Association between dietary factors and calcium oxalate and magnesium ammonium phosphate urolithiasis in cats

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Objective—To identify dietary factors associated with the increase in occurrence of calcium oxalate (CaOx) uroliths and the decrease in occurrence of magnesium ammonium phosphate (MAP) uroliths in cats.

Design—Case-control study.

Animals—173 cats with CaOx uroliths, 290 cats with MAP uroliths, and 827 cats without any urinary tract diseases.

Procedure—Univariate and multivariate logistic regression were performed.

Results—Cats fed diets low in sodium or potassium or formulated to maximize urine acidity had an increased risk of developing CaOx uroliths but a decreased risk of developing MAP uroliths. Additionally, compared with the lowest contents, diets with the highest moisture or protein contents and with moderate magnesium, phosphorus, or calcium contents were associated with decreased risk of CaOx urolith formation. In contrast, diets with moderate fat or carbohydrate contents were associated with increased risk of CaOx urolith formation. Diets with the highest magnesium, phosphorus, calcium, chloride, or fiber contents and moderate protein content were associated with increased risk of MAP urolith formation. On the other hand, diets with the highest fat content were associated with decreased risk of MAP urolith formation.

Conclusions and Clinical Relevance—Results suggest that diets formulated to contain higher protein, sodium, potassium, moisture, calcium, phosphorus, and magnesium contents and with decreased urine acidifying potential may minimize formation of CaOx uroliths in cats. Diets formulated to contain higher fat content and lower protein and potassium contents and with increased urine acidifying potential may minimize formation of MAP uroliths. (*J Am Vet Med Assoc* 2001;219:1228–1237)

The Minnesota Urolith Center has analyzed uroliths from cats for almost 2 decades. During this period, we have observed substantial changes in mineral composition. In 1981, for instance, uroliths from 69 cats were analyzed. Fifty-four (78%) cats had uroliths composed of **magnesium ammonium phosphate (MAP)**, and only 1 (1%) had uroliths composed of **calcium oxalate (CaOx)**.[1] In 1999, uroliths from 5,091 cats were analyzed. One thousand six hundred forty-seven (32%) had MAP uroliths, and 2,817 (55%) had CaOx uroliths.[2] This observation prompted us to question whether differences in interrelated risk factors were responsible, at least in part, for changes in prevalence of CaOx and MAP uroliths in cats.

Results of a previous study[3] performed at the Minnesota Urolith Center suggested that differences in breed, age, sex, and reproductive status did not contribute to the apparent reciprocal relationship between occurrences of CaOx and MAP uroliths in cats observed during recent years. Of interest is the fact that cats of particular breeds, ages, and sex had increased risks of developing both CaOx and MAP uroliths. These findings support the prevailing opinion that diet-related treatment designed to minimize recurrence of MAP uroliths and urethral plugs has resulted in a reciprocal increase in the occurrence of CaOx uroliths. Diet-induced urine acidification is an effective method of dissolving sterile MAP uroliths in cats and of preventing their formation,[4] but diet-induced urine acidification promotes hypercalciuria and, thus, is a risk factor for formation of CaOx uroliths.[5] Similarly, a reduction in the dietary magnesium content to minimize formation of sterile MAP uroliths in cats has been suggested to increase the risk of CaOx urolith formation, because urinary magnesium inhibits formation of CaOx crystals in human and rats.[6] However, these findings have not been substantiated in cats with naturally occurring urolithiasis. Although feeding diets designed to minimize formation of sterile MAP uroliths may contribute to the increased prevalence of CaOx uroliths and decreased prevalence of MAP uroliths, a cause-and-effect relationship has not yet been documented. The purpose of the study reported here was to identify dietary factors associated with the recent increase in the occurrence of CaOx uroliths and the decrease in the occurrence of MAP uroliths in cats.

Materials and Methods

Case selection—Case cats consisted of 2 groups of cats residing in the United States and Canada. One group consisted of cats with uroliths composed of at least 70% CaOx. The second group consisted of cats with uroliths composed of at least 70% MAP. All uroliths from both groups of cats had

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been submitted to the Minnesota Urolith Center for analysis between 1990 and 1992. Cats with uroliths were counted only once; data related to > 1 episode of urolithiasis were excluded. To provide the opportunity for staff of any veterinary hospital to submit uroliths, analysis was provided without charge. Quantitative analysis of uroliths was performed with the aid of optical crystallography and, when necessary, infrared spectroscopy.

Control selection—Control cats consisted of cats evaluated at the same veterinary hospitals as the case cats. Each control cat was examined by a veterinarian just prior to or immediately after a case cat.

Exclusion criteria—To evaluate the long-term effects of diets, cats that consumed a particular brand of diet for < 6 months were excluded from the study. To minimize confounding effects associated with recent treatment for urinary tract disease, cats with a history of any type of upper or lower urinary tract disease were also excluded. Likewise, cats consuming therapeutic diets because of urinary tract disease were excluded. Because the composition of diets fed to immature cats commonly changes during growth and because CaOx uroliths are uncommon in cats < 1 year of age,[6,7] cats < 1 year of age were also excluded.

Questionnaire design and administration—After CaOx and MAP uroliths were received at the Minnesota Urolith Center, a content-validated[8] multiple-choice questionnaire[a] designed to collect information about each cat's signalment, diet (types and quantities of food fed, feeding methods and frequency, duration of consumption, amount of human food given and how frequently human food was given, types of vitamin and mineral supplements given and frequency of administration, and types and amounts of treats given), source of drinking water, and medical history (current illness, previous illnesses, treatments, and therapeutic diets) at the date of urolith detection was mailed to owners, with the permission of the primary care veterinarians. The same questionnaire was mailed to owners of the control cats. Owners who did not respond were mailed reminder cards or contacted by telephone.

Diet evaluation—The questionnaire allowed the owner to designate 1, 2, or a combination of 3 brands of commercial diets consumed by the cat. Owners were asked to specify the quantity of each brand of diet fed to each cat. On the basis of this information, the brand fed in the largest quantity was designated as the primary brand. When equal amounts of 2 or more brands were fed or the amount fed was not reported, the first diet listed by the owner was designated as the primary brand. The owner's recall of how much of each diet was fed was not used to determine the quantity of diet consumed by each cat. Rather, the quantity of diet consumed by each cat was calculated on the basis of the daily adult maintenance caloric requirement.

Information about urine pH values in cats fed each diet and on the quantity of each dietary component (protein, carbohydrate, fat, fiber, calcium, phosphorus, magnesium, sodium, potassium, chloride, and moisture) was supplied for diets formulated during the study period by their manufacturers. Mean values for dietary components and urine acidifying potential were used. When a range of values for dietary components and urine acidifying potential was reported by manufacturers instead of a mean value, the midrange value was used. Quantities of dietary components were expressed as grams per 100 kcal for protein, carbohydrate, fat, and fiber and milligrams per kilocalorie for calcium, phosphorus, magnesium, sodium, potassium, and chloride. Moisture was expressed as percentage of water in the diet.

Statistical evaluation—Quantity of each dietary component was compared between case and control cats with the Tukey method.[9] Correlations among components were examined by use of the Pearson correlation method.[10] On the basis of guidelines recommended by Newton and Rudestam,[11] we interpreted correlation coefficients as follows: 0 to 0.29 and 0 to –0.29 = no correlation, 0.3 to 0.69 and –0.3 to –0.69 = weak correlation, and 0.7 to 1.0 and –0.7 to –1.0 = strong correlation.

To calculate crude **odds ratios (OR)** and 95% **confidence intervals (CI)**, quantities of each dietary component consumed by case and control cats were grouped into quartiles and analyzed as categorical variables by means of univariate logistic regression analysis, using the logarithmic approximation (Woolf method).[12] For these analyses, the lowest quartile of each dietary component was used as a basis for comparison.

Because it was impractical for participating veterinarians to match each case cat with a corresponding control cat on the basis of breed, age, sex, body condition, and living environment, multivariate OR and 95% CI for each dietary component adjusted for these potential confounding variables were calculated. Additionally, the χ^2 test for trends in OR was used to evaluate linear trends across quartiles of dietary components.[13]

Statistical and clinical significance—Odds ratio estimates were considered significantly different from 1 if the 95% CI did not include 1.0.[14] On the basis of recommendations by Lilienfeld and Stolley,[15] we classified significant OR between 1.1 and 1.9 and significant OR between 0.5 and 0.9 as weak associations. Likewise, we interpreted significant OR > 2 and < 0.5 as clinically (biologically) significant but requiring further experimental or prospective studies to support causality.

Results

Questionnaires were sent to owners of 400 cats with CaOx uroliths, 769 cats with MAP uroliths, and 2,240 control cats without any urinary tract diseases. Response rates were 89% for owners of cats with CaOx uroliths, 84% for owners of cats with MAP uroliths, and 81% for owners of control cats. After exclusion of cats on the basis of the a priori exclusion criteria, 1,642 (48%) questionnaires were available for evaluation; 216 were for cats with CaOx uroliths, 367 were for cats with MAP uroliths, and 1,059 were for control cats. Dietary component information for statistical analysis was available for 173 (80%) cats with CaOx uroliths, 290 (79%) cats with MAP uroliths, and 827 (78%) control cats.

Cats with CaOx uroliths—Compared with control cats, cats with CaOx uroliths were fed diets with significantly lower protein, calcium, phosphorus, potassium, and moisture contents and significantly higher carbohydrate content (**Table 1**). Also, cats with CaOx uroliths were fed diets formulated to produce the greatest reduction in urine pH. However, these differences may have been confounded by correlations between several dietary components (**Table 2**).

When the quantities of dietary components were divided into quartiles (**Table 3**), univariate logistic regression analyses indicated that cats fed diets with low quantities of protein, calcium, phosphorus, magnesium, sodium, potassium, or moisture had an increased risk of CaOx urolith formation (*P* value for trend, < 0.05). When urine pH values attributed to diet formulations were divided into quartiles, cats fed diets

Table 1—Contents of various dietary components and urine acidifying potential for diets fed to cats with calcium oxalate (CaOx) or magnesium ammonium phosphate (MAP) uroliths and to control cats without any urinary tract diseases

	Control cats			Cats with CaOx uroliths			Cats with MAP uroliths		
Component	**No. of cats**	**Mean**	**SE**	**No. of cats**	**Mean**	**SE**	**No. of cats**	**Mean**	**SE**
Protein (g/100 kcal)	827	9.42[a]	0.06	173	8.85[b]	0.14	290	9.32[a]	0.09
Carbohydrate (g/100 kcal)	827	6.95[a]	0.13	173	7.84[b]	0.23	290	7.78[b]	0.21
Fat (g/100 kcal)	827	4.47[a]	0.06	173	4.38[a,b]	0.10	290	4.09[b]	0.09
Fiber (g/100 kcal)	826	0.72	0.04	173	0.75	0.10	289	0.67	0.04
Calcium (mg/kcal)	827	3.04[a]	0.03	173	2.72[b]	0.07	290	3.26[c]	0.05
Phosphorus (mg/kcal)	827	2.58[a]	0.03	173	2.28[b]	0.08	290	2.83[c]	0.05
Magnesium (mg/kcal)	827	0.27[a]	0.01	173	0.24[a]	0.01	290	0.31[b]	0.02
Sodium (mg/kcal)	826	1.27[a]	0.02	173	1.15[a]	0.05	289	1.42[b]	0.04
Potassium (mg/kcal)	819	1.82[a]	0.02	172	1.72[b]	0.03	285	1.91[c]	0.03
Chloride (mg/kcal)	756	1.88[a,b]	0.03	164	1.78[a]	0.05	262	2.00[b]	0.05
Moisture (%)	827	32.02[a]	1.09	173	21.44[b]	1.98	290	28.38[a]	1.76
Urine acidifying potential*	763	6.28[a]	0.01	169	6.24[b]	0.01	262	6.35[c]	0.02

[a,b,c]In each row, values with different letter superscripts were significantly ($P < 0.05$) different.
*Urine pH expected after consumption of the diet; values were supplied by diet manufacturers.

Table 2—Bivariate correlations of the content of various diet components in diets fed to 1,290 cats

Variable	**Protein**	**Carbohydrate**	**Fat**	**Fiber**	**Calcium**	**Phosphorus**	**Magnesium**	**Sodium**	**Potassium**	**Chloride**	**Moisture**
Carbohydrate	–0.36										
Fat	0.06	–0.75									
Fiber	0.37	0.27	–0.37								
Calcium	0.44	–0.18	0.08	–0.06							
Phosphorus	0.36	–0.01*	–0.07	–0.03*	0.95						
Magnesium	0.13	0.27	–0.12	0.03*	0.50	0.55					
Sodium	0.26	–0.22	0.22	–0.04*	0.68	0.71	0.27				
Potassium	0.48	0.18	–0.30	0.27	0.36	0.36	0.35	0.10			
Chloride	0.46	–0.32	0.17	–0.06*	0.55	0.46	0.19	0.48	0.27		
Moisture	0.58	–0.85	0.67	–0.12	0.39	0.26	0.05*	0.42	0.11	0.58	
Urine acidifying potential	–0.40	0.38	–0.27	0.00*	0.08	0.18	0.31	0.03*	0.17	–0.49	–0.37

Values given are Pearson correlation coefficients.
*All coefficients were significantly ($P < 0.05$) different from 0, except for those marked with an asterisk.

formulated to decrease urine pH had an increased risk of CaOx urolith formation (*P* value for trend, < 0.05).

Distributions for breed, age, sex, body condition, and living environment were significantly ($P < 0.05$) different between case and control cats (**Table 4**). Therefore, multivariate logistic regression adjusting for these potential confounding variables was performed (Table 3). Cats fed diets with low quantities of protein, sodium, potassium, or moisture and fed diets formulated to maximize urine acidity had an increased risk of CaOx urolith formation (*P* value for trend, < 0.05). Although significant trends were not observed between the quantity of dietary calcium, phosphorus, or magnesium fed and CaOx urolith formation, a decreased risk of CaOx urolithiasis was observed for cats fed diets containing moderate quantities of dietary calcium, phosphorus, or magnesium.

Cats with MAP uroliths—Compared with control cats, cats with MAP uroliths were fed diets with significantly lower fat content and significantly higher carbohydrate, calcium, phosphorus, magnesium, sodium, and potassium contents (Table 1). Also, cats with MAP uroliths were fed diets formulated to produce the greatest increase in urine pH. However, these differences may have also been confounded by correlations between several dietary components (Table 2).

When the quantities of dietary components were divided into quartiles (Table 3), univariate logistic regression analyses indicated that cats fed diets with high quantities of fiber, calcium, phosphorus, magnesium, sodium, or potassium had an increased risk of MAP urolith formation (*P* value for trend, < 0.05). Cats fed diets with low quantities of fat or high quantities of carbohydrate also had a significantly increased risk of MAP urolith formation, but the magnitude of the increased risk was comparatively small (OR < 2). When urine pH values attributed to diet formulations were divided into quartiles, cats fed diets formulated to increase urine pH had an increased risk of MAP urolith formation (*P* value for trend, < 0.05).

Distributions for breed, age, sex, body condition, and living environment were significantly ($P < 0.05$) different between case and control cats (Table 4). Therefore, multivariate logistic regression adjusting for breed, age, sex, body condition, and living environment was performed (Table 3). Cats fed diets with high quantities of fiber, calcium, phosphorus, magnesium, sodium, potassium, or chloride had an increased risk of MAP urolith formation (*P* value for trend, < 0.05). Likewise, cats fed diets formulated to reduce urine acidity had an increased risk of MAP urolith formation (*P* value for trend, < 0.05). Cats fed diets with low quantities of fat had a significantly increased risk of MAP urolith formation, but the magnitude of this increase was comparatively small (OR < 2). Although

Table 3—Odds of CaOx and MAP urolithiasis in cats as a function of content of various diet components

Diet component*	Median content	CaOx urolithiasis				MAP urolithiasis			
		Univariate OR	95% CI	Multivariate OR†	95% CI	Univariate OR	95% CI	Multivariate OR	95% CI
Protein (g/100 kcal)									
5.15–7.98	7.57	1.00	NA	1.00	NA	1.00	NA	1.00	NA
7.99–8.83	8.56	0.32	0.18–0.54	0.48	0.27–0.87	2.31	1.58–3.40	3.26	2.14–4.98
8.84–10.47	9.59	0.52	0.34–0.79	0.65	0.40–1.05	1.45	0.98–2.13	2.02	1.32–3.07
10.48–13.75	11.89	0.46	0.29–0.71	0.44	0.27–0.73	1.12	0.74–1.70	1.18	0.75–1.83
P-value		< 0.001		0.005		0.805		0.914	
Carbohydrate (g/100 kcal)									
0.52–4.15	2.20	1.00	NA	1.00	NA	1.00	NA	1.00	NA
4.16–8.02	6.84	2.96	1.85–4.71	2.57	1.54–4.30	1.04	0.73–1.49	0.89	0.60–1.30
8.03–9.94	9.55	1.25	0.67–2.33	1.28	0.65–2.51	1.30	0.86–1.95	1.24	0.80–1.92
9.95–14.00	11.10	2.16	1.28–3.63	2.01	1.13–3.59	1.50	1.04–2.17	1.28	0.86–1.92
P-value		0.129		0.232		0.017		0.136	
Fat (g/100 kcal)									
2.02–2.86	2.69	1.00	NA	1.00	NA	1.00	NA	1.00	NA
2.87–5.02	3.23	1.30	0.80–2.14	1.59	0.91–2.80	0.84	0.59–1.22	0.93	0.63–1.38
5.03–5.24	5.22	2.20	1.43–3.38	2.20	1.35–3.59	0.55	0.38–0.81	0.52	0.35–0.78
5.25–8.94	5.99	0.68	0.40–1.16	0.84	0.47–1.51	0.63	0.44–0.90	0.75	0.51–1.10
P-value		0.904		0.782		0.002		0.045	
Fiber (g/100 kcal)									
0.06–0.30	0.24	1.00	NA	1.00	NA	1.00	NA	1.00	NA
0.31–0.51	0.39	1.01	0.67–1.53	0.83	0.52–1.33	1.99	1.36–2.92	1.97	1.32–2.96
0.52–0.70	0.56	1.15	0.71–1.86	1.23	0.71–2.12	2.26	1.47–3.48	2.51	1.59–3.98
0.71–11.57	1.10	0.86	0.53–1.39	0.68	0.39–1.17	2.33	1.56–3.50	2.12	1.38–3.26
P-value		0.716		0.454		< 0.001		0.002	
Calcium (mg/kcal)									
0.97–2.05	2.05	1.00	NA	1.00	NA	1.00	NA	1.00	NA
2.06–3.20	2.87	0.21	0.12–0.36	0.21	0.12–0.39	2.50	1.63–3.84	3.02	1.91–4.78
3.21–3.75	3.41	0.30	0.19–0.49	0.46	0.27–0.78	2.51	1.64–3.85	3.73	2.34–5.93
3.76–5.06	3.93	0.52	0.34–0.80	0.64	0.40–1.03	2.22	1.43–3.45	3.05	1.89–4.93
P-value		< 0.001		0.263		0.002		< 0.001	
Phosphorus (mg/kcal)									
0.85–1.76	1.33	1.00	NA	1.00	NA	1.00	NA	1.00	NA
1.77–2.79	2.40	0.19	0.11–0.33	0.20	0.11–0.36	1.88	1.20–2.92	2.15	1.34–3.45
2.80–3.16	2.97	0.32	0.20–0.50	0.44	0.27–0.74	3.07	2.02–4.66	4.44	2.81–7.01
3.17–4.70	3.90	0.53	0.35–0.83	0.69	0.42–1.14	2.50	1.60–3.93	3.56	2.18–5.81
P-value		< 0.001		0.291		< 0.001			< 0.001
Magnesium (mg/kcal)									
0.09–0.18	0.17	1.00	NA	1.00	NA	1.00	NA	1.00	NA
0.19–0.25	0.22	0.29	0.19–0.46	0.33	0.21–0.54	0.97	0.65–1.45	1.03	0.67–1.59
0.26–0.35	0.30	0.32	0.16–0.61	0.37	0.18–0.77	1.77	1.10–2.85	2.05	1.23–3.43
0.36–1.40	0.39	0.61	0.40–0.91	0.93	0.58–1.50	2.65	1.81–3.87	3.69	2.43–5.62
P-value		0.027		0.884		< 0.001		< 0.001	
Sodium (mg/kcal)									
0.48–0.77	0.70	1.00	NA	1.00	NA	1.00	NA	1.00	NA
0.78–1.07	0.92	0.28	0.17–0.46	0.37	0.22–0.64	2.84	1.82–4.41	3.79	2.36–6.10
1.08–1.42	1.28	0.46	0.29–0.71	0.57	0.35–0.95	2.62	1.65–4.14	3.48	2.12–5.71
1.43–3.70	1.93	0.39	0.25–0.62	0.48	0.29–0.80	3.01	1.92–4.70	4.10	2.54–6.62
P-value		< 0.001		0.013		< 0.001		< 0.001	
Potassium (mg/kcal)									
0.95–1.60	1.27	1.00	NA	1.00	NA	1.00	NA	1.00	NA
1.61–1.80	1.69	0.72	0.48–1.09	0.77	0.48–1.23	0.50	0.32–0.79	0.48	0.30–0.77
1.81–2.16	1.93	0.37	0.23–0.58	0.49	0.30–0.82	1.45	1.02–2.05	1.79	1.23–2.61
2.17–3.20	2.23	0.40	0.23–0.70	0.45	0.24–0.84	1.08	0.71–1.66	1.18	0.75–1.86
P-value		< 0.001		0.004		0.027		0.006	
Chloride (mg/kcal)									
0.80–1.40	1.16	1.00	NA	1.00	NA	1.00	NA	1.00	NA
1.41–1.66	1.50	0.98	0.63–1.52	1.12	0.67–1.85	1.29	0.84–1.96	1.44	0.92–2.26
1.67–2.20	1.89	0.35	0.21–0.61	0.57	0.31–1.04	1.16	0.76–1.75	1.57	1.01–2.46
2.21–3.82	2.56	0.91	0.57–1.45	1.28	0.75–2.18	1.61	1.06–2.45	2.19	1.39–3.46
P-value		0.099		0.650		0.053		< 0.001	
Moisture (%)									
7.0–7.9	7.5	1.00	NA	1.00	NA	1.00	NA	1.00	NA
8.0–10.0	9.0	0.69	0.47–1.02	0.76	0.49–1.19	0.97	0.69–1.38	0.91	0.63–1.32
10.1–74.3	12.0	0.36	0.20–0.63	0.37	0.20–0.70	0.87	0.57–1.32	0.98	0.63–1.54
74.4–81.2	76.2	0.31	0.19–0.52	0.38	0.22–0.67	0.81	0.56–1.17	0.94	0.63–1.39
P-value		< 0.001		< 0.001		0.204		0.832	
Urine acidifying potential (pH)									
5.99–6.15	6.10	1.00	NA	1.00	NA	1.00	NA	1.00	NA
6.16–6.25	6.15	1.75	1.13–2.70	1.05	0.63–1.75	0.64	0.36–1.14	0.45	0.24–0.83
6.26–6.49	6.40	0.45	0.27–0.77	0.52	0.29–0.92	1.25	0.86–1.83	1.41	0.94–2.12
6.50–6.90	6.50	0.39	0.22–0.67	0.34	0.19–0.62	1.97	1.41–2.77	1.99	1.38–2.87
P-value		< 0.001		0.002		< 0.001		< 0.001	

Cats with CaOx or MAP uroliths were compared with control cats without any urinary tract diseases; owners provided information on each cat's diet.
*Diet components are given as quartiles. †Adjusted for breed (Himalayan or Persian vs any other breed), age (quartile), sex (female vs male), body condition (overweight vs not overweight), and living environment (strictly indoor vs all other environments).
OR = Odds ratio. CI = Confidence interval. NA = Not applicable.

Table 4—Demographic characteristics of cats with CaOx or MAP uroliths and of control cats without any urinary tract diseases

	Control cats (n = 827)		Cats with CaOx uroliths (n = 173)					Cats with MAP uroliths (n = 290)				
Characteristic	**No.**	**%**	**No.**	**%**	**OR**	**95% CI**	***P*-value**	**No.**	**%**	**OR**	**95% CI**	***P*-value**
Breed												
Himalayan or Persian	44	5.3	36	20.8	4.7	2.9–7.5	< 0.001	30	10.3	2.1	1.3–3.3	0.003
Other	783	94.7	137	79.2	1	Reference		260	89.7	1	Reference	
Age												
1–< 3 yrs	262	31.7	8	4.6	1	Reference	< 0.001	53	18.3	1	Reference	< 0.001
3–5 yrs	184	22.3	43	24.9	7.7	3.5–16.7		90	31.0	2.1	1.6–3.6	
> 5–9 yrs	164	19.8	72	41.6	14.4	6.8–30.6		98	33.8	3.0	2.0–4.4	
> 9 yrs	217	26.2	50	28.9	7.5	3.5–16.3		49	16.9	1.1	0.7–1.7	
Sex												
Male	407	49.2	88	50.9	1.1	0.8–1.5	0.693	173	59.7	1.5	1.2–2.0	0.002
Female	420	50.8	85	49.1	1	Reference		117	40.3	1	Reference	
Body condition												
Overweight	167	20.2	71	41.0	2.8	1.9–3.9	< 0.001	127	43.8	3.1	2.3–4.1	< 0.001
Other	660	79.8	102	59.0	1	Reference		163	56.2	1	Reference	
Living environment												
Strictly indoors	357	43.2	120	69.4	3.0	2.1–4.2	< 0.001	162	55.9	1.7	1.3–2.2	< 0.001
Other	470	56.8	53	30.6	1	Reference		128	44.1	1	Reference	

a significant trend was not observed between the quantity of dietary protein fed and MAP urolith formation, an increased risk of MAP urolithiasis was observed for cats fed diets containing moderate quantities of dietary protein.

Discussion

On the basis of results of studies in humans, dogs, and rats,[16-18] dietary factors that reduce the occurrence of MAP uroliths in cats have been incriminated in the recent reciprocal increase in the occurrence of CaOx uroliths. Specifically, diets formulated to prevent MAP urolithiasis that are high in protein and sodium contents, low in phosphorus and magnesium contents, and intended to increase urine acidity have been implicated in the increase in occurrence of CaOx uroliths. The significance of suspected risk factors has often been described in an "all-or-none" qualitative fashion, rather than in a quantitative way on the basis of risk ratios or OR.[18] However, whether these dietary risk factors play a limited or substantial role in development or prevention of CaOx or MAP urolithiasis has not been conclusively determined. Because of confounding interactions between various dietary ingredients and demographic factors (eg, breed, age, sex, and reproductive status), individual dietary risk factors may not be of equal importance in every exposed cat.[3] For example, compared with other breeds, Himalayan and Persian cats were 5 times as likely to develop CaOx uroliths and 2 times as likely to develop MAP uroliths. Likewise, compared with cats that were 1 to < 2 years of age, cats that were 7 to < 10 years of age were 67 times as likely to develop CaOx uroliths and 11 times as likely to develop MAP uroliths.[3]

Results of the present study do not support the reciprocal relationship hypothesis that diets high in protein and sodium and low in phosphorus and magnesium are associated with an increased risk of CaOx uroliths and a decreased risk of MAP uroliths in cats. However, our results do support the hypothesis that diets formulated to decrease the risk of MAP uroliths by increasing urine acidity reciprocally increased the risk of CaOx uroliths. In addition, our results suggest that diets low in potassium and sodium increased the risk of CaOx uroliths and decreased the risk of MAP uroliths. Furthermore, an increased risk of CaOx, but not MAP, uroliths was observed in cats fed diets low in protein and moisture. In contrast, an increased risk of MAP, but not CaOx, uroliths was observed in cats fed diets low in fat and high in fiber, calcium, phosphorus, magnesium, and chloride. Neither increased nor decreased risk of CaOx and MAP uroliths was observed in cats fed high carbohydrate diets.

Our results support the hypothesis that diets designed to minimize MAP urolith formation through urine acidification may have inadvertently increased the occurrence of CaOx urolithiasis in cats. Several biological phenomena provide plausible explanations for this association. Whereas diet-mediated urine acidification enhances the solubility of MAP crystals in cats,[19,20] dietary acids promote CaOx crystalluria by inducing hypercalciuria.[5] This association between aciduria, acidemia, and CaOx urolithiasis may be explained, at least in part, by the fact that acidemia promotes mobilization of carbonate and phosphate from bone to buffer hydrogen ion.[4,21,22] Concomitant mobilization of bone calcium may result in hypercalciuria. In addition, metabolic acidosis in dogs, humans, and rats results in hypocitraturia.[23] If consumption of dietary acid precursors is associated with hypocitraturia in cats, it may increase the risk of CaOx uroliths, because citrate is an inhibitor of CaOx crystal formation.

It is interesting that our observation of a decrease in the occurrence of MAP uroliths in cats and an increase in the occurrence of CaOx uroliths coincided with an increased emphasis by the pet food industry to manufacture urine acidifying diets to dissolve and prevent struvite crystalluria.[24] In a recent epidemiologic study,[16] cats with CaOx uroliths were > 3 times as likely as hospital control cats to have been fed diets that produce a urine pH of 6.29 or less. Similar to our results, cats fed diets formulated to produce a urine pH

between 5.99 and 6.15 were 3 times as likely to develop CaOx uroliths as cats fed diets formulated to produce a urine pH between 6.5 and 6.9. In contrast, cats fed diets formulated to produce a urine pH between 6.5 and 6.9 were 2 times as likely to develop MAP uroliths as cats fed diets formulated to produce a urine pH between 5.99 and 6.15.

Unexpectedly, our results indicated that diets that were high in sodium were associated with a decreased risk of CaOx urolith formation. Cats fed diets containing the highest sodium contents (1.43 to 3.70 mg/kcal) were only about half as likely (OR, 0.48) to develop CaOx uroliths as were cats fed diets containing the lowest sodium contents (0.48 to 0.77 mg/kcal). The sodium content of many adult feline maintenance diets manufactured in the United States has been reported to be approximately 0.5 to 1 mg/kcal.[25] The association we observed in our study was unexpected, because results of studies[26,27,b] of healthy adult humans and healthy adult dogs were interpreted to indicate that high dietary sodium consumption increased the risk of CaOx urolith formation by promoting hypercalciuria. However, results of a recent study[28] designed to assess the short-term effects of consumption of high (4 mg of sodium per kilocalorie) and low (0.4 mg of sodium per kilocalorie) levels of dietary sodium on urine calcium concentration in healthy adult dogs emphasized the need to be cautious about generalizations regarding the effects of dietary sodium on urine calcium concentration. In that study, the urine concentration of sodium was significantly higher in dogs consuming a high sodium diet; however, urine concentrations of calcium and oxalic acid were not significantly affected by the level of dietary sodium intake. A plausible unifying explanation of these apparently conflicting results is that increased dietary sodium enhances urine calcium excretion but, by augmenting urine volume, may not increase urine calcium and oxalic acid concentrations. Conceivably, calcium or oxalic acid concentrations could even be reduced. Even if the total quantity of urinary calcium excretion per day increased, CaOx uroliths would not be expected to form unless the urine was oversaturated with calcium and oxalic acid.[29] This explanation is supported by several studies[30,31] indicating that increased dietary sodium consumption by clinically normal cats increases urine volume. Appropriately designed studies in cats prone to CaOx urolithiasis are required to test the hypothesis that increased consumption of dietary sodium will result in enhanced calcium excretion but reduced urine calcium and oxalic acid concentrations.

In the present study, cats fed diets containing 1.43 to 3.70 mg of sodium per kilocalorie were 4.1 times as likely to develop MAP uroliths as cats fed diets containing 0.48 to 0.77 mg of sodium per kilocalorie. This association was unexpected, because consumption of high sodium diets would be expected to increase urine volume and decrease urine concentration of calculogenic minerals. However, we observed a significant correlation between high sodium content and high phosphorus content in diets fed to cats with MAP uroliths. Our findings are consistent with those of Finco et al[32] who observed that feeding clinically normal cats a high sodium diet (3.6 mg/kcal) resulted in increased urinary phosphorus excretion and increased phosphorus concentration, compared with feeding cats a lower sodium diet (1.6 mg/kcal). It is of interest that many diets contain monosodium phosphate or sodium tripolyphosphate as a source of sodium and phosphorus.[33] Thus, the association of high dietary sodium content and increased risk of MAP urolithiasis may be linked to the type of sodium salt in the diet.

Our results also indicated that diets high in potassium were associated with a decreased risk for CaOx urolith formation. Cats fed diets containing 2.17 to 3.20 mg of potassium per kilocalorie were less than half as likely (OR, 0.45) to develop CaOx uroliths as were cats fed diets containing 0.95 to 1.60 mg of potassium per kilocalorie. The reduced occurrence of CaOx urolith formation associated with dietary potassium may be related to potassium-induced alterations in urinary calcium excretion. A study[26] in healthy adult humans demonstrated that reducing dietary potassium by substituting KCl with NaCl or substituting $KHCO_3$ with $NaHCO_3$ was accompanied by increased urinary calcium excretion. Additionally, in another study[34] of healthy adult humans, potassium supplementation reduced calcium excretion. If a similar effect occurs in cats, it would provide a plausible explanation of why cats fed diets with high potassium contents had a decreased risk of CaOx urolithiasis.

Results from our study indicated that cats fed high potassium diets were 1.18 times as likely to develop MAP uroliths as were cats fed low potassium diets. However, we do not consider this association to be biologically significant.

Our results revealed that cats fed diets with a high moisture content (74.4 to 81.2%) were about a third as likely (OR, 0.38) to develop CaOx uroliths as were cats fed diets low in moisture (7.0 to 7.9%). This finding is consistent with observations in humans,[35] dogs,[36] and cattle,[37] in which increased water consumption associated with an increased volume of less-concentrated urine was an effective strategy to minimize formation of uroliths if it decreased urinary mineral concentration. Results of several studies[38-40] of clinically normal cats have also revealed that consumption of high moisture diets was associated with production of greater volumes of less-concentrated urine, compared with consumption of low moisture diets.

Unexpectedly, we did not observe an association between high moisture diets and a decreased risk of MAP urolithiasis. However, to our knowledge, an association between consumption of high moisture diets and reduced risk of MAP urolithiasis has not been documented in previous appropriately designed studies. In cats, it is a conceivable that dietary moisture-induced increases in urine volume have less influence on MAP urolith formation than on CaOx urolith formation. This hypothesis is supported by the observation that increasing water intake by adding sodium chloride to the diet of healthy adult male cats did not significantly influence production of magnesium phosphate uroliths in cats.[30] In another experimental study[41] of adult healthy male cats, a correlation between water consumption and magnesium phosphate urolith formation was not observed.

There is a general consensus that consumption of high protein diets increases the risk of CaOx urolith formation in humans and dogs by promoting acidosis and subsequent hypercalciuria.[35,42,43] Therefore, our observation that cats fed diets high in protein (10.48 to 13.75 g of protein per 100 kcal) were less than half as likely (OR, 0.44) to develop CaOx uroliths as cats fed diets low in protein (5.15 to 7.98 g of protein per 100 kcal) was unexpected. However, in a study of healthy cats,[44] consumption of a high protein diet (13.7 g/100 kcal) increased water consumption and urine volume. Additionally, feeding high protein diets to these cats did not increase urinary calcium excretion. On the other hand, urinary phosphorus excretion was increased. Results of a study[45] in humans indicated that increased urinary phosphorus excretion reduced the risk of CaOx urolithiasis by enhancing the urine concentration of pyrophosphate, a CaOx crystal inhibitor. One other plausible mechanism that may explain, at least in part, why CaOx uroliths formed less frequently in cats fed diets high in animal protein content is that such diets contain relatively high quantities of potassium.[46] In our study, cats fed diets high in potassium were half as likely (OR, 0.45) to develop CaOx uroliths as were cats fed low potassium diets. Verification of the significance of this hypothesis requires additional studies.

An experimental study[44] involving healthy adult cats revealed that increased consumption of dietary protein resulted in a significant increase in urine volume and urine acidification. It was therefore hypothesized that these changes would reduce the risk of MAP urolith formation. Consistent with these observations, results of our study revealed that there were significant correlations between dietary protein content, dietary moisture content, and dietary urine acidifying potential. However, we did not observe a reduction in the risk of MAP urolith formation in cats fed high protein diets. Additional studies are needed to clarify the effect of dietary protein on MAP urolith formation in cats.

Magnesium has been hypothesized to be an inhibitor of CaOx urolithiasis on the basis of several lines of evidence. For example, in vitro studies,[47,48] using synthetic human urine, revealed that the addition of magnesium reduced CaOx supersaturation by combining with oxalic acid. In addition, supplemental magnesium has been reported to prevent CaOx urolithiasis in humans,[49] although the benefits have not been clearly substantiated by controlled clinical trials. Observations such as these, coupled with the reciprocal increase in occurrence of CaOx urolithiasis in cats in association with widespread use of magnesium-restricted struvite prevention diets, have led to the hypothesis that a low urine concentration of magnesium is a risk factor for CaOx urolith formation in cats.[17] Our results are consistent with this hypothesis, as diets with the lowest magnesium content (0.09 to 0.18 mg/kcal) were associated with an increased risk of CaOx urolith formation, compared with diets with moderate magnesium content (0.19 to 0.35 mg/kcal). On the other hand, by causing hypercalciuria, consumption of excessive magnesium may also be a risk factor for CaOx urolith formation. For example, oral administration of magnesium oxide to humans with CaOx uroliths was associated with increased urinary calcium excretion.[50] Additionally, when 6 healthy dogs consumed a diet containing 2.5 mg of magnesium per kilocalorie, urinary calcium excretion was 5 times that observed when the same dogs consumed the same diet, except with only 0.2 mg of magnesium per kilocalorie.[b] Our results are consistent with these findings, as diets with the highest magnesium content (0.36 to 1.40 mg/kcal) were associated with an increased risk of CaOx urolith formation, compared with diets with moderate magnesium contents (0.19 to 0.35 mg/kcal). Therefore, to minimize the risk of CaOx urolith formation, our results suggest that dietary magnesium should not be restricted or supplemented. Further studies in cats with CaOx urolithiasis are needed to evaluate these observations.

Feeding healthy cats diets supplemented with magnesium results in formation of MAP crystals and uroliths.[41,51] The observation in our study that cats fed diets high in magnesium (0.36 to 1.40 mg of magnesium per kilocalorie) were 3.69 times as likely to develop MAP uroliths as cats fed diets low in magnesium (0.09 to 0.18 mg of magnesium per kilocalorie) is consistent with these findings.

Oral consumption of phosphorus has also been hypothesized to reduce the risk of CaOx urolithiasis. The hypocalciuric effect of dietary phosphorus is well established in humans.[52] In fact, humans with CaOx uroliths are often given neutral phosphate supplements to reduce urinary calcium excretion, CaOx crystalluria, and recurrence of CaOx uroliths.[53,54] In addition, salts of orthophosphate enhance urinary excretion of pyrophosphates and citrate.[55,56] Pyrophosphates and citrate are CaOx crystallization inhibitors. In contrast, diets deficient in phosphorus may stimulate calcitriol production, which in turn promotes intestinal absorption of calcium and phosphorus.[54] Also, diets deficient in phosphorus may enhance intestinal absorption and renal excretion of calcium that has not combined with phosphorus to form an insoluble salt.[42] On the other hand, excessive dietary phosphorus could form insoluble salts with dietary calcium, which in turn could increase the availability of noncomplexed oxalic acid for intestinal absorption and renal excretion. Our results are consistent with these observations in that the risk of CaOx urolith formation in cats fed diets with the lowest phosphorus content (0.85 to 1.76 mg/kcal) was up to 5 times the risk in cats fed diets with moderate phosphorus content (1.77 to 3.16 mg/kcal). In addition, diets with the highest phosphorus content (3.17 to 4.70 mg/kcal) were associated with an increased risk of CaOx urolith formation, compared with diets with moderate content (1.77 to 3.16 mg/kcal). These associations suggest that to reduce the risk of CaOx urolithiasis, dietary phosphorus should not be restricted or supplemented.

In our study, cats fed diets high in phosphorus (3.17 to 4.70 mg/kcal) were 3.56 times as likely to develop MAP uroliths as were cats fed diets low in phosphorus (0.85 to 1.76 mg/kcal). This observation was expected, because high consumption of phosphorus enhances urinary phosphorus excretion and, there-

fore, promotes supersaturation of urine with magnesium, ammonium, and phosphate.[32]

For decades, the prevailing consensus was that restriction of dietary calcium would reduce urinary calcium excretion and, therefore, reduce CaOx urolith formation. However, results of recent epidemiologic studies[27,57] in humans revealed that restriction of dietary calcium was a risk factor for CaOx urolith formation. Humans who consumed higher quantities of dietary calcium had the lower risk of CaOx urolithiasis. It was postulated that consumption of high dietary calcium increased formation of nonabsorbable CaOx in the intestinal lumen, resulting in reduced urinary oxalic acid excretion. Results of the present study parallel these findings, as cats fed diets with moderate quantities (2.06 to 3.75 mg/kcal) of calcium were a fourth to a half as likely to form CaOx uroliths, compared with cats fed diets with the lowest quantity (0.97 to 2.05 mg/kcal) of calcium. In addition, diets with the highest quantity (3.76 to 5.06 mg/kcal) of calcium were associated with an increased risk of CaOx urolith formation, compared with diets with moderate quantities (2.06 to 3.75 mg/kcal) of calcium. These associations suggest that to minimize CaOx urolithiasis in cats, dietary calcium should not be restricted or supplemented.

In the present study, increased consumption of dietary calcium was associated with a progressive increase in the risk of MAP urolith formation. One plausible explanation for this association is that consumption and intestinal absorption of dietary calcium results in hypercalcemia, which in turn reduces parathyroid hormone secretion. Reduction of parathyroid hormone secretion would be expected to decrease renal tubular reabsorption of magnesium and would promote supersaturation of urine with magnesium, ammonium, and phosphate.[58] Additionally, there is a direct correlation between the quantities of dietary calcium and phosphorus needed to maintain the recommended ratio between these minerals in feline commercial diets.[33] Therefore, diets with high calcium content would be expected to have correspondingly high phosphorus content, which would increase urinary phosphorus excretion.

In the present study, a significant association between dietary chloride and CaOx urolith formation was not observed. In contrast, cats fed diets high in chloride (2.21 to 3.82 mg/kcal) were 2.19 times as likely to develop MAP uroliths as cats fed diets lower in chloride (0.8 to 1.4 mg/kcal). Because several types of chloride salts (eg, sodium, potassium, calcium, choline [vitamin B_4], and pyridoxine [vitamin B_6]) are commonly used in many commercial diets,[33] associations between chloride content and MAP urolithiasis may be confounded. For example, in our study, the quantity of dietary chloride was directly correlated to the quantity of dietary calcium and dietary sodium, both of which were associated with an increased risk of MAP urolith formation.

A significant association between dietary fiber and CaOx urolith formation was not observed in our study. However, consumption of rice bran and soy bran by healthy people significantly reduced urinary calcium excretion.[59,60] This effect was attributed, at least in part, to reduced intestinal absorption of calcium as a result of rapid movement of ingesta through the intestinal tract.[61] Further, when large amounts of wheat bran were given to humans, the rate of CaOx urolith formation decreased.[61,c] However, results of another study[60] of healthy humans suggested that physical and chemical properties of different types of bran in diets had different effects on urinary calcium and oxalic acid excretion. Our study was not designed to identify quantities of specific types of fiber fed to case and control cats, and additional studies are needed to determine the effects of various types of dietary fiber on CaOx urolithiasis in cats.

Our results indicate that cats fed high fiber diets (0.71 to 11.57 g/100 kcal) were 2.12 times as likely to develop MAP uroliths as were cats fed low fiber diets (0.06 to 0.30 g/100 kcal). A plausible explanation for this observation is unknown to us. Further studies are needed to verify this finding in cats.

In our study, high fat diets were not consistently associated with an increased risk of CaOx urolith formation but were weakly associated with a decreased risk of MAP urolith formation. However, an increased risk of CaOx urolithiasis was observed in rats fed high fat diets.[35] Increased intestinal absorption and renal excretion of oxalic acid as a result of formation of insoluble nonabsorbable fatty acid-calcium salts in the intestinal lumen was postulated as a mechanism that could explain this observation.

In our study, high carbohydrate diets were not associated with an increased or decreased risk of CaOx or MAP urolith formation. However, consumption of high carbohydrate diets by humans may increase the risk of CaOx urolithiasis by increasing calcium excretion.[62] In healthy dogs[63] and humans,[64] a transient hypercalciuric response to dietary carbohydrates has been observed. Postprandial increases in plasma insulin concentration, which in turn impaired proximal renal tubular reabsorption of calcium, were suggested as one plausible explanation of this phenomenon.

Although results of our previous study[3] did not support the hypothesis that changes in breed, age, sex, and reproductive status contributed to the apparent reciprocal relationship between prevalences of CaOx and MAP urolithiasis in cats, certain associations with formation of CaOx and MAP uroliths were detected. For example, results of the present and previous studies indicated that Himalayan and Persian cats were 5 times as likely to develop CaOx uroliths and 2 times as likely to develop MAP uroliths as were cats of other breeds. Therefore, surveillance and diet modification may be necessary in some cats, especially older male Himalayan and Persian cats.

Because the present study was not designed to identify underlying mechanisms by which various dietary components promote or prevent CaOx and MAP urolithiasis, associations that we identified should not be interpreted as proof of cause-and-effect relationships. However, they may be used to help formulate hypotheses for prospective studies designed to reduce the risk of CaOx urolithiasis in cats. For example, on the basis of results of our epidemiologic study

Table 5—Summary of dietary formulations hypothesized to reduce risk of CaOx and MAP urolith formation in cats

Dietary factor	Minimum requirement*	CaOx uroliths	MAP uroliths
Protein (g/100 kcal)	6.5	10.5–13.8	5.2–8.0
Carbohydrate (g/100 kcal)	NR	0.5–4.2	0.5–4.2
Fat (g/100 kcal)	2.25	2.0–2.9	5.2–8.9
Fiber (g/100 kcal)	NR	0.06–0.3	0.06–0.3
Calcium (mg/kcal)	1.5	2.1–3.2	1.0–2.1
Phosphorus (mg/kcal)	1.25	1.7–2.8	0.9–1.8
Magnesium (mg/kcal)	0.1	0.2–0.3	0.1–0.2
Sodium (mg/kcal)	0.5	1.4–3.7	0.5–0.8
Potassium (mg/kcal)	1.5	2.2–3.2	1.0–1.6
Chloride (mg/kcal)	0.75	0.8–1.4	0.8–1.4
Moisture (%)	NR	74–81	7–81
Urine acidifying potential (pH)	NR	6.5–6.9	6.2–6.3

*Minimum requirement for adult cats recommended by the Association of American Feed Control Officials. Adapted from Debraekeleer J. Table J-8. In: Hand MS, Thatcher CD, Remillard RL, et al, eds. *Small animal clinical nutrition.* Marceline, Mo: Walsworth Publishing Co, 2000;1055.
NR = No specific requirement.

and in contrast to current recommendations by the **Association of American Feed Control Officials (AAFCO)**, we hypothesize that diets formulated to contain substantially higher contents of protein, sodium, potassium, and moisture; higher contents of calcium, phosphorus, and magnesium; and normal contents of carbohydrate, fat, fiber, and chloride may minimize formation of CaOx uroliths in cats (**Table 5**). In addition, modification of diets to reduce their urine acidifying potential may be beneficial. Furthermore, in contrast to current recommendations by the AAFCO, we hypothesize that diets formulated to contain a higher content of fat; normal contents of carbohydrate, fiber, calcium, phosphorus, magnesium, sodium, chloride, and moisture; and lower contents of protein and potassium may minimize formation of MAP uroliths. In addition, modification of diets to increase their urine acidifying potential may be beneficial. However, before these hypotheses about dietary modifications are adopted by food manufacturers, they should be investigated by appropriately designed clinical studies of cats with CaOx and MAP urolithiasis. Because demographic factors may also significantly affect the likelihood of urolithiasis,[3] these factors must be considered when evaluating dietary risk factors. To minimize potential confounding effects, such controlled studies should be designed to match cats with CaOx or MAP uroliths with control cats on the basis of breed, age, sex, and reproductive status.[3]

[a]Questionnaire available by request from Jody P. Lulich, Department of Small Animal Clinical Sciences, St Paul, MN 55108.

[b]Lulich JP. *Canine calcium oxalate urolithiasis: etiology, pathophysiology, and therapy*. PhD thesis, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St Paul, Minn, 1991.

[c]Jarrar K, Graef V, Guttmann W. The use of wheat bran in the calcium oxalate metaphylaxis and the decrease of calcium excretion (abstr). *Urol Res* 1984;12:42.

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