Chapter 41

Canine Calcium Phosphate Urolithiasis: Causes, Detection and Prevention

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"If misinterpreted observations are accepted as facts, the result may be misdiagnosis leading to ineffective or even contraindicated treatment."
Carl A. Osborne

PREVALENCE AND MINERAL COMPOSITION

Uroliths composed predominantly of calcium phosphate have been infrequently identified in dogs and cats. However, calcium phosphate is commonly found as a minor component in naturally occurring struvite and calcium oxalate uroliths. Occasionally a shell of calcium phosphate will form around a urolith composed primarily of struvite.

At least four mineral types have been identified in calcium phosphate uroliths **(Table 41-1)**. The most common form identified in calcium phosphate uroliths from dogs and cats is hydroxyapatite, followed by brushite. Calcium carbonate uncommonly exists as a pure compound in canine and feline uroliths. Calcium carbonate often occurs in equine, rabbit, guinea pig and caprine uroliths (Osborne et al, 1989). In the presence of conditions associated with urinary tract infections (UTIs) caused by urease-positive bacteria, carbonate radicals may be generated that associate with the complex apatite structure to form a carbonate apatite lattice (Osborne et al, 1985). Uncommonly identified crystalline forms of calcium phosphate in uroliths include whitlockite and octacalcium phosphate.

More than one crystalline form of calcium phosphate may be present in a single urolith. In alkaline urine, brushite is readily transformed to apatite; it is possible that some apatite identified in uroliths originated from brushite (Pak et al, 1971). In addition, mixtures of calcium phosphate and calcium oxalate often occur. With the exception of brushite, canine calcium phosphate uroliths do not appear to have a characteristic shape.

Calcium phosphate accounted for 0.51% (1,801) of all (350,803) canine uroliths submitted to the Minnesota Urolith Center from 1981 to 2007 (Table 38-8), and 0.67% (273 of 40,612) of the uroliths submitted in the year 2007. Calcium phosphate accounted for 1.6% of canine upper tract uroliths analyzed at the Minnesota Urolith Center from 2000 to 2006 (Table 38-9). Calcium phosphate accounted for 2.8% of uroliths retrieved from dogs less than 12 months old. Of 1,801 canine

Table 41-1. Common characteristics of canine calcium phosphate uroliths.

Variations in mineral composition
Calcium apatite only
Brushite only
Calcium apatite mixed with calcium oxalate
Brushite mixed with calcium oxalate
In dogs, the carbonate apatite form of calcium phosphate is most commonly detected as a minor component of infection-induced struvite
Physical characteristics
Color: Calcium phosphate uroliths are usually cream or tan. Blood clots mineralized with calcium phosphate are typically black.
Shape: Variable. With the exception of brushite, calcium phosphate uroliths do not have a characteristic shape. The external surface of brushite uroliths is typically round and smooth.
Nuclei: Brushite uroliths are often laminated.
Density: Generally dense and brittle, sometimes chalk-like. Mineralized blood clots may be softer. All forms of calcium phosphate are radiodense compared to soft tissue.
Number: Single or multiple
Location: Kidneys, ureters, urinary bladder (most common) and/or urethra
Size: Variable, with smaller sizes more common
Prevalence
Approximately 0.5% of all canine uroliths. Approximately 1.6% of canine upper tract uroliths.
Characteristics of affected canine patients
No gender prevalence for calcium apatite. Brushite is more common in males. Mean age at diagnosis is seven years (range <1 to >16 years).

hydroxyapatite and carbonate apatite uroliths, 473 were composed entirely (100%) of calcium phosphate, and 694 were composed of at least 70% of these minerals. Of 693 canine brushite uroliths, 233 were composed entirely (100%) of calcium phosphate, and 460 were composed of at least 70% of this mineral. The mean age of dogs at the time of urolith retrieval was approximately nine years (range one month to 19 years). Calcium phosphate accounted for less than 2.3% of calcium phosphate uroliths formed by dogs less than 12 months old. Males were affected (57%) more commonly than females (43%). Forty different breeds were affected including cocker spaniels (10%), mixed breeds (20%), miniature schnauzers (10%), Yorkshire terriers (7%), Shih Tzus (6%) and springer spaniels (5%). Hydroxyapatite uroliths were more commonly removed from the lower urinary tract (81%) than the upper urinary tract (8%). The location of 11% of the hydroxyapatite uroliths was not specified.

ETIOPATHOGENESIS AND RISK FACTORS

Solubility of Calcium Phosphates in Urine

Overview

The solubility of calcium phosphates in urine depends on: 1) urinary pH, 2) urine calcium ion concentration, 3) total urine inorganic phosphate concentration, 4) urine concentration of inhibitors of calcium crystallization and 5) urine concentration of potentiators of crystallization. Factors that decrease calcium phosphate solubility predispose patients to urolith formation.

Urinary pH

Urinary pH has a profound effect on the solubility of some forms of calcium phosphate (Elliot, 1957). With the exception of brushite, calcium phosphate solubility markedly decreases in alkaline urine and increases in acidic urine. Increased urinary pH increases the availability of ionic PO_4^{3-} and HPO_4^{2-}, which are available for incorporation into calcium phosphates (Asplin et al, 1996). Apatite will not crystallize from human urine unless the pH is 6.6 or greater (Elliot, 1968). Approximately 400 mg of calcium phosphate/l can be held in solution at a pH of 5.5, whereas only 32 mg of calcium phosphate/l will be held in solution at a pH of 7.8 (Elliot, 1965). Therefore, people with disorders associated with persistent elevation of urinary pH (e.g., distal renal tubular acidosis [RTA]) are predisposed to calcium phosphate urolith formation. In contrast to carbonate apatite and hydroxyapatite, the solubility of brushite decreases in acidic urine.

Hypercalciuria

Hypercalciuria decreases calcium phosphate solubility and may result in oversaturation with calcium phosphate (Pak, 1978). Hypercalciuria may result from: 1) excessive resorption of calcium from bone, 2) enhanced intestinal absorption of calcium, 3) impaired renal tubular reabsorption of calcium and/or 4) combinations of these factors. Urine specimens obtained from human patients with hypercalciuria and calcium uroliths are usually supersaturated with brushite.

Controversy exists as to the relative importance of urinary pH and hypercalciuria as determinants of calcium phosphate solubility in vivo. Some investigators believe that calcium phosphate crystallization is primarily governed by changes in urinary pH; they minimize the importance of hypercalciuria (Elliot, 1968). However, other investigators suggest that persistent hypercalciuria tends to increase the calcium phosphate saturation of urine so that small increases in urinary pH will result in calcium phosphate crystalluria. Apparently, there have been no studies reported on the relative effect of hypercalciuria and urinary pH on the solubility of different types of calcium phosphate in canine urine.

Crystallization Inhibitors

Normally, urine contains calcium phosphate crystal inhibitors. One mechanism by which inhibitors prevent urolith formation is by chelating urolith constituents, making them unavailable for nidus formation or crystal growth. In addition, crystallization inhibitors may alter crystalline structure in such a way that crystal growth and aggregation are prevented. Inhibitors of calcium phosphate crystallization include inorganic pyrophosphates, citric acid ions, magnesium ions and nephrocalcin (Bisaz et al, 1978; Ito and Coe, 1977). In healthy human urine, these inhibitors provide 70 to 80% of the inhibitory capacity to calcium phosphate crystallization (Asplin et al, 1996). As yet unidentified low-molecular-weight inhibitors provide the remaining 20 to 30%.

Pyrophosphates increase the upper limit of urine calcium phosphate saturation at which spontaneous precipitation

occurs. Pyrophosphates also retard growth of hydroxyapatite crystals by adsorbing to their surfaces and blocking active growth sites. In addition, pyrophosphates inhibit transformation of amorphous calcium phosphate into a crystalline form (Fleisch, 1978). Citrate forms soluble complexes with calcium, thereby decreasing the availability of calcium for incorporation into crystals. Magnesium may replace calcium on the surface of growing crystals and thus block epitaxial growth.

Crystallization Promoters

Formation of calcium phosphate uroliths may be promoted by epitaxy. Epitaxy is the process by which crystals of one salt induce the formation of crystals of another salt. Epitaxic induction occurs between crystals having similar lattice dimensions. Calcium phosphate precipitation has been reported to be stimulated by calcium oxalate and monosodium urate crystals (Fleisch, 1978).

Disorders Associated with Formation of Calcium Phosphate Uroliths

Overview

Calcium phosphate uroliths may occur in patients with: 1) primary hyperparathyroidism, 2) other hypercalcemic disorders, 3) distal RTA and 4) idiopathic hypercalciuria (**Table 41-2**) (Asplin et al, 1996; Curhan et al, 1997; Menon et al, 1998). Because the prevalence of calcium phosphate uroliths in dogs is low, and because appropriate metabolic studies have rarely been performed in affected cases, the association of calcium phosphate uroliths with other canine metabolic disorders has not been as well established.

Primary Hyperparathyroidism

Between 18 to 20% of human patients with primary hyperparathyroidism have uroliths at the time of diagnosis (Nikkila et al, 1989). In one series of 72 dogs with primary hyperparathyroidism, 22 (31%) had uroliths (Feldman and Nelson, 1996). Uroliths from patients with primary hyperparathyroidism are typically composed of calcium phosphate, calcium oxalate or a mixture of the two. Uroliths composed predominantly of calcium phosphate are more commonly identified in people and dogs with primary hyperparathyroidism; uroliths composed primarily of calcium oxalate are more commonly identified in people and dogs with normocalcemic hypercalciuria (Klausner and Osborne, 1986). Bladder uroliths composed primarily of calcium phosphate have been experimentally induced in dogs following injections of parathyroid hormone (PTH) (Leberman, 1940).

Factors that predispose patients with primary hyperparathyroidism to calcium phosphate urolith formation include: hypercalciuria, increased urinary pH and increased renal excretion of metabolites that promote spontaneous precipitation of calcium salts (**Table 41-3**). Hypercalcemia results from PTH-induced bone resorption and renal tubular reabsorption of calcium. In addition, increased intestinal absorption of calcium results from PTH-stimulated conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (1,25-vitamin D) (Pak, 1978).

Table 41-2. Comparison of disorders that may predispose dogs, people and cats to formation of calcium phosphate uroliths.

Disorders	Dogs	People	Cats
Primary hyperparathyroidism*	Yes	Yes	NR
Other hypercalcemic disorders			
Hypercalcemia of malignancy**	–	Yes	NR
Vitamin D intoxication**	NR	Yes	NR
Excessive calcium consumption**	NR	Yes	NR
Thyrotoxicosis**	NR	Yes	NR
Hyperadrenocorticism***	Yes	Yes	NR
Granulomatous disease**	NR	Yes	NR
Immobilization**	NR	Yes	NR
Distal renal tubular acidosis†	NR	Yes	NR
Normocalcemic hypercalciuria			
Intestinal hyperabsorption**	NR	Yes	NR
Renal leak	Yes	Yes	NR

Key: NR = not reported.
*Adapted from Broadus A. Nephrolithiasis in primary hyperparathyroidism. In: Coe F, Brenner B, Stein J, eds. Nephrolithiasis. New York, NY: Churchill Livingstone, 1980; 59. Goulden BE, MacKenzie CP. Suspected primary hyperparathyroidism in the dog. New Zealand Veterinary Journal 1968; 16: 13. Klausner JS, Osborne CA. Canine calcium phosphate uroliths. Veterinary Clinics of North America: Small Animal Practice 1986; 16: 171. Krook L. Spontaneous hyperparathyroidism in the dog. A pathological-anatomical study. Acta Pathology and Microbiology Scandinavia 1957; Suppl. 122: 27.
**Adapted from Menon M, Bhalchondra GP, Drach GW. Urinary lithiasis: Etiology, diagnosis, and medical management. In: Walsh PC, Retik AB, Vaughan ED, et al, eds. Campbell's Urology, 7th ed. Philadelphia, PA: WB Saunders Co, 1998; 2661.
***Adapted from Hess RS, Kass PH, Ward CR. Association between hyperadrenocorticism and development of calcium-containing uroliths in dogs with urolithiasis. Journal of the American Veterinary Medical Association 1998; 212: 1889. Menon M, Bhalchondra GP, Drach GW. Urinary lithiasis: Etiology, diagnosis, and medical management. In: Walsh PC, Retik AB, Vaughan ED, et al, eds. Campbell's Urology, 7th ed. Philadelphia, PA: WB Saunders Co, 1998; 2661.
†Adapted from Caruana RJ, Buckalew VM. The syndrome of distal (type 1) renal tubular acidosis: Clinical and laboratory findings in 58 cases. Medicine 1988; 67: 84.

Hypercalcemia results in increased glomerular filtration of calcium and hypercalciuria, which in turn enhances the likelihood of urolith formation by increasing urine saturation with brushite and calcium oxalate (Pak, 1978). The urine of most hypercalciuric people with primary hyperparathyroidism is supersaturated with brushite and calcium oxalate. Hypercalciuria and hyperphosphaturia have been documented to occur in dogs with primary hyperparathyroidism and calcium uroliths (Klausner and Osborne, 1986; Klausner et al, 1987).

Persistent elevation in urinary pH may predispose some patients with primary hyperparathyroidism to calcium phosphate urolithiasis. Urinary pH is elevated in these patients because of impaired renal tubular reabsorption of bicarbonate (Broadus, 1980). This abnormality may explain, at least in part, the increased occurrence of calcium phosphate uroliths in patients with primary hyperparathyroidism compared with patients with other hypercalciuric diseases.

It has been suggested that some human patients with pri-

Table 41-3. Some potential risk factors for canine calcium phosphate uroliths.

Food	Urine	Metabolic	Drugs
Alkalinizing potential	Alkaline pH	Hypercalcemia	Urine alkalinizing drugs
High calcium content	Hypercalciuria	Distal renal tubular acidosis	Furosemide
High sodium content	High phosphate ion concentration		Glucocorticoids
High phosphorus content?	Increased concentration of promoters		Sodium chloride
Low-moisture content	Decreased concentration of inhibitors		Vitamin D
Excessive vitamin D content	Hypocitraturia		
High protein content	Hypomagnesuria		
Low magnesium content	Blood clots in renal pelvis or bladder lumen		
	Urine concentration		
	Urine retention		

Table 41-4. Diagnostic characteristics of disorders that predispose to calcium phosphate uroliths.

Test	Absorptive hypercalciuria	Renal-leak hypercalciuria	Primary hyperparathyroidism	Distal renal tubular acidosis
Serum				
Calcium concentration	Normal	Normal	Increased	Normal to decreased
PO_4 concentration	Normal to decreased	Normal	Normal to decreased	Normal to decreased
HCO_3 concentration	Normal	Increased	Normal to decreased	Decreased
PTH concentration	Normal to decreased	Increased	Normal to increased	Normal to increased
1,25-vitamin D concentration	Variable	Increased	Increased	Normal
Urine				
Fasting 24-hour calcium excretion	Normal	Increased	Increased	Normal to increased
Fed 24-hour calcium excretion?	Increased	Increased	Increased	Normal to increased
pH	Variable	Variable	Variable	>6.0

Key: PTH = parathyroid hormone.

mary hyperparathyroidism excrete a substance in their urine that facilitates calcium phosphate and calcium oxalate precipitation (Pak, 1978). The specific nature of this urolithiasis-promoting factor has not been determined.

Other Hypercalcemic Disorders

In addition to primary hyperparathyroidism, other hypercalcemic disorders may predispose patients to formation of calcium phosphate uroliths. Uroliths have been identified in human patients with hypervitaminosis D, neoplastic disorders, Cushing's syndrome and in some patients who are immobilized for long periods (**Table 41-2**) (Menon et al, 1998). Although calcium phosphate is the most frequently identified mineral in uroliths obtained from these patients, calcium oxalate may also be present. Because the frequency of occurrence of uroliths in patients with these hypercalcemic disorders is low, it is likely that factors in addition to hypercalcemia are involved.

Distal Renal Tubular Acidosis

Nephrolithiasis is a common manifestation of hereditary, acquired and idiopathic forms of RTA (Type I) in people (Caruana and Buckalew, 1988). Uroliths are typically composed entirely of calcium phosphate, calcium oxalate and struvite (Backman et al, 1980). Urolith formation has also been observed occasionally in patients with proximal RTA (Type II) (Menon et al, 1998). To the best of our knowledge, struvite uroliths are the only urolith type observed in canine patients with RTA (Bovee et al, 1979; Polzin et al, 1986).

Distal RTA results from functional inability of the distal nephron to establish a hydrogen ion gradient between blood and tubular fluid, regardless of the severity of acidemia. The disorder in people is characterized by the inability to decrease urinary pH below 5.4, hypokalemia, hyperchloremia, hypophosphatemia, hypocalcemia, metabolic acidosis, osteomalacia, nephrocalcinosis and urolithiasis (Caruana and Buckalew, 1988; Menon et al, 1998).

Hypercalciuria, alkaline urine, low urine citrate concentration and excessive urine phosphate excretion contribute to formation of calcium phosphate uroliths observed in patients with distal RTA (**Table 41-4**) (Caruana and Buckalew, 1988; Menon et al, 1998). Hypercalciuria and hyperphosphaturia tend to increase urine saturation with calcium phosphate. Acidosis increases calcium mobilization from bone, causing an increase in the quantity of calcium excreted in urine (Klausner and Osborne, 1986). In addition, acidosis decreases renal tubular reabsorption of calcium, further increasing calcium excretion. Acidosis may alter renal tubular calcium transport, the response of the tubules to PTH or both.

Elevated urinary pH increases the availability of PO_4^{3-} and HPO_4^{2-}, which may be incorporated into ionic octacalcium phosphate and brushite, respectively (Asplin et al, 1996). Increased urinary pH is considered more important than hypercalciuria in predisposing patients with distal RTA to calcium phosphate urolith formation (Asplin et al, 1996).

Patients with distal RTA consistently excrete decreased amounts of citrate in their urine (Caruana and Buckalew, 1988). Hypocitratemia in patients with distal RTA has been attributed to: 1) increased proximal tubule reabsorption of citrate as a consequence of intracellular acidosis, 2) a primary

defect in tubular function and 3) the effects of hypokalemia (Caruana and Buckalew, 1988). Because citrate is a major chelator of calcium, hypocitraturia decreases calcium solubility and may represent an important risk factor in the pathogenesis of calcium phosphate and calcium oxalate uroliths associated with RTA (Menon et al, 1998).

In human patients, distal RTA sometimes occurs as an incomplete form in which urolith formation occurs without systemic acidosis. Urolithiasis may be the only clinical manifestation of this disorder (Konnak et al, 1982). The tubular defect can be recognized by an abnormal response to an ammonium chloride loading test.

Normocalcemic Hypercalciuria

Normocalcemic hypercalciuria is a syndrome characterized by normal serum calcium concentration, increased urinary excretion of calcium, absence of systemic disease and increased tendency for formation of calcium phosphate or calcium oxalate uroliths (Curhan et al, 2007). Approximately 33% of human calcium urolith formers have normocalcemic hypercalciuria (Menon et al, 1998). Normocalcemic hypercalciuria has also been recognized in dogs (Lulich et al, 1991). It has not been documented to occur in cats, likely due to little effort to detect it.

Two types of normocalcemic hypercalciuria have been recognized in dogs (Lulich et al, 1991). One type, called absorptive hypercalciuria, is associated with increased intestinal absorption of calcium. The subsequent increase in serum calcium concentration suppresses PTH secretion, resulting in decreased tubular reabsorption of calcium and hypercalciuria. Hyperabsorption of calcium from the intestinal tract may result from a primary intestinal disturbance in calcium transport. It is also possible that increased calcium absorption results from increased synthesis of 1,25-vitamin D. Absorptive hypercalciuria has been divided into subtypes based on urinary calcium excretion following consumption of different levels of dietary calcium (Menon et al, 1998).

The second type of normocalcemic hypercalciuria, termed renal-leak hypercalciuria, is thought to result from impaired ability of the proximal tubules to reabsorb filtered calcium (Lulich et al, 1991a; Menon et al, 1998). A defect in reabsorption of magnesium may also be present. Renal calcium loss stimulates 1,25-vitamin D and PTH synthesis, resulting in an increase in intestinal absorption of calcium.

Hypercalciuria is probably not the only factor involved in urolith formation in patients with normocalcemic hypercalciuria because many hypercalciuric patients do not form uroliths. Crystallization inhibitor and promoter interaction are also important contributing factors.

The diagnosis of idiopathic hypercalciuria is established by demonstrating an increase in 24-hour urinary calcium excretion and by eliminating other nonhypercalcemic, hypercalciuric disorders such as RTA (**Table 41-4**) (Lulich et al, 1991a, 1991; Menon et al, 1998). Unlike absorptive hypercalciuria, renal-leak hypercalciuria is not affected by withholding food. **Table 41-5** presents a problem-specific database for dogs suspected of having calcium phosphate uroliths, and is a useful clinical tool.

Mineralization of Blood Clots

Nephroliths, urocystoliths and urethroliths composed of blood clots mineralized with calcium phosphate have been observed on numerous occasions in dogs (and cats). Formation of highly concentrated urine in patients with gross hematuria may favor formation of mineralized blood clots. Contrary to one theory, these black-colored uroliths are not composed of bile metabolites.

BIOLOGIC BEHAVIOR

Calcium phosphate uroliths may increase in size and number if underlying causes persist. In our experience, blood clots within the urinary tract that have become mineralized with calcium phosphate often remain inactive for years.

KEY NUTRITIONAL FACTORS

The determination of key nutritional factors for prevention of calcium phosphate uroliths is complicated because these uroliths occur relatively infrequently and there are several different potentially underlying causes. Dietary dissolution of calcium phosphate uroliths has not been successful. Depending on the size, calcium phosphate uroliths are readily removed by surgery, lithotripsy, voiding urohydropropulsion (Figure 38-5 and Table 38-7) (Lulich et al, 1993) or aspiration through a urinary catheter (Figure 38-6) (Lulich and Osborne, 1992). Thus, dietary therapy of patients with recurring calcium phosphate uroliths is limited to removing or minimizing risk factors that contribute to supersaturation of urine with calcium phosphate.

The solubility of calcium phosphates in urine depends on: 1) urinary pH, 2) urine calcium ion concentration, 3) total urine inorganic phosphate concentration, 4) urine concentration of inhibitors of calcium crystallization and 5) urine concentration of potentiators of crystallization. The key nutritional factors that are thought to increase calcium phosphate solubility to help prevent recurrence of uroliths are summarized in **Table 41-6** and are discussed in more detail below.

Water

Dogs eating dry commercial foods are probably at greater risk for urolith formation than dogs consuming moist foods because dry foods tend to be associated with production of a reduced volume of more concentrated urine. Low urine volume is a risk factor for all types of uroliths because it increases the relative urine saturation of lithogenic constituents. However, it is highly improbable that low urine volume alone would create an environment conducive to calcium phosphate urolith formation.

Although understandably difficult in some patients, encouraging fluid consumption throughout the day with the goal of promoting a consistently large volume of urine is likely to be of benefit. Enhancing urine volume by feeding a moist food may

Table 41-5. Problem-specific database for dogs suspected of having calcium phosphate uroliths.

Blood, serum and plasma tests

Urea nitrogen and creatinine	Calcium
Phosphorus	Sodium
Chloride	Potassium
Blood gases or total CO_2	Intact parathyroid hormone
25-hydroxy-vitamin D	Magnesium
	Low dose dexamethasone suppression or corticotrophin stimulation test

Urine tests

Complete urinalysis, including careful evaluation of pH and crystals
Quantitative urine culture
Consider 24-hour urine collection for:

Volume	Creatinine
Calcium	Phosphorus
Magnesium	Citric acid
Oxalic acid	

Table 41-6. Key nutritional factors for foods for the prevention of recurrence of calcium phosphate urolithiasis in dogs.*

Factors	Recommended levels
Water	Water intake should be encouraged to achieve a urine specific gravity <1.020 Moist food will increase water consumption and formation of less concentrated urine
Protein	10 to 25%
Calcium	0.4 to 0.7%
Phosphorus	0.3 to 0.6%
Ca:P ratio	1.1:1 to 2:1
Sodium	<0.3%
Magnesium	0.06 to 0.15%
Vitamin D	500 to 1,500 IU/kg
Urinary pH	6.2 to 6.6**

Key: Ca:P ratio = calcium-phosphorus ratio.
*Nutrients expressed on a dry matter basis.
**Alkaline urine is recommended for patients with distal renal tubular acidosis.

be helpful. Water intake should be encouraged to achieve a urine specific gravity <1.020.

Protein

Foods with a high protein content tend to contribute to hypocitraturia. Citric acid ions inhibit calcium phosphate crystallization. Citrate forms soluble complexes with calcium, thereby decreasing the availability of calcium for incorporation into crystals.

High-protein foods also contribute to hypercalciuria and hyperphosphaturia. Some of the consequences of eating high-protein foods result from obligatory acid excretion associated with protein metabolism. Hypercalciuria occurs in normal dogs fed high-protein foods (40% dry matter [DM]). Therefore, excessive dietary protein consumption should be avoided in dogs at risk for recurrence of calcium phosphate urolithiasis. The recommended range for dietary protein is 10 to 25% DM; the lower end of this range is probably better. The minimum recommended allowance for protein in foods for healthy adult dogs is 10% DM (NRC, 2006).

Calcium and Phosphorus

Hypercalciuria decreases calcium phosphate solubility and may result in oversaturation with calcium phosphate (Pak, 1978). Reduction of dietary calcium appears to be a logical goal for prevention of calcium phosphate urolithiasis because intestinal hyperabsorption of calcium has been identified as one mechanism promoting hypercalciuria in dogs with calcium oxalate uroliths.

Foods with higher levels of phosphorus tend to augment hyperphosphaturia and may predispose hypercalciuric patients to form calcium phosphate uroliths. However, excessive restriction of dietary phosphorus may enhance the availability of dietary calcium for intestinal absorption. It may also enhance production of 1,25-vitamin D by the kidneys, thereby promoting hypercalciuria.

The optimal levels of dietary calcium and phosphorus for dogs with calcium phosphate urolithiasis have not been determined. The following recommendations are the same as for prevention of recurrence of calcium oxalate uroliths (Chapter 40): foods for prevention of calcium phosphate urolith recurrence should contain 0.4 to 0.7% DM calcium and 0.3 to 0.6% DM phosphorus with a calcium-phosphorus ratio range of 1.1:1 to 2:1. The minimum recommended allowances for calcium and phosphorus in foods for healthy adult dogs are 0.4 and 0.3% DM, respectively (NRC, 2006). One survey of the average calcium content of numerous dry grocery brand dog foods was shown to be 1.36% DM and for moist foods 1.73% DM (Debraekeleer, 2000).

In people, some high-fiber foods have been shown to reduce intestinal absorption and urinary excretion of calcium (Menon et al, 1998).

Sodium

Foods with higher quantities of sodium and/or oral administration of sodium chloride are often empirically recommended for prevention of all forms of urolithiasis. However, such excess sodium intake may promote hypercalciuria and enhance the risk of calcium phosphate urolith formation. Therefore, oral sodium chloride therapy is not recommended to promote diuresis in dogs with uroliths containing calcium salts.

Sodium content of foods for canine patients at risk for recurrence of calcium phosphate uroliths should be moderately restricted (<0.3% DM sodium). Typically, commercial dog foods contain two to three times this amount. The minimum recommended allowance for sodium in foods for healthy adult dogs is 0.08% DM (NRC, 2006).

Magnesium

Normally, urine contains calcium phosphate crystal inhibitors. One mechanism by which inhibitors prevent urolith formation is by chelating urolith constituents, making them unavailable

for nidus formation or crystal growth. In addition, crystallization inhibitors may alter crystalline structure in such a way that crystal growth and aggregation are prevented. Magnesium ions are inhibitors of calcium phosphate crystallization (Bisaz et al, 1978; Ito and Coe, 1977).

However, increased urinary excretion of calcium by normal dogs given supplemental magnesium has been observed. Urinary calcium excretion was 0.5 ± 0.2 mg/kg body weight/day in six normal dogs consuming a food containing 0.03% DM magnesium vs. 2.65 ± 1.7 mg/kg body weight/day when the same dogs consumed a food containing 0.38% DM magnesium (Lulich, 1991b). Pending further studies, dietary magnesium restriction or supplementation is not recommended for treatment of canine calcium phosphate uroliths. A moderate range of 0.06 to 0.15% DM is recommended. The minimum recommended allowance for magnesium content of foods for healthy adult dogs is 0.06% DM (NRC, 2006).

Vitamin D

Foods with higher quantities of vitamin D or excessive supplementation with vitamin D may promote hypercalciuria (**Table 41-4**). Vitamin D promotes intestinal absorption of calcium. Commercial foods typically have adequate vitamin D content and should not be further supplemented. Excessive supplementation of homemade foods with vitamin D could also pose a risk. For prevention of calcium phosphate urolithiasis, restrict vitamin D in foods to between 500 to 1,500 IU/kg DM. The recommended minimum allowance for foods for healthy adult dogs is 552 IU/kg DM (NRC, 2006).

Urinary pH

Urinary pH profoundly affects the solubility of some forms of calcium phosphate (Elliot, 1957). With the exception of brushite, calcium phosphate solubility markedly decreases in alkaline urine and increases in acidic urine. Increased urinary pH increases the availability of ionic PO_4^{3-} and HPO_4^{2-}, which are available for incorporation into calcium phosphates (Asplin et al, 1996). Apatite will not crystallize from human urine unless the pH is 6.6 or greater (Elliot, 1968). As mentioned above, approximately 400 mg of calcium phosphate/l can be held in solution at a pH of 5.5, whereas only 32 mg of calcium phosphate/l will be held in solution at a pH of 7.8 (Elliot, 1965). Therefore, people with disorders associated with persistent elevation of urinary pH (e.g., distal RTA) are predisposed to calcium phosphate urolith formation. In contrast to carbonate apatite and hydroxyapatite, the solubility of brushite decreases in acidic urine. Acidification to the degree that induces acidosis should be avoided because it promotes hypercalciuria and hypocitraturia.

For prevention of recurrence of calcium phosphate uroliths in most patients (non-distal RTA patients and non-brushite urolith patients), the food should produce a urinary pH of 6.2 to 6.6.

Long-term alkalinization therapy appears to be beneficial in preventing calcium phosphate urolith formation in people with distal RTA (Caruana and Buckalew, 1988; Menon et al, 1998). Such therapy has been advocated for patients with complete or incomplete forms of distal RTA because it decreases urolith formation and nephrocalcinosis, and it increases urine citrate concentration.

FEEDING PLAN

Patients with primary hyperparathyroidism usually require surgery (Feldman and Nelson, 1996). Parathyroidectomy may result in dissolution of uroliths and generally prevents their recurrence. Parathyroidectomy in a dog with primary hyperparathyroidism and recurrent calcium phosphate uroliths resulted in decreased urinary calcium excretion and prevention of new urolith formation (Klausner et al, 1987).

Surgery and/or lithotripsy are the most reliable ways to remove active calcium phosphate uroliths from the urinary tract. However, surgery may be unnecessary for clinically inactive calcium phosphate uroliths. Voiding urohydropropulsion may be used to remove small urocystoliths (Figure 38-5 and Table 38-7) (Lulich et al, 1993). Although calcium-chelating agents have been reported to be of value in dissolving calcium phosphate uroliths in people, the feasibility of this type of therapy has not yet been reported in dogs and cats.

The frequency of recurrence of calcium phosphate uroliths following removal is not well established. However, unless the underlying cause(s) have been eliminated or controlled, recurrence is likely. Therefore, patients should be periodically monitored by urinalysis, radiographic procedures, and, if indicated, blood and urine tests (**Table 41-7**). If recurrent urocystoliths are detected when they are small, they may be removed by nonsurgical means as described above. Dietary or combined dietary and medical therapy of patients with recurring calcium phosphate uroliths should then be directed at removing or minimizing risk factors that contribute to supersaturation of urine with calcium phosphate.

Assess and Select the Food

Formulation of an optimal food remains a goal for the future. Until such a food becomes available, it is reasonable to recommend trial therapy with foods that most nearly match the key nutritional factor recommendations. **Table 41-8** lists selected veterinary therapeutic foods that can be considered for prevention of calcium phosphate urolith recurrence and compares their key nutritional factor content to the recommended levels. Select the food that most closely matches the key nutritional factor levels described above for preventing the recurrence of calcium phosphate uroliths. Because these foods are intended for long-term feeding, they should also be approved by the Association of American Feed Control Officials (AAFCO), or some other credible regulatory agency. Dogs consuming dry foods may be at greater risk for urolithiasis than dogs consuming moist foods. Dry foods are often associated with higher urine concentrations of urolith constituents and more concentrated urine. Therefore, when possible, moist foods should be selected.

The sodium content of treats should be checked. Treats should not contain more than 0.3% DM sodium and they should be limited to less than 10% of the total food regimen

Table 41-7. Summary of recommendations for managing canine calcium phosphate uroliths.

1. Surgery remains the most reliable way to remove active calcium phosphate uroliths from the urinary tract. However, surgery may be unnecessary for clinically inactive calcium phosphate uroliths. Small urocystoliths may be nonsurgically removed by lithotripsy, voiding urohydropropulsion (Figure 38-5 and Table 38-7) or by aspiration through a urinary catheter (Figure 38-6). Medical therapy of patients with recurrent calcium phosphate uroliths should then be directed at removing or minimizing risk factors that contribute to supersaturation of urine with calcium phosphate.
2. Patients with hypercalcemia and primary hyperparathyroidism usually require surgery. Parathyroidectomy may result in dissolution of uroliths and prevent recurrence in cases that have been properly managed.
3. Several different medical protocols have been reported to be of value in people with normocalcemic hypercalciuria. Ideally, the choice of therapy should be based on the cause of idiopathic hypercalciuria.
   a. There has been little clinical experience with the use of drugs in dogs and cats with calcium phosphate uroliths. However, medications that can enhance urine calcium excretion such as glucocorticoids, furosemide and those containing large quantities of sodium should be avoided (if possible).
   b. Foods designed to avoid excessive protein, sodium, calcium and vitamin D may be of benefit. Excessive restriction or supplementation of dietary phosphorus should probably be avoided. Enhancing urine volume by feeding a moist food (and/or a protein-restricted food to dogs to reduce renal medullary urea concentrations) and encouraging water consumption may be of benefit. Although understandably difficult to accomplish in some patients, fluid intake should be encouraged throughout the day to promote a constantly high urine volume. In people, some high-fiber diets reduce intestinal absorption and urinary excretion of calcium.
   c. With the exception of brushite, calcium phosphates tend to be less soluble in alkaline urine. Whether or not patients with such mineral types would benefit from appropriate dosages of urine acidifiers is unknown. Acidification tends to enhance urine calcium excretion and is a risk factor for calcium oxalate urolith formation. Pending further studies, routine use of urine acidifiers for patients with calcium phosphate urolithiasis is not recommended.
4. Medical dissolution of calcium phosphate uroliths has not been attempted in dogs with distal renal tubular acidosis (RTA). Foods designed to dissolve struvite uroliths would generally not be expected to promote dissolution of calcium phosphate uroliths, in part because they may tend to promote acidemia and aciduria, thus potentially enhancing hypercalciuria and hypocitraturia. However, correction of hypercalciuria, hyperphosphaturia and hypocitraturia by alkalinization therapy with potassium citrate might promote dissolution of these uroliths in patients with complete or incomplete distal RTA. Long-term alkalinization therapy appears to be beneficial in preventing calcium phosphate urolith formation in people with distal RTA. Alkalinization of urine has been advocated for human patients with complete or incomplete forms of distal RTA because it decreases urolith formation and nephrocalcinosis and increases urine citrate concentration. Oral administration of sodium chloride, long recommended for all forms of urolithiasis, may promote hypercalciuria and calcium phosphate urolith formation. Therefore, oral salt therapy is not recommended to promote diuresis in dogs with uroliths containing calcium salts.

(volume or weight basis).

Moderate urinary acidification is recommended for prevention of recurrent calcium phosphate uroliths in most patients. However, for distal RTA patients, long-term alkalinization therapy appears to be beneficial.

Another criterion for selecting a food that may become increasingly important in the future is evidence-based clinical nutrition. Practitioners should know how to determine risks and benefits of nutritional regimens and counsel pet owners accordingly. Currently, veterinary medical education and continuing education are not always based on rigorous assessment of evidence for or against particular management options. Still, studies have been published to establish the nutritional benefits of certain pet foods. Chapter 2 describes evidence-based clinical nutrition in detail and applies its concepts to various veterinary therapeutic foods.

Assess and Determine the Feeding Method

Transitioning a patient from the current food to a new food to help prevent recurrence of calcium phosphate uroliths should be done gradually. Begin the transition by feeding 75% of the current food and 25% of the new food on Day 1. On Day 2, feed half of each food. On Day 3, feed 75% of the new food and 25% of the old food. Feed only the new food beginning on Day 4.

Because moist foods increase water intake and produce a more dilute urine, feeding specific amounts (meal fed) of food two to three times per day is preferred to free-choice feeding. Moist foods can spoil if left at room temperature for several hours (Chapter 11). Opened containers of moist foods should be refrigerated and the feeding bowl should be kept clean.

Besides offering moist foods, several additional ways can facilitate increased water intake. These include: 1) Ensuring multiple bowls are available in prominent locations in the dog's environment; this may mean providing several bowls outside in a large enclosure or a bowl on each level of the house. 2) Bowls should be clean and always be filled with fresh water. 3) Small amounts of flavoring substances (e.g., salt-free bouillon) can be added to water sources. 4) Ice cubes can be offered as treats or snacks. 5) If a dry food is selected, add liberal quantities of water; however, potential food safety issues might arise from leaving moistened dry foods out for prolonged intervals (Chapter 11).

If the patient has a normal body condition score (BCS 2.5/5 to 3.5/5), the amount fed previously was probably appropriate. On an energy basis, a similar amount of the new food would be a good starting place.

ADJUNCTIVE MEDICAL AND SURGICAL MANAGEMENT

Urine Acidifying and Alkalinizing Agents

With the exception of brushite, calcium phosphates tend to be less soluble in alkaline urine. Acidification reduces urine concentrations of ionic phosphate (PO_4^{3-}) and hydroxyl ions (OH^-). However, whether or not patients with calcium phos-

Table 41-8. Levels of key nutritional factors in selected commercial veterinary therapeutic foods used to minimize recurrence of calcium phosphate urolithiasis in dogs compared to recommended levels.*

Dry foods	Protein (%)	Calcium (%)	Phosphorus (%)	Ca:P ratio	Sodium (%)	Magnesium (%)	Vitamin D (IU/kg)	Urinary pH
Recommended levels	**10-25**	**0.4-0.7**	**0.3-0.6**	**1.1:1-2:1**	**<0.3**	**0.06-0.15**	**500-1,500**	**6.2-6.6****
Hill's Prescription Diet c/d Canine	22.3	0.82	0.59	1.4:1	0.28	0.111	618	6.22
Hill's Prescription Diet w/d Canine	18.9	0.66	0.56	1.2:1	0.22	0.088	632	6.40
Hill's Prescription Diet w/d with Chicken Canine	19.1	0.66	0.56	1.2:1	0.27	0.080	677	6.30
Medi-Cal Urinary SO 13	16.7	1.0	**0.6**	na	1.3	0.2	na	5.5-6.0
Moist foods	**Protein (%)**	**Calcium (%)**	**Phosphorus (%)**	**Ca:P ratio**	**Sodium (%)**	**Magnesium (%)**	**Vitamin D (IU/kg)**	**Urinary pH**
Recommended levels	**10-25**	**0.4-0.7**	**0.3-0.6**	**1.1:1-2:1**	**<0.3**	**0.06-0.15**	**500-1,500**	**6.2-6.6****
Hill's Prescription Diet c/d Canine	23.6	0.68	0.51	1.3:3	0.27	0.079	1,370	6.16
Hill's Prescription Diet w/d Canine	17.9	0.64	0.52	1.2:1	0.24	0.088	1,745	6.40
Medi-Cal Urinary SO	18.7	1.0	0.8	na	1.1	0.1	na	5.5-6.0

Key: na = information not available from the manufacturer.
*This list represents products with the largest market share for which published information is available. Nutrient levels expressed on a dry matter basis. Moist foods are best.
**Alkaline urine recommended for patients with distal renal tubular acidosis.

phate uroliths would benefit from appropriate dosages of urine acidifiers is unknown. Overacidification tends to enhance urine calcium excretion and is a risk factor for calcium oxalate urolith formation. Pending further studies, we do not recommend routine use of urine acidifiers with urine acidifying foods for patients with calcium phosphate urolithiasis.

Because calcium hydrogen phosphate dihydrate (brushite) is less soluble in acidic urine, it might seem logical to promote formation of alkaline urine in patients with brushite uroliths. However, brushite may be converted to other insoluble forms of calcium phosphate in alkaline urine (Pak et al, 1971). Use of potassium citrate, an alkalinizing agent, might be rationalized on the basis of minimizing acidosis-induced hypercalciuria, and formation of soluble calcium citrate rather than insoluble calcium phosphate in urine. The benefits or detrimental effects of orally administered potassium citrate to dogs and cats with calcium phosphate urolithiasis, however, have not been carefully evaluated. Consult Chapter 40 (canine calcium oxalate urolithiasis) for additional therapeutic information about potassium citrate.

Thiazide Diuretics

Because thiazide diuretics decrease renal calcium excretion, they may be considered to minimize renal-leak hypercalciuria (Pak, 1982). However, because the long-term effects of thiazide diuretics have not been reported, appropriate caution should be used when giving them to prevent recurrence of calcium-containing uroliths. Patients should be monitored for dehydration, hypercalcemia, hypokalemia and magnesium depletion. Hydrochlorothiazide may be given on a trial basis at a dosage of 2 to 4 mg/kg body weight q12h. Thiazide diuretic therapy is not recommended to treat absorptive hypercalciuria because it does not correct the hyperabsorptive state and may promote positive systemic calcium balance that in turn would predispose the patient to soft-tissue calcification.

Other Drugs

Other drugs have been used in an attempt to minimize hypercalciuria in people (Asplin et al, 1996). Sodium cellulose phosphate, the sodium salt of the phosphoric ester of cellulose, is an ion-exchange cellulose with special affinity for divalent ions. In the gastrointestinal tract it exchanges sodium for dietary calcium, which is then eliminated in the feces. It also binds calcium secreted into the gastrointestinal tract, minimizing its reabsorption. Oral administration of orthophosphates to people with normocalcemic hypercalciuria reduces urine excretion of calcium and increases urine crystal inhibitory activity by increasing the urine concentration of pyrophosphates (Pak, 1982). We have had minimal experience with the use of sodium cellulose phosphate.

REASSESSMENT

Therapy should be initiated in a stepwise fashion (**Table 41-7**). The likelihood of recurrence of calcium phosphate uroliths following removal is not well established. Therefore, patients should be periodically monitored by urinalysis, radiographic or ultrasonographic procedures and other hematologic and urologic laboratory tests, as indicated (**Table 41-7**). Small, recurrent urocystoliths may be removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7) (Lulich et al, 1993), by aspi-

ration through a urinary catheter (Figure 38-6) (Lulich and Osborne, 1992) or by lithotripsy. Dietary and combined dietary and medical therapy of patients with recurring calcium phosphate uroliths should be directed at removing or minimizing risk factors that contribute to supersaturation of urine with calcium phosphate.

REFERENCES

The references for **Chapter 41** can be found at www.markmorris.org.