Immune function and serum vitamin D in shelter dogs: a case-control study. Vet J 2020;261:105477.
15. Osuga T, Nakamura K, Morita T, et al. Vitamin D status in different stages of disease severity in dogs with chronic valvular heart disease. J Vet Intern Med 2015;29:1518–23.
16. Allenspach K, Rizzo J, Jergens AE, et al. Hypovitaminosis D is associated with negative outcome in dogs with protein losing enteropathy: a retrospective study of 43 cases. BMC Vet Res 2017;13:96.
17. Zafalon RVA, Risolia LW, Pedrinelli V, et al. Vitamin D metabolism in dogs and cats and its relation to diseases not associated with bone metabolism. J Anim Physiol Anim Nutr 2020;104:322–42.
18. Pallauf J, Rimbach G. Nutritional significance of phytic acid and phytase. Arch Tierernahr 1997;50:301–19.
19. Coltherd JC, Staunton R, Colyer A, et al. Not all forms of dietary phosphorus are equal: an evaluation of postprandial phosphorus concentrations in the plasma of the cat. Br J Nutr 2019;121:270–84.
20. Dobenecker B, Webel A, Reese S, et al. Effect of a high phosphorus diet on indicators of renal health in cats. J Feline Med Surg 2018;20:339–43.
21. Alexander J, Stockman J, Atwal J, et al. Effects of the long-term feeding of diets enriched with inorganic phosphorus on the adult feline kidney and phosphorus metabolism. Br J Nutr 2018;121:1–21.
22. Morris JG. Cats discriminate between cholecalciferol and ergocalciferol. J Anim Physiol Anim Nutr (Berl) 2002;86:229–38.
23. Delaney SJ. Serum ionized calcium, 25-hydroxyvitamin D, and parathyroid hormone in two dogs fed a homemade diet fortified with vitamin D2. In: 2015 Annual AAVN Symposium Order of Abstracts. J Anim Physiol Anim Nutr 2015;99:810–24.
24. Goedegebuure SA, Hazewinkel HA. Morphological findings in young dogs chronically fed a diet containing excess calcium. Vet Pathol 1986;23:594–605.
25. Hazewinkel HA, Van den Brom WE, Van 'T Klooster AT, et al. Calcium metabolism in great Dane dogs fed diets with various calcium and phosphorus levels. J Nutr 1991;121:S99–106.
26. Lauten SD, Cox NR, Brawner WR Jr, et al. Influence of dietary calcium and phosphorus content in a fixed ratio on growth and development in great Danes. Am J Vet Res 2002;63:1036–47.

27. Tryfonidou MA, Holl MS, Stevenhagen JJ, et al. Dietary 135-fold cholecalciferol supplementation severely disturbs the endochondral ossification in growing dogs. Domest Anim Endocrin 2003;24:265–85.
28. Hazewinkel HAW, Schoenmakers I. Hormonal and skeletal effects of excessive calcium intake during partial weaning and at prepubertal age in dogs. Compend Contin Educ Vet 2006;28(SUPPL):55.
29. Hazewinkel HAW, Tryfonidou MA. Vitamin D3 metabolism in dogs. Mol Cell Endocrinol 2002;197:23–33.
30. Verbrugghe A, Paepe D, Verhaert L, et al. Metabolic bone disease and hyperparathyroidism in an adult dog fed an unbalanced homemade diet. Vlaams Diergeneeskundig Tijdschrift 2011;80:61–8.
31. Kiefer-Hecker B, Bauer A, Dobenecker B. Effects of low phosphorus intake on serum calcium, phosphorus, alkaline phosphatase activity and parathyroid hormone in growing dogs. J Anim Physiol Anim Nutr 2018;102:1749–58.
32. Corbee RJ, Mars A. Enostosis, a diet induced disorder? In: ESVCN Congress Cirencester 2017 Proceedings, Royal Agricultural University Cirencester, September 20th-23rd 2017. p. 56.
33. Bartges J, Kirk C. Nutritional management of lower urinary tract disease. In: Fascetti AJ, Delaney SJ, editors. Applied veterinary clinical nutrition. New York: Wiley & Sons; 2012. p. 269–87.
34. Gupta M, Bhayana S, Sikka S. Role of urinary inhibitors and promoters in calcium oxalate crystallisation. Int J Res Pharm Chem 2011;1:793–8.
35. Mo L, Huang H-Y, Zhu X-H, et al. Tamm-Horsfall protein is a critical renal defense factor protecting against calcium oxalate crystal formation. Kidney Int 2004;66:1159–66.
36. Hess B. The role of Tamm-Horsfall glycoprotein and nephrocalcin in calcium oxalate monohydrate crystallization processes. Scan Electron Microsc 1991;5:689.
37. Lulich JP, Osborne CA, Thumchai R, et al. Epidemiology of canine calcium oxalate uroliths: identifying risk factors. Vet Clin North Am Small Anim Pract 1999;29:113–22.
38. Midkiff A, Chew D, Randolph J, et al. Idiopathic hypercalcemia in cats. J Vet Int Med 2000;14:619–26.
39. de Brito Galvao JF, Nagode LA, Schenck PA, et al. Calcitriol, calcidiol, parathyroid hormone, and fibroblast growth factor-23 interactions in chronic kidney disease. J Vet Emerg Crit Care (San Antonio) 2013;23:134–62.
40. de Brito Galvão JF, Parker V, Schenck PA, et al. Update on feline ionized hypercalcemia. Vet Clin North Am Small Anim Pract 2017;47:273–92.
41. Dijcker JC, Kummeling A, Hagen-Plantinga EA, et al. Urinary oxalate and calcium excretion by dogs and cats diagnosed with calcium oxalate urolithiasis. Vet Rec 2012;171:646.
42. Furrow E, Patterson E, Armstrong P, et al. Fasting urinary calcium-to-creatinine and oxalate-to-creatinine ratios in dogs with calcium oxalate urolithiasis and breed-matched controls. J Vet Int Med 2015;29:113–9.
43. Luskin AC, Lulich JP, Gresch SC, et al. Bone resorption in dogs with calcium oxalate urolithiasis and idiopathic hypercalciuria. Res Vet Sci 2019;123:129–34.
44. Ching SV, Fettman MJ, Hamar DW, et al. The effect of chronic dietary acidification using ammonium chloride on acid-base and mineral metabolism in the adult cat. J Nutr 1989;119:902–15.
45. Arnett TR. Acidosis, hypoxia and bone. Arch Biochem Biophys 2010;503:103–9.

46. Hiroshi H, Suzuki T, Kasai T, et al. Ingestion of guar gum hydrolysate, a soluble fiber, increases calcium absorption in totally gastrectomized rats. J Nutr 1999; 129:39–45.
47. Fantinati M, Priymenko N. Managing feline idiopathic hypercalcemia with chia seeds (Salvia hispanica L.): a case series. Front Vet Sci 2020;7:421.
48. McClain HM, Barsanti JA, Bartges JW. Hypercalcemia and calcium oxalate urolithiasis in cats: a report of five cases. J Am Anim Hosp Assoc 1999;35:297–301.
49. Pastoor F, Van't Klooster AT, Mathot J, et al. Increasing calcium intakes lower urinary concentrations of phosphorus and magnesium in adult ovariectomized cats. J Nutr 1994;124:299–304.
50. Rizzoli R, Fleisch H, Bonjour J-P. Role of 1,25-dihydroxyvitamin D3 on intestinal phosphate absorption in rats with a normal vitamin D supply. J Clin Invest 1977;60:639–47.
51. Calabrò S, Tudisco R, Bianchi S, et al. Management of struvite uroliths in dogs. Br J Nutr 2011;106:S191–3.
52. Dear JD, Larsen JA, Bannasch M, et al. Evaluation of a dry therapeutic urinary diet and concurrent administration of antimicrobials for struvite cystolith dissolution in dogs. BMC Vet Res 2019;15:273.
53. Torres-Henderson C, Bunkers J, Contreras ET, et al. Use of Purina Pro Plan Veterinary Diet UR Urinary St/Ox to dissolve struvite cystoliths. Top Companion Anim Med 2017;32:49–54.
54. Tarttelin MF. Feline struvite urolithiasis: factors affecting urine pH may be more important than magnesium levels in food. Vet Rec 1987;121:227–30.
55. Osborne C, Klausner J, Lulich J. Canine and feline calcium phosphate urolithiasis. In: Current veterinary therapy XII Kirk. Philadelphia: WB Saunders; 1995. p. 996–1001.
56. Adams L, Syme H. Canine ureteral and lower urinary tract diseases. In: Ettinger, Stephen J, Feldman, et al, editors. Textbook of veterinary internal medicine: diseases of the dog and the cat. 7th edition. St. Louis (MO): Elsevier Saunders; 2010. p. 2087.
57. Boyd L, Langston C, Thompson K, et al. Survival in cats with naturally occurring chronic kidney disease (2000–2002). J Vet Int Med 2008;22:1111–7.
58. Kuwahara Y, Ohba Y, Kitoh K, et al. Association of laboratory data and death within one month in cats with chronic renal failure. J Small Anim Pract 2006;47: 446–50.
59. Elliott J, Barber P. Feline chronic renal failure: clinical findings in 80 cases diagnosed between 1992 and 1995. J Small Anim Pract 1998;39:78–85.
60. Geddes RF, Finch NC, Syme HM, et al. The role of phosphorus in the pathophysiology of chronic kidney disease. J Vet Emerg Crit Care (San Antonio) 2013;23: 122–33.
61. Sargent HJ, Jepson RE, Chang Y-m, et al. Fibroblast growth factor 23 and symmetric dimethylarginine concentrations in geriatric cats. J Vet Intern Med 2019; 33:2657–64.
62. Finch N, Syme H, Elliott J. Risk factors for development of chronic kidney disease in cats. J Vet Intern Med 2016;30:602–10.
63. Finch NC, Syme HM, Elliott J. Parathyroid hormone concentration in geriatric cats with various degrees of renal function. J Am Vet Med Assoc 2012;241:1326–35.
64. Ross L, Finco D, Crowell WA. Effect of dietary phosphorus restriction on the kidneys of cats with reduced renal mass. Am J Vet Res 1982;43:1023–6.

65. Ross SJ, Osborne CA, Kirk CA, et al. Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. J Am Vet Med Assoc 2006;229:949–57.
66. Brown SA, Rickertsen M, Sheldon S. Effects of an intestinal phosphorus binder on serum phosphorus and parathyroid hormone concentration in cats with reduced renal function. Int J Appl Res 2008;6:155–60.
67. Elliott J, Rawlings J, Markwell P, et al. Survival of cats with naturally occurring chronic renal failure: effect of dietary management. J Small Anim Pract 2000; 41:235–42.
68. Bikle DD Vitamin D. Biochemistry and physiology. In: Liao E, editor. Extraskeletal effects of vitamin D. contemporary endocrinology. Cham (Switzerland): Humana Press; 2018. p. 1–40.
69. Zhao H, Zhang H, Wu H, et al. Protective role of 1,25(OH)2vitamin D3 in the mucosal injury and epithelial barrier disruption in DSS-induced acute colitis in mice. BMC Gastroenterol 2012;12. Article number 57.
70. Chen A, Davis BH, Bissonnette M, et al. 1,25-Dihydroxyvitamin D3 stimulates activator protein-1-dependent Caco-2 cell differentiation. J Biol Chem 1999;274: 35505–13.
71. Barbáchano A, Fernández-Barral A, Ferrer-Mayorga G, et al. The endocrine vitamin D system in the gut. Mol Cell Endocrinol 2017;453:79–87.
72. Parravicini V, Caserta S. The immunomodulatory roles of vitamin D: new tricks for an old dog. Mol Interv 2010;10:204–8.
73. Ferrer-Mayorga G, Gómez-López G, Barbáchano A, et al. Vitamin D receptor expression and associated gene signature in tumour stromal fibroblasts predict clinical outcome in colorectal cancer. Gut 2017;66:1449–62.
74. Tao Q, Wang B, Zheng Y, et al. Vitamin D prevents the intestinal fibrosis via induction of vitamin D receptor and inhibition of transforming growth factor-beta1/ Smad3 pathway. Dig Dis Sci 2015;60:868–75.
75. Corbee RJ, Tryfonidou MA, Grinwis GCM, et al. Skeletal and hepatic changes induced by chronic vitamin A supplementation in cats. Vet J 2014;202:503–9.