Comparison of urine composition of healthy Labrador Retrievers and Miniature Schnauzers

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Objective—To compare urine composition in Labrador Retrievers (LR) and Miniature Schnauzers (MS) fed the same dog food.

Animals—8 healthy LR (mean [± SD] age, 3.1 ± 1.7 years) and 8 healthy MS (mean age, 3.7 ± 1.3 years).

Procedure—A nutritionally complete dry dog food was fed to the dogs for 24 days. Urinary pH, volume, specific gravity, frequency of urination, and urinary concentrations of 12 analytes were measured for each dog; urinary relative supersaturation (RSS) with calcium oxalate and brushite (calcium hydrogen phosphate dihydrate) were calculated from these values.

Results—MS urinated significantly less often and had a lower urine volume (ml/kg of body weight per d) and a significantly higher urine pH, compared with LR. Urinary calcium concentration and brushite RSS were significantly higher in the urine of MS. As a result of a high calorie requirement, primarily as a result of high surface area to volume ratio, MS had significantly higher intake (per kg body weight) of dietary minerals, compared with LR.

Conclusions and Clinical Relevance—Differences in urine composition exist between breeds fed the same diet, some of which, including lower urine volume, higher calcium concentration, and higher brushite RSS, may contribute to the high prevalence of calcium oxalate uroliths observed in MS. Differences between breeds should be considered when evaluating strategies for controlling calcium oxalate stone formation. (*Am J Vet Res* 2001;62:1782–1786)

Uroliths composed primarily of struvite (magnesium ammonium phosphate) or **calcium oxalate (CaOx)** are the types found most commonly in dogs. Struvite represented approximately 50% of canine uroliths submitted for analysis during a 17-year period at 1 center.[1] The underlying cause of struvite formation in most dogs is the presence of a urinary tract infection with urease producing bacteria such as *Staphylococcus intermedius* or *Proteus* spp.[a] Calcium oxalate was the second most common mineral type found in uroliths submitted to this center, making up 31% of the total.[1] Calcium oxalate uroliths can be pure, but more commonly present in combination with variable amounts of calcium phosphate, or less commonly with struvite or ammonium acid urate.[1] The proportion of CaOx uroliths submitted has increased over time from 5.3% in 1981 to 35.1% in 1997.[2] The reasons behind this increase are not known. Over the years, as the understanding of the pathophysiologic changes associated with struvite urolithiasis formation has increased, the management and prevention of this urolith type has increased. As a result, struvite formation and the submission of struvite uroliths for analysis may have decreased, resulting in a proportional increase in calcium oxalate uroliths.[3] Other possible reasons include the fact that dogs are living longer and CaOx formation is documented to develop more commonly in old dogs[2,3] Thus, it is logical to postulate that the prevalence of CaOx would increase. As the lifestyle of humans has changed within the developed world, a relative increase in CaOx urolith formation has also been documented.[4] Common links in environmental factors between humans and dogs have yet to be identified.

Another predisposing factor for CaOx formation is breed of dog. Although 120 breeds were affected in the data compiled by an analysis center in North America, 58% of CaOx uroliths developed in only 6 breeds, with 25% developing in Miniature Schnauzers.[1,5] Likewise, data from uroliths analyzed by other centers within the United States,[6] the United Kingdom,[3] Germany,[7] and Sweden, and Norway[8] also found certain breeds of dog were more commonly affected with CaOx urolithiasis. When examining these breeds, it becomes apparent that this condition develops almost exclusively in small and toy breed dogs such as **Miniature Schnauzers (MS)**, Cairn Terriers, Yorkshire Terriers, Bichon Frise, Lhasa Apsos, Pekingese, Papillons, Maltese Terriers, and Cavalier King Charles Spaniels. This high prevalence in certain breeds has led to the suggestion that some of the factors promoting the formation of CaOx uroliths in dogs may be inherited.[2] Genetic abnormalities have been identified as factors in the formation of other less common canine uroliths such as urate and cystine.[9,10] Likewise, the familial predisposition of humans to CaOx kidney stones suggests that genetic factors are involved in the pathogenesis.[11] The transmission of nephrolithiasis, hypercalciuria, and hyperoxaluria through generations of people indicates that they are inherited traits, although expression depends on factors including sex, age, and diet.[12] Additionally, the selective breeding of hypercalciuric rats increased the intensity and frequency of hypercalciuria in the offspring and provided evidence for hereditary hypercalciuria.[13] Although a genetic basis has not been established as a cause of CaOx formation in dogs, inherited differences in mineral metabolism and urine composition may provide an explanation for the increased development of CaOx urolithiasis in certain breeds of dog.

The purpose of the study reported here was to compare urine composition in healthy dogs of 2 breeds fed the same dog food. Miniature Schnauzers (MS) were selected as a breed predisposed toward CaOx urolithiasis and compared with a breed rarely found to form CaOx urolithiasis (**Labrador Retriever [LR]**).

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Variables compared included the frequency of urination, urine pH, volume, and specific gravity, and urinary concentrations of calcium, oxalate, and phosphate. Urinary **relative supersaturation (RSS)** with CaOx and brushite (calcium hydrogen phosphate, dihydrate), defined as the activity product/solubility product, were also calculated.

Materials and Methods

Dogs—Sixteen healthy adult dogs consisting of 8 LR (2 sexually intact females, 6 spayed females; mean [± SD] age, 3.1 ± 1.7 years) and 8 MS (4 sexually intact females, 3 spayed females, 1 castrated male; mean age, 3.7 ± 1.3 years) were used in our study. Two dogs from each breed were from the same litter; individuals from both breeds were sired from 4 different dogs.

Study design—The dogs were individually fed a nutritionally complete dry dog food (**Appendix**) once daily at 10:30 AM for 24 days. Food allowances were calculated according to adult maintenance energy requirements (110 $W^{0.75}$ kcal/d, where W is body weight expressed in kg)[b] and adjusted during our study to ensure body weight maintenance within ± 5% of original weight. Daily food intake and feces quality were recorded throughout the trial. All dietary nutrients were analyzed by previously described methods.[14] Water was provided ad libitum.

Housing details—Dogs were housed separately as described by Stevenson et al[15] for six 48-hour periods during days 3 to 4, 7 to 8, 11 to 12, 15 to 16, 19 to 20, and 23 to 24 to enable collection of naturally voided urine. During the remaining days the dogs were housed in pairs. During this time all the dogs were walked once daily for approximately 15 minutes and group-exercised in grass paddock areas for 1 to 2 hours.

Urinary measurements—While the dogs were individually housed, urine pH was continuously measured, using the noninvasive automated urine pH measuring system described previously.[15] Immediately after each naturally voided urination, the sample was collected in a glass bottle, using previously described methods,[15] and individually processed. The time and frequency of urination were recorded; urine volume and specific gravity were also recorded. Each sample was then titrated to pH 2 with 37% hydrochloric acid,[c] frozen, and stored at –20 C.

Urinalysis—Samples were prepared and analyzed by previously described methods.[14,16] Urinalysis data were then entered into a computer program,[17] which calculated RSS values for CaOx and brushite.

Blood samples—Food was withheld from all dogs overnight on day 24. A blood sample was collected from the jugular vein and analyzed for hematologic findings,[d] serum biochemical values,[e] and blood gas variables.[f]

Statistical analyses—Data from each urination were grouped together for each dog and expressed as mean (± SD) values, so that n = 8 for each breed. Unpaired 2-tailed Student *t*-tests were used to assess the effect of breed on urine volume, specific gravity and pH, frequency of urination, urinary RSS with calcium oxalate and brushite, urinary concentrations of calcium, phosphate, and oxalate, and blood measurements. Data were also compiled into mean (± SD) diurnal profiles with data from each breed grouped into 2-hour blocks. The number of data points varied from 4 to 20 between blocks; data within each block were compared using unpaired 2-tailed Student *t*-tests. For all statistical tests significance was set at $P < 0.05$.

Results

Food intake and body weight maintenance—All food offered to the dogs was consumed every day. Body weight remained stable throughout the trial with an overall weight change of 0.4%.

Dietary mineral intakes—The mean daily intakes of calcium, phosphorus, sodium, potassium (g/kg of body weight per day), oxalate (mg/kg of body weight per day), and energy (kcal/kg of body weight per day) were significantly higher ($P \leq 0.001$) in MS than in LR (**Table 1**). Magnesium intake was not significantly different between the breeds. When converted to intake per kilogram of **metabolic body weight ($BWT^{0.75}$)**, no differences in mineral intakes were found between the 2 breeds.

Urinary measurements—Miniature Schnauzers urinated significantly less often during each 24 hour

Table 1—Mean (± SD) daily intakes of minerals, oxalate, and energy (per kg of body weight per day) in 8 healthy Labrador Retrievers (LR) and 8 healthy Miniature Schnauzers (MS) fed a commercially prepared dog food for 24 days.

	Mineral intake (g)						
Breed	Ca	P	Na	K	Mg	Oxalate (mg)	Energy (kcal)
LR	0.24 ± 0.02[a]	0.19 ± 0.01[a]	0.039 ± 0.010[a]	0.12 ± 0.01[a]	0.018 ± 0.001[a]	2.58 ± 0.18[a]	62.28 ± 4 .31[a]
MS	0.31 ± 0.04[b]	0.25 ± 0.03[b]	0.050 ± 0.008[b]	0.16 ± 0.01[b]	0.024 ± 0.001[a]	3.35 ± 0.42[b]	80.66 ± 10.13[b]

Ca = Calcium. P = Phosphorus. Na = Sodium. K = Potassium. Mg = Magnesium.
[a,b]Within a column, values with different superscripts are significantly ($P < 0.05$) different.

Table 2—Mean (± SD) daily urine volume (ml/kg of body weight per day), urine specific gravity, urinary relative supersaturation of calcium oxalate and brushite, and urinary concentrations of calcium (mmol/L), oxalate (mmol/L), and phosphate (mmol/L) in 8 healthy LR and 8 healthy MS fed a commercially prepared dog food for 24 days

	Urinary measurements								
Breed	pH	Volume	Specific gravity	No. of urinations	RSS CaOx	RSS B	Ca	Ox	PO_4
LR	6.14 ± 0.34[a]	22 ± 15[b]	1.023 ± 0.010[a]	2.9 ± 1.1[b]	4.60 ± 1.66[a]	0.47 ± 0.23[a]	0.61 ± 0.23[a]	1.16 ± 0.48[a]	63.03 ± 22.27[a]
MS	6.52 ± 0.18[b]	12 ± 3[a]	1.030 ± 0.008[a]	1.5 ± 0.5[a]	5.31 ± 1.62[a]	1.22 ± 0.31[b]	0.93 ± 0.25[b]	0.82 ± 0.22[a]	79.25 ± 15.24[a]

RSS = Urinary relative supersaturation calculated as activity product/solubility product. CaOx = Calcium oxalate. B = Brushite. Ox = Oxalate. PO_4 = Phosphate.
See Table 1 for remainder of key.

period ($P = 0.002$; MS ranged between 0.6 and 1.8 urinations/24 h; LR ranged between 1.5 and 4.5 urinations/24 h) producing a significantly ($P = 0.04$) lower volume of urine with a significantly ($P = 0.007$) higher urine pH than LR (**Table 2**). The mean diurnal urine pH profiles indicated that MS maintained a higher urine pH than LR across a 24-hour period (**Fig 1**). Urine specific gravity was not significantly different between the breeds ($P = 0.06$). Nevertheless, the mean diurnal profile suggested that the urine from MS had a higher specific gravity than that of LR for most of the 24-hour period (**Fig 2**).

Urinary mineral concentrations—No significant differences in urinary concentrations of phosphate ($P = 0.06$) or oxalate ($P = 0.09$) were detected between breeds. Urinary calcium concentration was significantly ($P = 0.009$) higher in urine of MS than in that of LR (Table 2).

Urinary RSS—The CaOx RSS was not significantly affected by breed (Table 2). Urine of MS had a significantly higher brushite RSS than urine of LR ($P < 0.001$).

Blood measurements—All blood measurements remained within the reference ranges for clinically normal dogs. Total and ionized serum calcium concentrations were unaffected by breed (data not shown).

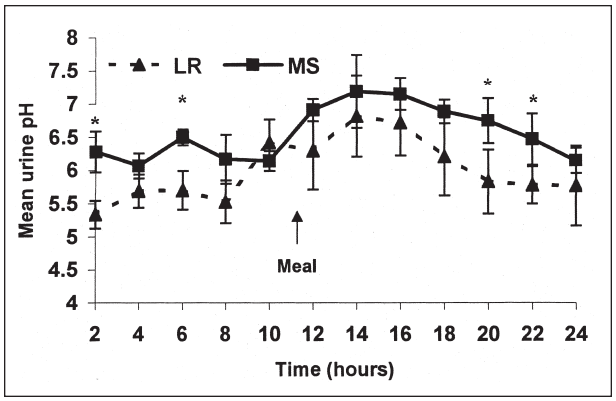

Figure 1—Mean (± SD) diurnal urine pH profile for 8 Labrador Retrievers (LR) and 8 Miniature Schnauzers (MS) fed a commercially prepared dog food for 24 days. *Significant ($P < 0.05$) difference detected between breeds.

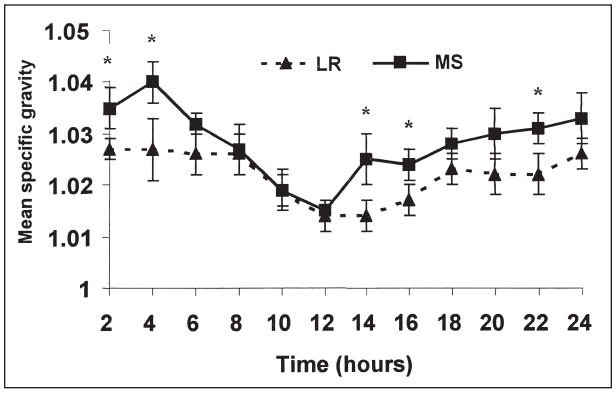

Figure 2—Mean (± SD) diurnal urine specific gravity profile for 8 LR and 8 MS fed a commercially prepared dog food for 24 days. *See* Figure 1 for key.

Discussion

The results of our study indicate that MS urinated significantly less often and had a lower urine volume than LR. Urine specific gravity was not significantly different between the breeds, although it tended to be higher in MS ($P = 0.06$). These data suggest that more concentrated urine was retained for a greater length of time in the bladders of MS, factors that could increase the likelihood of crystallization and subsequent crystal growth and aggregation. Within the human field, many workers have examined the risk factors for CaOx urolithiasis.[18-20] The risk factor model developed by Robertson[4] identified low urine volume as the most important risk factor for stone formation in humans. Excretion rates of most of the constituents of calcium-containing stones are independent of urinary flow; therefore, any decrease in urine volume would increase the concentrations of calcium, phosphate, and oxalate in the urine. A decrease in urine volume may increase the concentration of crystallization inhibitors, although this effect will largely be offset by a concurrent increase in promoters. The net balance of these effects is an increased risk of mineral crystallization and stone formation.

The main factors in humans leading to a low urine volume are a low fluid intake, percutaneous losses (minimal in dogs), or fluid losses through diarrhea.[4] The dogs in our study all had well-formed feces; therefore, the likely cause of the lower urine volume of MS was a lower water intake. However, it can also be postulated that MS had an increased requirement for calories when compared with LR because of a higher activity level, leading to increased greater insensible water loss. Although no formal measure of energy expenditure was made, the higher calorie intake required by MS to maintain body weight was more likely to be a function of an higher surface area to volume ratio, as with other small breed dogs. If these urinary characteristics are typical of MS, they may contribute to the high risk of CaOx urolithiasis recognized in this breed.

High urinary calcium concentration may also be a factor leading to calcium stone formation in dogs. Miniature Schnauzers in our study had significantly higher urinary calcium concentrations than that of LR, inferring an increased risk of CaOx formation. In a previous study, urinary calcium concentrations in a group of 16 CaOx stone-forming dogs averaged 2.33 ± 1.30 mmol/L, considerably higher than concentrations reported in healthy dogs.[21,g] Urinary CaOx RSS averaged 20.43 ± 16.12 mmol/L in the dogs around the time of stone formation, indicating the presence of urine in a state of labile supersaturation (oversaturation). Although the urinary calcium concentration of MS in our study was higher than that of LR, concentrations were substantially lower than those seen in the stone-forming dogs. Hypercalciuria is a common disorder encountered in around 60% of human subjects with urolithiasis.[22] This condition is an important risk factor for the formation of calcium uroliths (oxalate and phosphate), because it will result in increased urinary saturation with calcium oxalate and calcium phosphate.[22,23] Miniature Schnauzers had a significantly higher intake of dietary calcium per kilogram of body weight than LR,

which may have facilitated the increase in urinary calcium. However, there were no significant differences in any other urinary minerals despite equally high dietary intakes. Thus, although high dietary calcium may contribute, it is likely that other mechanisms are facilitating the high urinary calcium seen in this breed. From the results of our study, it is apparent that the high urinary calcium concentration developed in the absence of hypercalcemia, as indicated by the blood results. However, further research is required to determine the nature of these mechanisms.

Miniature Schnauzers had lower but not significantly different ($P = 0.09$) urinary oxalate concentrations than LR, despite a higher intake (Table 1). A high urinary oxalate excretion has been linked to calcium oxalate stone formation, and hyperoxaluria can be detected in up to 50% of humans with calcium oxalate stones.[24] In a human risk factor assessment, hyperoxaluria was second only to low urine volume as a risk factor for stone formation.[4] In contrast, there appear to be no reports of hyperoxaluria in CaOx stone-forming dogs. Indeed, in a previous study reporting urine variables in dogs, daily urinary oxalate excretion was found to be significantly lower in stone-forming MS compared with healthy Beagles.[25] Thus, urinary oxalate may not be a factor driving CaOx formation in dogs.

The specific gravity measured over 24 hours in our study indicated that there was a mild increase in the urine collected overnight (between 7:00 PM and 7:00 AM), an effect that was more pronounced in MS (Fig 2). Studies examining diurnal changes in humans found the greatest risk of calcium oxalate formation developed overnight.[26] During this time the urine volume decreases while concentration increases and body temperature is also at its lowest, facilitating an increase in urine supersaturation and, hence, an increase in the potential for crystallization and stone growth in susceptible individuals.[27] It is likely that diurnal profiles in dogs are affected by similar factors.

Urinary pH is not constant and fluctuates during the course of a 24-hour period (Fig 1). In our study, the same observation was found in both breeds with increased urine pH during the day, peaking between 2 and 5 hours after feeding. This effect was thought to be partly attributable to a postprandial alkaline tide and partly to an increase in activity. A similar pattern has been observed in humans. Factors including exercise, pulmonary ventilation, dietary habits, and emotional status are all known to influence urine pH in humans, and as a result of these diurnal variations, pH is usually lowest throughout the night and highest during the day.[28]

Calcium oxalate uroliths can form across the entire range of urine pH values (4.8 to 7.4) in humans, and urine pH is not considered to be a major risk factor for calcium oxalate formation.[4,h] Urine pH does, however, exert control on the minerals that coprecipitate with calcium oxalate.[4] A urine pH above 6.2 increases the risk of calcium phosphate crystallization through the deprotonation of phosphate ions, which then readily precipitate with calcium ions. The volume of calcium phosphate crystalluria increases sharply as urinary pH exceeds 6.2. Likewise, at urine pH < 5.3, there is a strong likelihood of uric acid being included as a minor component of the calcium oxalate stone.[4] The urine pH of MS was significantly higher than LR. In addition, the urinary concentration of phosphate of MS was higher than LR, although the difference was not significant ($P = 0.06$). These factors together with a higher urinary calcium concentration resulted in production of urine with a significantly higher brushite RSS.

Calcium phosphate crystals are known to trigger calcium oxalate crystallization in humans, as they allow heterogeneous crystallization processes to take place, which develop at a lower amount of urinary saturation than homogeneous crystallization.[29,30] Although the most common form of calcium phosphate that precipitates with calcium oxalate is apatite, brushite is a thermodynamically metastable compound known to be a precursor for apatite formation.[31] Thus, the measurement of brushite RSS together with urine pH provides a method of assessment for the risk of calcium phosphate formation. Production of urine with a pH < 6.2 increases the solubility of calcium phosphate crystals and has been shown to decrease brushite RSS in humans.[31] Miniature Schnauzers maintained a urine pH above 6.2 throughout the 24 hour period, indicating an increased risk of calcium phosphate crystallization. In contrast, LR had a striking decrease in urine pH (< 6.0) between 8:00 PM and 8:00 AM. At this time, any preformed calcium phosphate crystals would be expected to dissolve. In dogs, calcium oxalate coprecipitates with calcium phosphate more commonly than it develops in the pure form or with other coprecipitates.[1] Thus, the risks associated with calcium phosphate formation also require consideration when examining the factors contributing to calcium oxalate formation in dogs.

Markedly acidic urine pH has been associated with an increased risk of calcium oxalate urolithiasis in epidemiologic studies in cats.[32] Recent data indicates, however, that urinary calcium concentrations may only be increased as urine pH approaches the value at which there is a risk of metabolic acidosis.[33] Similar studies appear not to have been reported in dogs, although it has been suggested that urinary acidifiers that are associated with acidosis are risk factors for calcium oxalate urolithiasis in this species.[34] During metabolic acidosis, acidifying metabolites are neutralized by phosphates and carbonates mobilized from bone. Bone calcium is released with the phosphorus resulting in hypercalciuria.[34] In our study, MS had urine with a higher pH than LR despite receiving the same diet and, therefore, a similar acid load on a metabolic body weight basis ($BWT^{0.75}$), yet urinary calcium concentration was also higher. Further research is necessary to determine whether urine pH within a range that avoids metabolic acidosis has a significant effect on urinary calcium concentration and the risk of CaOx stone formation in dogs.

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[c]BDH Laboratory Supplies, Poole, UK.

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[e]Cobas MIRA Plus biochemistry analyser, Roche Diagnostic Systems, Branchburg, NJ.

[f]AVL Omni 288 blood gas system, AVL Medical Instruments Ltd, GmbH Medizintechnik, Hans-List Platz 1, 8020 Graz, Austria.

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Appendix 1

Nutrient content of the commercially prepared dog food

Nutrient	Unit	Amount (per 100 kcal)
Moisture	g	1.8
Protein	g	7.12
Fat	g	4.44
Ash	g	2.15
Linoleic acid	g	1.09
Linolenic acid	g	0.12
Linoleic acid and arachidonic acid	g	1.10
Calcium	g	0.38
Phosphorus	g	0.30
Ca:P	NA	0.31
Sodium	g	0.06
Magnesium	g	0.03
Iron	mg	7.92
Copper	mg	0.23
Manganese	mg	0.48
Zinc	mg	4.14
Oxalate	mg	4.14
Vitamin A	U	1,235.22
Vitamin E	mg	5.14
Thiamin	mg	0.05
Riboflavin	mg	0.18
Niacin	mg	0.93
Pyridoxine	mg	0.03
Pantothenic acid	mg	1.14
Folic acid	µg	50.47
Vitamin B12	µg	3.72
Choline	mg	61.10
Methionine	g	0.10
Methionine and cystine	g	0.18

NA = Not applicable.

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