Article

Analysis of canine urolith submissions to the Canadian Veterinary Urolith Centre, 1998–2014

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Abstract — Understanding urolith trends and risk factors is important for understanding urolithiasis, which is a common problem in dogs. This study evaluated 75 674 canine cystolith submissions to the Canadian Veterinary Urolith Centre between 1998 and 2014. Struvite and calcium oxalate uroliths comprised 80.8% of all uroliths, with calcium oxalate outnumbering struvite. There were significant increases in the proportions of calcium oxalate, mixed and cystine uroliths, and significant decreases in struvite, urate, silica, and calcium phosphate carbonate over the study period. Breeds associated with increased risk of calcium oxalate urolithiasis tended to be small breeds, while those that were at increased risk of struvite urolith formation were larger breeds. Dalmatians were at increased risk of forming both urate and xanthine uroliths while Scottish deerhounds had a remarkably high association with cystine urolithiasis. Males were more likely to form calcium oxalate and metabolic uroliths and females were more likely to develop struvite and mixed uroliths.

Résumé — Analyse des soumissions d'urolithes canins au Canadian Veterinary Urolith Centre, 1998–2014. Il est important de comprendre les tendances et les facteurs de risque des urolithes pour comprendre l'urolithiase, qui est un problème fréquent chez les chiens. Cette étude a évalué 75 674 soumissions d'urolithes canins au Canadian Veterinary Urolith Centre entre 1998 et 2014. Les urolithes de struvite et d'oxalate de calcium représentaient 80,8 % de tous les urolithes, et le nombre de soumissions d'oxalate de calcium dépassait celui des soumissions de struvite. Il y avait des hausses importantes dans les proportions d'oxalate de calcium, des urolithes mixtes et de cystine et des baisses importantes de la struvite, de l'urate, de la silice et du carbonate de phosphate de calcium pendant la période à l'étude. Les races associées à un risque accru d'urolithiase d'oxalate de calcium étaient surtout des petites races tandis que celles qui présentaient un risque accru de formation d'urolithes de struvite étaient les grandes races. Les Dalmatiens présentaient un risque accru de formation d'urolithes d'urate et de xanthine tandis que les Deerhounds avaient une association remarquablement élevée avec l'urolithiase de cystine. Il était plus probable que les mâles forment des urolithes d'oxalate de calcium et des urolithes métaboliques et il était plus probable que les femelles développent des urolithes de struvite et mixtes.

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Introduction

Urolithiasis is an important problem in dogs and cystoliths of various compositions can be encountered. While relative proportions of urolith types vary, struvite (magnesium ammonium phosphate hexahydrate) and calcium oxalate are the predominant types, followed by ammonium urate/uric acid (1–8). Various other urolith types, such as calcium phosphate, silica, xanthine, cystine, and sodium pyrophosphate are uncommon.

Understanding factors associated with urolith formation is important for client counseling and implementation of control measures. Breed predilections worldwide for canine struvite and calcium oxalate urolithiasis have been reported to include a number of small breed dogs (2,3,5,9). The Dalmatian breed is over represented with urate uroliths (3,7). Gender predispositions have also been reported, with calcium oxalate and urate uroliths tending to occur in male dogs and struvite in females (3,10).

The incidence of urolithiasis and ability of veterinarians to submit uroliths for analysis results in accumulation of large amounts of data regarding canine urolithiasis. Analysis of large datasets can provide additional insight into risk factors and trends in canine urolithiasis. The objectives of this study were to describe the composition of uroliths submitted to the Canadian Veterinary Urolith Centre (CVUC) from 1998 to 2014, to evaluate changes in urolith types in Canadian dogs over time, and to evaluate associations of breed and gender with urolith types in Canadian submissions.

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Materials and methods

A computer-assisted search of data from questionnaires submitted to the CVUC was used to compile information about all urinary bladder calculi from dogs analyzed between February 1, 1998 and November 30, 2014. Uroliths could have been surgically removed, naturally voided, voided with assistance, or fragmented with lithotripsy and removed. Urethral plugs and uroliths from the upper urinary tract were excluded.

Urolith composition was assessed using various assays. After sectioning, each layer was analyzed by optical crystallography, using polarized light microscopy. If additional clarification was needed, another technique such as X-ray microanalysis coupled with scanning electron microscopy or Fourier transformation infrared spectroscopy was used. Uroliths consisting of at least 70% of a single mineral were classified as that mineral type. If 2 mineral types were present in separate, distinct layers within the same urolith, the urolith was classified as compound. Uroliths containing < 70% of a single mineral component and without an obvious nidus or surface layers were classified as mixed. Uroliths comprised of calcium oxalate monohydrate or calcium oxalate dihydrate or both were classified as calcium oxalate. Uroliths comprised of any of the salts of uric acid (ammonium, potassium, and sodium acid urate) were classified as urate. Calcium phosphates represented calcium phosphate apatite, calcium phosphate carbonate, and brushite.

Changes in proportions of urolith types over time were assessed using linear regression. Associations between breed and urolith type were evaluated using logistic regression analyses, with mixed breed dogs as the referent for breed and urolith comparisons involving the targeted urolith compared to other urolith types combined. Odds ratios and 95% confidence intervals (CI) were calculated for breeds for which a significant association was identified. The association between gender and urolith type was also evaluated using logistic regression. A P-value of < 0.05 was considered significant for all comparisons. Statistical analyses were performed using JMP 11 (SAS Institute, Toronto, Ontario).

Results

A total of 101 391 uroliths were submitted to the CVUC from Feb 1, 1998 to November 30, 2014. Of these, 79 965 (78.9%) were from dogs, with 75 674 (94.6%) of those from Canada and 4291 (5.4%) from other countries.

Of the 75 674 Canadian submissions, 42 581 (56%) were from females, 32 530 (43%) were from males, while gender was not reported for 563. Calcium oxalate was the most common submission (n = 34 270, 45%), followed by struvite (27 086, 36%), mixed (7782, 10.3%), ammonium urate (2445, 3.2%) and compound (1632, 2.2%) (Table 1). Ammonium urate uroliths consisted of ammonium urate (2270/2445, 93%), sodium urate (95 2445, 3.9%), and uric acid (80/2445, 3.3%).

During the study period, there was a significant increase in the prevalence of calcium oxalate (P = 0.016) and a significant decrease in struvite ($P < 0.0001$) submissions (Figure 1). There were also significant increases in the prevalence of mixed ($P < 0.0001$) and cystine ($P < 0.0001$) uroliths and decreases in urate ($P < 0.001$), silica ($P < 0.0001$), and calcium phosphate carbonate ($P \leq 0.0001$) uroliths over the study period, but no change in the other urolith types.

Table 1. Composition of 75 674 uroliths from Canadian dogs submitted to the Canadian Veterinary Urolith Centre between February 1, 1998 and November 30, 2014

	Number of submissions	% of submissions
Struvite	27 086	35.8
Calcium oxalate	34 270	45.3
Urate	2445	3.2
CaP	1432	1.9
Silica	511	0.7
Cystine	480	0.6
Xanthine	36	0.05
Compound	1632	2.2
Other/mixed (until 2013 included compound)	7782	10.3
Totals	75 674	100

Females were over-represented amongst struvite ($P < 0.0001$), mixed ($P < 0.0001$), calcium phosphate carbonate ($P < 0.001$), and compound (P = 0.0002) submissions, while males were significantly associated with calcium oxalate, urate, cystine, silica, and calcium phosphate apatite (all $P < 0.0001$).

Breed associations are presented in Tables 2 to 4. There were no breed associations for silica uroliths. Breed associations were not investigated for compound or mixed uroliths because of the non-homogenous nature of those urolith types.

Twenty-three breeds were associated with calcium oxalate stone urolith submissions. Of these, 17 (74%) were small breed dogs including the miniature schnauzer, bichon frise, Yorkshire terrier and Lhasa apso, while 3/17 (18%) breeds associated with struvite uroliths were classified as small breed dogs (Pekingese, pug, and shih tzu).

The Dalmatian was at highest risk for urate urolithiasis (926/988; 93.7%) with males accounting for 98% of the urate submissions. The Dalmatian was the only breed identified at risk for xanthine. Cystine uroliths were most common in the Scottish deerhound, mastiff, and Newfoundland dog. Calcium phosphate urolith associations mainly involved small breed dogs and in particular, the papillon, pomeranian, bichon frise, and lhaso apso breeds.

Discussion

Analysis of large databases such as this can allow for detailed study of factors associated with urolithiasis and identify novel associations, as was apparent here. The significant increase in calcium oxalate submissions from Canada is consistent with a change that has been noted in many countries since the early to mid 2000s, with predominance of calcium oxalate submissions in most countries (1,3,5,6,11). This is a change from earlier timepoints, during which struvite submissions tended to predominate internationally (2,6,8,10,12). Reasons for this change have not been specifically studied, but it could be, in part, a result of increasing medical management to dissolve struvite uroliths with continued surgical removal of (undissolvable) calcium oxalate uroliths. Another possible reason is more prompt

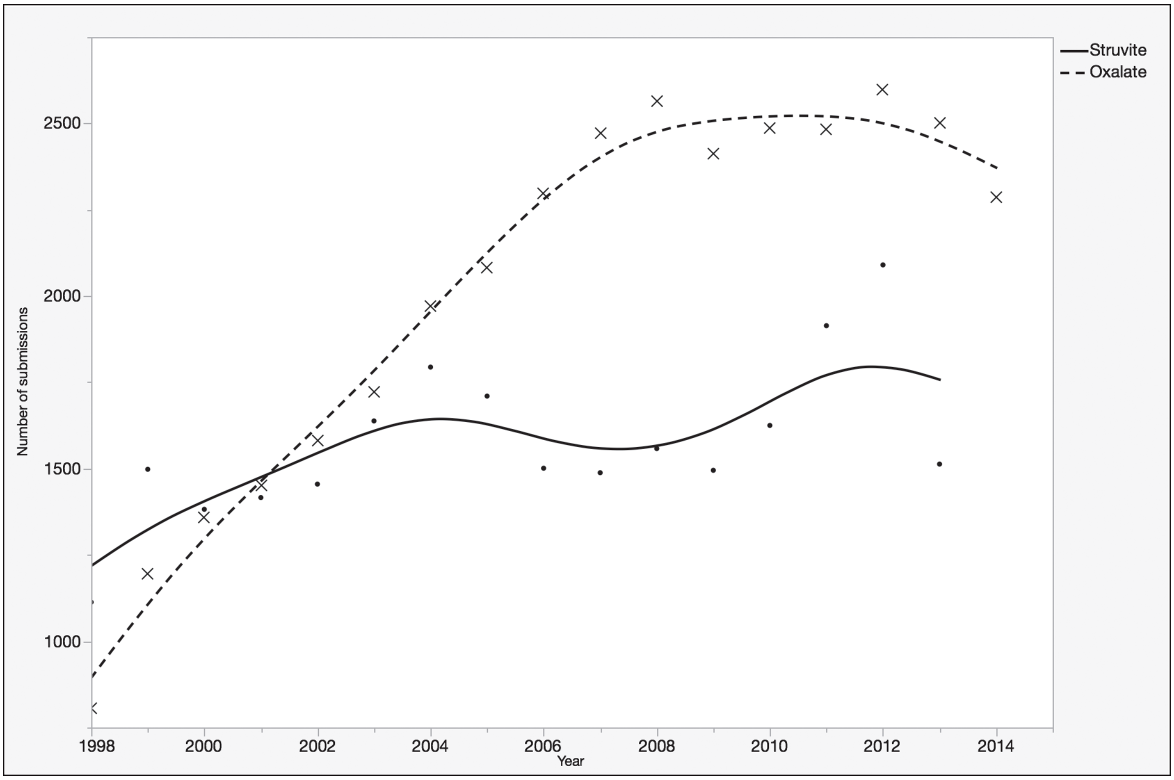

Figure 1. Changing trend for struvite and calcium oxalate urolith submissions in dogs from February 1, 1998 to December 31, 2013.

or effective diagnosis and treatment of urinary tract infections, as struvite urolithiasis is often associated with infection.

Alternatively, or additionally, the changing ratio of calcium oxalate:struvite urolith submissions could relate to a true increase in calcium oxalate urolithiasis. Theories on the cause of the increasing incidence of calcium oxalate over the last couple of decades include changes in dietary content of calcium, magnesium, phosphorus, or calcium oxalate, decreased water consumption, an increase in sedentary lifestyles of many dogs, and an aging population of small breed dogs that are more prone to calcium oxalate uroliths.

Previous publications have reported a predisposition for both struvite and calcium oxalate uroliths in toy and small breeds (1,7,10,11). In the present study, toy and small breeed dogs accounted for most of the breeds that were significantly associated with calcium oxalate urolithasis compared to mixed breed dogs, while struvite uroliths tended to be over-represented in medium and large breed dogs, most notably the Saint Bernard, Labrador retriever, and golden retriever.

The breed predispositions for calcium oxalate uroliths identified here are consistent with small breed predispositions reported in other regions of the world. The predisposition of small breed dogs is not fully understood but may include size or breed associated differences in mineral metabolism and urine composition. For example, miniature schnauzers urinate significantly less often and have a smaller urine volume than Labrador retrievers, leading to a more concentrated urine that is retained longer in the bladder and has higher urinary calcium and oxalate concentrations (13–15). Hypercalciuria is associated with calcium oxalate urolithiasis in the miniature schnauzer, bichon frise, and shih tzu. Genetic mapping in the miniature schnauzer identified *Slc39a10* as a potential calcium oxalate susceptibility gene (16) and it is possible that similar genetic factors could account for calcium oxalate predispositions in other breeds.

The male predisposition to calcium oxalate was expected as it has been previously reported in dogs (17) and humans (18). In humans and rats, an association between testosterone and calcium urolithiasis has been identified (19). However, castration should reduce or negate this effect, and most of the male dogs were castrated. The predisposition may simply reflect a lower risk of infection-associated struvite uroliths in male dogs, leaving them over-represented in metabolic urolith groups. Obesity may also be a contributor to earlier onset of calcium oxalate urolithiasis in high risk breeds (20). Body condition data were not available to assess this.

The association of struvite uroliths with female dogs is consistent with the infection-associated nature of struvite uroliths. However, urinary tract infections can occur in any breed and reasons for breed associations with struvite urolithiasis have been minimally investigated. In a previous study, the odds of struvite urolithiasis were approximately 3.0 times as great in toy-breed dogs and 2.4 times as great in small-breed dogs, compared with medium-breed dogs, but were not significantly different between medium- and large-breed dogs (21). This is in contrast with the current study in which many medium and large breeds were identified as predisposed.

The reason that the proportion of urate submissions significantly decreased during the study period is unclear. This is in contrast to somewhat older data from the UK, in which the relative frequency of urate increased from 7% to 12% over a 10-year

Table 2. Significant associations between calcium oxalate and breed among 75 674 uroliths from dogs

Urolith type	Breed	Prevalence	Odds ratio (95% CI)	*P*-value
Calcium oxalate	Bichon frise	3133/7215 (43.4%)	1.1 (1.05 to 1.18)	< 0.0001
	Boston terrier	55/102 (54%)	1.7 (1.1 to 2.5)	0.0078
	Cairn terrier	251/356 (71%)	3.5 (2.8 to 4.4)	< 0.0001
	Cavalier King Charles spaniel	102/217 (47%)	1.3 (1.0 to 1.7)	0.049
	Chihuahua	629/921 (68%)	3.5 (3.0 to 4.0)	< 0.0001
	Doberman pinscher	69/108 (64%)	2.6 (1.7 to 3.8)	< 0.0001
	Fox terrier	125/158 (79%)	5.5 (3.8 to 8.2)	< 0.0001
	Havanese	118/238 (50%)	1.4 (1.1 to 1.8)	0.008
	Jack Russell terrier	793/1322 (60%)	2.2 (1.9 to 2.4)	< 0.0001
	Keeshond	52/97 (54%)	1.7 (1.1 to 2.5)	0.0113
	Kerry blue terrier	29/42 (69%)	3.2 (1.7 to 6.4)	0.0002
	Lhasa apso	1609/2577 (62%)	2.4 (2.2 to 2.6)	< 0.0001
	Maltese	601/842 (71%)	3.6 (3.1 to 4.2)	< 0.0001
	Miniature pinscher	186/254 (73%)	4.0 (3.0 to 5.3)	< 0.0001
	Miniature poodle	620/1097 (57%)	1.9 (1.6 to 2.1)	< 0.0001
	Miniature schnauzer	6039/9309 (65%)	2.7 (2.5 to 2.8)	< 0.0001
	Papillon	255/370 (69%)	3.2 (2.6 to 4.0)	< 0.0001
	Pomeranian	1182/1640 (72%)	3.7 (3.4 to 4.2)	< 0.0001
	Standard poodle	152/257 (59%)	2.1 (1.6 to 2.7)	< 0.0001
	Portuguese water dog	75/108 (69%)	3.3 (2.2 to 5.0)	< 0.0001
	Schnauzer	117/164 (71%)	3.6 (2.6 to 5.1)	< 0.0001
	Wire fox terrier	47/58 (81%)	6.2 (3.3 to 13)	< 0.0001
	Yorkshire terrier	1677/2720 (62%)	2.3 (2.1 to 2.5)	< 0.0001
	Mixed breed	8789/21 468 (41%)	Ref	

Ref — referent.

Table 3. Significant associations between struvite and breed among 75 674 uroliths from dogs

Urolith type	Breed	Prevalence	Odds ratio (95% CI)	*P*-value
Struvite	Australian shepherd	49/79 (62%)	2.3 (1.5 to 3.6)	0.0003
	Beagle	244/425 (57%)	1.9 (1.6 to 2.3)	< 0.0001
	Bernese mountain dog	75/117 (64%)	2.5 (1.7 to 3.7)	< 0.0001
	Border collie	112/154 (64%)	3.7 (2.6 to 5.4)	< 0.0001
	Boxer	65/96 (68%)	2.9 (1.9 to 4.6)	< 0.0001
	Chow chow	86/124 (69%)	3.2 (2.2 to 4.7)	< 0.0001
	Cocker spaniel	464/690 (67%)	2.9 (2.5 to 3.4)	< 0.0001
	Corgi	141/206 (68%)	2.9 (2.0 to 4.1)	< 0.0001
	German shepherd	109/163 (67%)	2.8 (2.0 to 3.9)	< 0.0001
	Golden retriever	281/365 (77%)	4.7 (3.7 to 6.0)	< 0.0001
	Labrador retriever	443/550 (81%)	5.8 (4.7 to 7.2)	< 0.0001
	Pekingese	262/485 (54%)	1.7 (1.4 to 2.0)	< 0.0001
	Pug	1014/1842 (55%)	1.7 (1.6 to 1.9)	< 0.0001
	Rottweiler	109/151 (72%)	3.6 (2.6 to 5.2)	< 0.0001
	Saint Bernard	12/13 (92%)	17 (3.3 to 306)	< 0.0001
	Scottish terrier	87/127 (69%)	3.1 (2.1 to 4.6)	< 0.0001
	Shih tzu	5132/11 212 (46%)	1.1 (1.05 to 1.2)	0.0003
	Mixed breed	8911/21 468 (42%)	Ref	

Ref — referent.

period (1997 to 2006) (12). The most common breed for urate urolithiasis remains the Dalmatian and a hyperuricosuria genetic mutation responsible for that has been identified (22). While the focus of this mutation has been on Dalmatians, it has been identified in some other breeds, including giant schnauzers and Jack Russell terriers (22), 2 of the breeds identified as over-represented in this study.

Cystine uroliths continued to be uncommon. Breeds reported to be at risk include the Newfoundland, Scottish deerhound, English bulldog, Chihuahua, and Staffordshire bull terrier (12). All except the Staffordshire bull terrier were also identified as associated with cystine uroliths in this study, in addition to a number of other breeds. While the number of submissions was small, the odds ratios were remarkable for many breeds, including the Scottish deerhound (OR 2203), basenji (OR 275), mastiff (OR 346), Newfoundland (OR 394), and whippet (OR 252), strongly supportive of a genetic link. Recently, a classification scheme for dogs with cystinuria based on mode of inheritance, androgen dependence, and genetics has been published and it is hoped that screening and selective breeding will ultimately diminish cystine urolith submission numbers (23).

It is important to remember that these data do not indicate breed-level associations with urolithiasis, as that would require corresponding breed incidence data from dogs without uroliths. Rather, this study identified breeds at increased risk of certain urolith types, compared with a referent population, mixed breed dogs. As with any study, the study population must be considered. Since CVUC analysis is performed at no cost to

Table 4. Significant associations between cystine, xanathine, urate, and calcium phosphate uroliths and breed among 75 674 uroliths from dogs

Urolith type	Breed	Prevalence	Odds ratio (95% CI)	*P*-value
Cystine	Basenji	7/15 (47%)	275 (94 to 788)	< 0.0001
	Bull mastiff	5/21 (24%)	98 (31 to 259)	< 0.0001
	Bulldog	44/183 (24%)	100 (66 to 150)	< 0.0001
	Chihuahua	32/921 (3.5%)	11 (7.3 to 17)	< 0.0001
	Dachshund	39/985 (4%)	12 (8.3 to 18)	< 0.0001
	English bulldog	53/247 (21%)	86 (58 to 126)	< 0.0001
	French bulldog	24/74 (32%)	151 (87 to 258)	< 0.0001
	Great Dane	7/26 (27%)	116 (44 to 273)	< 0.0001
	Mastiff	11/21 (52%)	346 (141 to 857)	< 0.0001
	Miniature pinscher	16/252 (6.3%)	21 (12 to 36)	< 0.0001
	Newfoundland	20/36 (56%)	394 (196 to 802)	< 0.0001
	Pit bull	16/62 (26%)	109 (58 to 199)	< 0.0001
	Scottish deerhound	7/8 (88%)	2203 (385 to 41 463)	< 0.0001
	Whippet	4/9 (44%)	252 (61 to 972)	< 0.0001
	Mixed breed	68/21 468 (0.32%)	Ref	
Xanthine	Dalmatian	8/991 (0.81%)	24 (8.9 to 71)	< 0.0001
	Mixed breed	7/21 468 (0.03%)	Ref	
Urate	American bulldog	21/29 (72%)	226 (103 to 549)	< 0.0001
	Black Russian terrier	8/13 (62%)	138 (46 to 459)	< 0.0001
	Bulldog	67/183 (37%)	9.1 (1.4 to 31)	< 0.0001
	Chihuahua	29/921 (3.2%)	2.8 (1.8 to 4.1)	< 0.0001
	Dachshund	22/1024 (2.2%)	1.8 (1.1 to 2.8)	0.0132
	Dalmatian	928/991 (94%)	1270 (962 to 1704)	< 0.0001
	English bulldog	92/247 (37%)	51 (38 to 68)	< 0.0001
	Giant schnauzer	3/7 (43%)	65 (12.7 to 295)	< 0.0001
	Havanese	10/239 (4.2%)	3.8 (1.8 to 6.8)	0.001
	Jack Russell terrier	42/1322 (3.2%)	2.8 (2.0 to 3.9)	< 0.0001
	Miniature schnauzer	166/9308 (1.8%)	1.6 (1.3 to 1.9)	< 0.0001
	Pekingese	15/485 (3.1%)	2.8 (1.6 to 4.5)	0.0011
	Pit bull	21/62 (34%)	44 (25 to 75)	< 0.0001
	Pug	62/1842 (3.4%)	3.0 (2.2 to 4.0)	< 0.0001
	Shih tzu	281/11 212 (2.5%)	2.1 (1.8 to 2.5)	< 0.0001
	Yorkshire terrier	162/2720 (6.0%)	5.5 (4.4 to 6.7)	< 0.0001
	Mixed breed	255/21468 (1.2%)	Ref	
Calcium phosphate	Bichon frise	196/7215 (2.7%)	1.5 (1.3 to 1.8)	< 0.0001
	Lhasa apso	71/2577 (2.8%)	1.5 (1.2 to 2.0)	0.002
	Papillon	22/370 (6.0%)	3.4 (2.1 to 5.2)	< 0.0001
	Pomeranian	62/1640 (3.8%)	2.1 (1.6 to 2.8)	< 0.0001
	Mixed breed	391/21 468 (1.8%)	Ref	

Ref — referent.

the veterinary clinic or owner, potential submission biases are reduced. However, it is possible that there is still some submission bias if veterinarians select uroliths to submit. It is more likely, though, that such bias would decrease the ability to detect associations that have been previously reported, since it could lead to decreased submission of uroliths from known at risk breeds on the assumption that the urolith type can be readily predicted (e.g., urate uroliths in Dalmatians). Accordingly, this should not impact the numerous new associations that were identified.

Continued study of factors associated with urolithiasis is important to better understand and manage this common condition. In particular, identifying breed associations can be useful for client counseling and targeted study to identify genetic predispositions and potentially allow for eradication or reduction in some breed predispositions. Changes in urolith trends occur, as noted here, and determining reasons for those trends might also be useful for management and client education. This study has identified numerous associations that require further study to better manage urolithiasis in dogs.

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