Evaluation of the association between sex and risk of forming urate uroliths in Dalmatians

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Objective—To test the hypothesis that urate uroliths are uncommonly detected in female Dalmatians, compared with males.

Design—Case-control study.

Sample Population—Medical records of dogs evaluated at veterinary teaching hospitals in North America from 1981 to 2002 and compiled by the Veterinary Medical Database, and records of dogs with uroliths submitted for quantitative analyses to the Minnesota Urolith Center from 1981 to 2002.

Procedures—Crude odds ratios (ORs) and 95% confidence intervals were calculated to assess whether sex (male vs female) was a risk factor for urate urolithiasis.

Results—In Dalmatians evaluated by veterinary teaching hospitals in North America, males were more likely (OR, 13.0) to form uroliths, compared with females. In Dalmatians that formed uroliths analyzed by the Minnesota Urolith Center, males were more likely (OR, 14.0) to form urate uroliths, compared with females. In all dogs (Dalmatian and non-Dalmatian) that formed uroliths analyzed by the Minnesota Urolith Center, males were also more likely (OR, 48.0) to form urate uroliths, compared with females.

Conclusions and Clinical Relevance—When conducting studies and formulating generalities about urate urolithiasis in Dalmatians, it is important to consider sex-related differences in urolith occurrence. Long-term dietary or drug protocols designed to minimize formation of urate uroliths in male Dalmatians may not be warranted in female Dalmatians. (*J Am Vet Med Assoc* 2005;227:565–569)

The formation of urate uroliths in Dalmatians is a breed-specific disorder associated with hyperuricemia and hyperuricuria caused by dysfunction in the metabolism of purines.[1-3] Because of a defective transport system in the hepatocytes of Dalmatians, they excrete uric acid in their urine as the end product of purine metabolism rather than allantoin.[4] Whereas allantoin is highly soluble in urine, uric acid and salts of uric acid are relatively insoluble.[5-7] In addition to reduced hepatic conversion of uric acid to allantoin, a membrane transport defect has been identified in the kidneys of Dalmatians that reduces renal tubular reabsorption of uric acid.[8-10] Dalmatians also remove some uric acid from the general circulation by renal tubular secretion.[11-14] Whereas the daily urinary excretion of uric acid by non-Dalmatian breeds is approximately 15 to 50 mg, the daily urinary excretion of uric acid by Dalmatians is 200 to 800 mg.[15] Hyperuricuria predisposes Dalmatians to urate urolithiasis.

The major causes of high morbidity and mortality rates recognized in association with this disorder in Dalmatians are sequelae of urolith formation. However, for as yet unidentified reasons, not all hyperuricuric Dalmatians form uroliths. Although the formation of uroliths in Dalmatians appears to be associated with a genetic trait, the hyperuricuria associated with defective purine metabolism is a predisposing factor rather than a sole cause of urate urolith formation.

Many clinicians and investigators describe the high rate of occurrence of urate uroliths in Dalmatians without reference to sex. However, it has been our clinical observation that urate uroliths are detected almost exclusively in male Dalmatians. This prompts the question of whether generalities about the diagnosis, treatment, and prevention of urate uroliths should be applied to female Dalmatians as well as males. The primary purpose of this retrospective case-control study was to validate the hypothesis that urate uroliths are uncommonly detected in female Dalmatians, compared with males.

Materials and Methods

Case selection—Records of all Dalmatians from the **Veterinary Medical Database (VMDB)**[a] from 1981 to 2002 were retrieved. Cases consisted of Dalmatians with uroliths; the control group consisted of Dalmatians without urinary tract disease.

Records of all canine urolith submissions to the Minnesota Urolith Center from 1981 to 2002 were also reviewed. Cases consisted of Dalmatians with urate uroliths; control groups consisted of Dalmatians with nonurate uroliths and all urolith-forming dogs other than Dalmatians.

Urolith analysis—At the Minnesota Urolith Center, urolith composition was determined by optical crystallography, infrared spectroscopy, and, in some instances, x-ray diffraction.[16] A urolith without a nidus or shell that contained ≥ 70% of 1 type of mineral was identified by that mineral. A urolith with an identifiable nidus with 1 or more surrounding layers of different mineral composition was called a compound urolith. A urolith with < 70% of 1 mineral but without a nidus or shell was referred to as a mixed urolith.[17] In this study, all stones composed primarily of uric acid and salts of uric acid (eg, ammonium urate, sodium urate, calci-

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um urate, and uric acid) were collectively referred to as urate. The VMDB did not distinguish between uroliths of different mineral composition.

Statistical analyses—Frequency distributions of urolith type were calculated on the basis of sex. Crude **odds ratios (ORs)** and 95% **confidence intervals (CIs)** were calculated by the Woolf method by use of computer software[b] to assess whether sex (male vs female) was a risk factor for urate urolithiasis.[18] The estimation of OR was considered significant if the 95% CI for the OR did not include 1.0.[19] On the basis of the recommendations of Lilienfeld and Stolley,[20] we classified significant ORs from 1.1 to 1.9 or from 0.5 to 0.9 as weak associations. Likewise, we interpreted significant ORs that were > 2.0 (ie, risk) or < 0.5 (ie, protective) as clinically (biologically) important, yet requiring further experimental or prospective studies to support causality.

Results

Urolith formation in female Dalmatians—For the period from 1981 to 2002, records of 10,214 Dalmatians from the VMDB were reviewed; 5,028 were females, and 5,186 were males (**Table 1; Figure 1**). Dalmatians that had urinary tract diseases other than uroliths (171 females and 217 males) were excluded from the calculations of ORs and CIs. Compared with 4,814 female and 4,463 male Dalmatians without urinary tract diseases, odds of urolith formation in female Dalmatians were lower (OR, 0.08; 95% CI, 0.06 to 0.11), compared with males. In other words, compared with Dalmatians without urinary tract diseases, odds of urolith formation in male Dalmatians were higher (OR, 12.7; 95% CI, 9.3 to 17.4), compared with females.

Urate urolith formation in female Dalmatians—From 1981 to 2002, uroliths from 9,514 Dalmatians were analyzed at the Minnesota Urolith Center (**Table 2**). Of these uroliths, 9,095 (96%) were urate. Of the Dalmatians that formed urate uroliths, 261 (2.9%) were females and 8,546 (94%) were males (the sex of 288 Dalmatians was not reported). Compared with Dalmatians with nonurate uroliths, odds of urate urolith formation in females were lower (OR, 0.07; 95% CI, 0.06 to 0.09) than in males. However, of 381 female Dalmatians that formed uroliths, urate was the predominant (69%) form. In other words, compared with Dalmatians with nonurate uroliths, odds of urate urolith formation in males were higher (OR, 13.5; 95% CI, 10.6 to 17.3) than in females. Compared with non-Dalmatians with uroliths (98,435 females, 67,645 males, and 5,879 for which sex was not specified), odds of urate urolith formation in female Dalmatians were also lower (OR, 0.021; 95% CI, 0.019 to 0.024; **Table 3**) than in males. Compared with all non-Dalmatians with uroliths, odds of urate urolith formation in male Dalmatians were higher (OR, 47.6; 95% CI, 42.1 to 53.9) than in females.

Other types of urolith formation in female Dalmatians—Uroliths from the 419 Dalmatians that did not form urate uroliths (120 females, 291 males, and 8 for which sex was not reported) were composed of several types of minerals (Table 2). As with urate uroliths, the actual number of other types of uroliths occurred more commonly in males (69%) than females (29%). However, the proportions of struvite uroliths, compound uroliths, and mixed uroliths were greater in female Dalmatians than male Dalmatians.

Table 1—Distribution of sex of 10,214 Dalmatians recorded in the Veterinary Medical Database from 1981 to 2002.

	Female		Male		Total	
Dalmatians	**No.**	**%**	**No.**	**%**	**No.**	**%**
With urinary tract disease	214	22.8	723	77.2	937	9.2
Uroliths	43	7.8	506	92.2	549	58.6
Other	171	44.1	217	55.9	388	41.4
Without urinary tract disease	4,814	51.9	4,463	48.1	9,277	90.8
Total	**5,028**	**49.2**	**5,186**	**50.8**	**10,214**	**100.0**

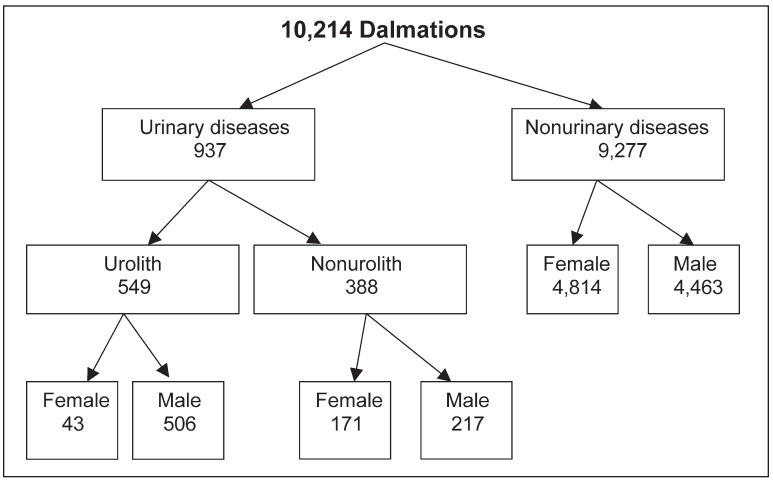

Figure 1—Distribution (No. of dogs) by disease and sex of all Dalmatians for which data were entered in the Veterinary Medical Database from 1981 to 2002.

Table 2—Distribution of urolith types among 381 female and 8,837 male Dalmatians (Minnesota Urolith Center, 1981 to 2002).

	Female		Male		Unknown		Total	
Mineral composition	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Purines	261	2.9	8,546	94.0	288	3.1	9,095	95.6
Ammonium acid urate	232	3.2	6,703	93.7	218	3.0	7,153	78.6
Sodium acid urate	7	0.6	1,184	95.9	44	3.5	1,235	13.8
Sodium calcium urate	5	1.1	441	95.7	15	3.2	461	5.1
Uric acid	15	8.8	149	87.6	6	3.6	170	1.9
Xanthine	2	2.6	69	90.8	5	6.6	76	0.8
Magnesium ammonium phosphate	10	24.4	31	75.6	0	0	41	0.4
Magnesium hydrogen phosphate	0	0	2	100	0	0	2	< 0.1
Calcium oxalate	0	0	20	95.2	1	4.8	21	0.2
Calcium phosphate	0	0	3	100	0	0	3	< 0.1
Cystine	0	0	3	100	0	0	3	< 0.1
Silica	0	0	4	100	0	0	4	< 0.1
Mixed	68	36.8	113	61.1	4	2.1	185	1.9
Compound	42	27.1	110	71.0	3	1.9	155	1.6
Matrix	0	0	5	100	0	0	5	< 0.1
Total	**381**	**4.0**	**8,837**	**92.9**	**296**	**3.1**	**9,514**	**100.0**

Table 3—Distribution of urolith types among 98,435 female and 67,645 male non-Dalmatians (Minnesota Urolith Center, 1981 to 2002).

	Female		Male		Unknown		Total	
Mineral composition	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Purines	949	22.4	3,133	73.9	158	3.7	4,240	2.5
Ammonium acid urate	914	22.6	2,989	73.7	145	3.7	4,053	95.6
Sodium acid urate	8	9.6	67	80.8	8	9.6	83	2.0
Sodium calcium urate	3	9.1	30	90.9	0	0	33	0.8
Uric acid	12	42.9	16	57.1	0	0	28	0.7
Xanthine	12	25.0	31	64.6	5	10.4	48	1.1
Magnesium ammonium phosphate	69,276	83.6	10,757	13.0	2,847	3.4	82,850	48.1
Magnesium hydrogen phosphate	17	48.6	15	42.9	3	8.5	35	< 0.1
Calcium oxalate	15,920	24.9	45,883	71.8	2,090	3.3	63,893	37.2
Calcium phosphate	360	40.4	494	55.4	37	4.2	891	0.5
Cystine	29	1.8	1,550	94.4	62	3.8	1,641	1.0
Silica	42	4.3	898	92.9	27	2.8	967	0.5
Other	4	21.1	14	73.7	1	5.2	19	0.1
Dolomite	0	0	1	100	0	0	1	< 0.1
Mixed	2,317	64.8	1,128	31.5	133	3.7	3,578	2.1
Compound	9,482	69.1	3,722	27.1	515	3.8	13,719	8.0
Matrix	32	39.5	43	53.1	6	7.4	81	< 0.1
Drug metabolite	7	50.0	7	50.0	0	0	14	< 0.1
Total	**98,435**	**57.2**	**67,645**	**39.3**	**5,879**	**3.5**	**171,959**	**100.0**

Discussion

The combined results derived from the VMDB and the Minnesota Urolith Center strongly support the hypothesis that urate uroliths are uncommonly detected in female Dalmatians, compared with males. Further support is derived from results of a similar case-control study reported by Ling et al[21] in which female Dalmatians (n = 16) formed urate uroliths approximately 31 times less frequently than male Dalmatians (534).

These observations prompt the question as to whether the difference in the rate of detection of urate uroliths in male and female Dalmatians is associated with a sex-linked modification in purine metabolism. Our study was not designed to answer this question, and we were unable to find references to controlled studies designed to specifically answer this question. Although there have been several studies[9-11,22-26] performed to investigate purine metabolism in Dalmatians, the investigators did not specify the sex of the dogs. However, in 6 studies[8,27-31] encompassing 13 adult female and 6 adult male Dalmatians, substantial differences between sexes were not observed in serum uric acid concentration and urine uric acid concentration and excretion. Results of those studies suggest that the difference in rate of occurrence of urate uroliths in male and female Dalmatians is unlikely to be associated with sex-related differences in purine metabolism. However, the results of those studies are questionable because the methods used to collect and store urine samples for measurement of uric acid apparently did not incorporate steps to keep uric acid in solution. In vitro precipitation after voiding may result in erroneously low concentrations of urates that mask in vivo differences in urine uric acid excretion and concentration.[32,33] This caveat is supported by Ling,[15] who stated that non–stone-forming male Dalmatians that are older than 5 years typically excrete more urinary urate than do non–stone-forming female Dalmatians of comparable age. In addition, Ling[15] stated that male Dalmatians that form stones excrete more urate than do dogs of either sex that do not form stones. Further studies of purine metabolism in urate urolith–forming male and female Dalmatians encompassing age- and sex-matched controls are warranted.

Another possibility that may contribute to the difference in the rate of occurrence of urate uroliths in male and female Dalmatians is that the composition of urine of female Dalmatians may be different from males. A large body of evidence indicates that urine normally contains

metabolites that inhibit the formation, growth, and aggregation of calcium oxalate crystals. They include **Tamm-Horsfall mucoprotein (THP)**, nephrocalcin, and osteopontin.[34,35] An in vitro study[36] of human urine suggests that glycosaminoglycans may also play a role in inhibiting formation of uric acid crystals. A recent study[37] of urate urolith–forming male Dalmatians reveals that they excreted significantly less THP in their urine, compared with age-matched healthy male Dalmatians. Sperling et al[38] suggest that the solubility of uric acid is maintained by THP and that increased uric acid content may result in decreased quantities of THP or reduced activity of THP. Recall that results of some studies[8,27-31] of purine metabolism in Dalmatians were interpreted to indicate that the magnitude of increased serum and urine uric acid concentrations was similar in males and females. If those observations are valid, they indicate that increased urine uric acid concentration would likely decrease urine THP concentration in male and female Dalmatians and therefore would be unlikely to explain the sex-related difference in detection of urate uroliths. Further studies are warranted to evaluate promoters and inhibitors of uric acid crystals in male and female Dalmatians.

Another possibility that may explain the different rate of occurrence of urate uroliths in male and female Dalmatians is that there are substantially fewer female than male Dalmatians in the general population. However, we can find no reported studies of the number of male and female Dalmatians in the general population. Unfortunately, records of purebred Dalmatians kept by the American Kennel Club are not designed to readily provide access to this information. However, on the basis of our empirical clinical experience, we are of the opinion that it is unlikely that the number of female Dalmatians in the general population is significantly lower than the number of males. The observation that the total number of male and female Dalmatians evaluated by veterinary teaching hospitals that contributed data to the VMDB was similar supports our impression. The similarity of the numbers of males and females reported in a recent study[39] designed to evaluate deafness in male and female Dalmatians also supports our impression.

A more plausible explanation of the sex-related difference in urate urolith detection in Dalmatians is related to the anatomic difference in the lower portion of the urinary tract between males and females. Urate uroliths are usually spherical and typically have a smooth surface. Because the urethra of female Dalmatians is wider, shorter, and more distensible than the urethra of males, small urate uroliths may be voided before they cause clinical signs. The fact that most urate uroliths cannot be detected by survey radiography likely contributes to the infrequency with which they are detected in females that do not have clinical signs. However, in males, uroliths of comparable size tend to lodge in the urethra as it enters the narrow groove of the os penis and often are associated with clinical signs of outflow obstruction. This would also account for the observation that other types of uroliths found in Dalmatians were more common in males than females. Likewise, it would account for the observation that ammonium urate uroliths have been detected less frequently in non-Dalmatian female dogs, compared with non-Dalmatian male dogs.

Identification of the precise mechanisms for the disparity between the frequency of urate uroliths in female and male Dalmatians requires further study. Irrespective of the underlying causes, our observations indicate that the risk for clinical urate urolithiasis is substantially less in females. However, female Dalmatians may form uroliths composed of minerals other than urate. This observation underscores the importance of quantitative analysis of uroliths retrieved from all Dalmatians. In addition, long-term dietary or drug protocols designed to minimize urate uroliths in male Dalmatians with a history of urate urolithiasis may not be warranted in female Dalmatians.

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