Epidemiology of struvite uroliths in ferrets: 272 cases (1981–2007)

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Objective—To confirm that the predominant mineral type in naturally occurring uroliths in ferrets is struvite; to determine whether age, breed, sex, reproductive status, geographic location, season, and anatomic location are risk factors associated with urolith formation in ferrets; to compare features of struvite uroliths in cats with those in ferrets; and to determine whether there is a logical evidence-based rationale for clinical trials of the safety and efficacy of diet-induced dissolution of struvite uroliths in ferrets.

Design—Retrospective case-control study.

Animals—408 ferrets with uroliths (272 struvite uroliths) from the Minnesota Urolith Center, and 6,528 control ferrets from the Veterinary Medical Database.

Procedures—Historical information was obtained about each ferret. The association between proposed risk factors and outcome (struvite urolith formation) was assessed.

Results—Sterile struvite was the predominant mineral in uroliths in ferrets. Neutered male ferrets had a significantly increased risk of developing sterile struvite uroliths. A significant association was also found between increasing age and the detection of struvite uroliths. Struvite uroliths in ferrets were more likely to be retrieved from the lower urinary tract than from the upper urinary tract.

Conclusions and Clinical Relevance—Knowledge of predominant mineral type in uroliths along with insight into etiologic, demographic, and environmental risk and protective factors for urolithiasis may facilitate development of surveillance strategies that result in earlier detection of uroliths in ferrets. Modification of risk factors, including dietary risk factors, may help to minimize urolith formation, dissolve existing uroliths, and minimize urolith recurrence. (J Am Vet Med Assoc 2011;239:1319–1324)

Ferrets are becoming increasingly popular as household pets. As the population of pet ferrets increases, uroliths are being recognized with increased frequency. For example, in 1981, the Minnesota Urolith Center analyzed uroliths from only 2 ferrets. In comparison, in 2007, uroliths from 176 ferrets were submitted for analysis. As the frequency of detection of uroliths in ferrets increases, knowledge of different mineral types of uroliths affecting ferrets and associated risk factors for urolith formation is needed to develop effective diagnostic, management, and prevention strategies.

The purpose of the study reported here was to determine the predominant mineral type in naturally occurring uroliths in ferrets submitted to the Minnesota Urolith Center and to determine whether the ferret’s age, breed, sex, reproductive status, and geographic location; season of detection; and location within the urinary tract were risk factors associated with struvite urolith formation in ferrets. Risk factors associated with sterile struvite uroliths were then compared with risk factors associated with sterile struvite uroliths in cats with the goal of determining whether ferrets would be candidates for dietary trials for diet-induced sterile struvite urolith dissolution. Because we had limited access to ferrets with uroliths, we directed our efforts toward evaluation of the epidemiological features of this disorder.

Materials and Methods

Cases—Medical records of urolith submissions to the Minnesota Urolith Center of the University of Minnesota College of Veterinary Medicine were reviewed. Patients included 408 ferrets with uroliths, of which 272 were struvite uroliths submitted by veterinarians in the United States between January 1, 1981, and December 31, 2007. Uroliths retrieved from ferrets evalu-
ated at the Minnesota Urolith Center were counted only once for each year. To minimize confounding of the data by inclusion of ferrets with a history of recurrent uroliths, data related to recurrences were excluded.

**Controls**—The control group consisted of 6,528 ferrets without urinary tract disorders admitted to veterinary teaching hospitals in the United States between January 1, 1981, and December 31, 2007. They were identified by searching the records of the Veterinary Medical Database, which is responsible for compiling patients’ encounter data from nearly all North American veterinary medical colleges. Because preliminary evaluation indicated that uroliths were not detected in ferrets < 2 months of age, ferrets < 2 months of age were also excluded from the study.

**Urolith analysis**—The mineral composition of uroliths was determined by means of optical crystallography. When the composition of uroliths could not be determined by means of optical crystallography, the mineral composition was determined by means of infrared spectroscopy. Only ferrets with uroliths composed of at least 70% of the primary mineral were included. Uroliths containing nuclei and shell of different mineral types were classified as compound. Uroliths without a nidus or shell and containing < 70% of a single mineral component were classified as mixed.

**Evaluation of struvite uroliths for microbes**—By use of a table of random numbers, struvite uroliths from 10 ferrets were randomly selected from the collection of 272 archived air-dried struvite urolith submissions. They were immersed in separate containers of 2% malin for 12 hours to fix noncrystalline matrix components. These uroliths were then immersed in a de-calcifying solution containing 1% dilute hydrochloric acid and 95% EDTA for 10 minutes. The demineralized uroliths were placed in 1-piece tissue cassettes, embedded in paraffin, and stored at room temperature (20ºC [68ºF]) overnight. Then, they were cut at a thickness of 5 µm with a microtome and a section of each struvite urolith was stained with H&E as well as Gram stain. All sections were examined via light microscopy to detect bacteria. In a similar manner, 30 uroliths were randomly selected for bacterial aerobic culture by use of a technique previously described.

**Statistical analysis**—Standard statistical software was used to determine descriptive statistics of age, sex, reproductive status, and geographic area in the West of the United States and geographic location of the urolith within the urinary tract, and season of urolith submission. Ferrets were assigned to 1 of 6 age groups (2 to < 6 months, 6 months to < 1 year, 1 to < 2 years, 2 to < 4 years, 4 to < 7 years, and ≥ 7 years).

Crude ORs, adjusted ORs, and logistic regression were calculated at 95% CIs by use of the Woolf method to assess whether age, sex (male vs female), reproductive status (neutered vs sexually intact), season (fall vs spring vs winter vs summer), anatomic location (lower vs upper urinary tract), and geographic location (Midwest vs Southwest vs West vs Southeast vs Northeast) were associated with the occurrence of struvite uroliths. If any expected cell frequency in a contingency table was < 5, the Fisher exact test was used. In the present study, age group 2 to < 6 months, females, sexually intact reproductive status, winter, struvite uroliths anatomic location in the upper urinary tract, and geographic area in the West of the United States were arbitrarily chosen as reference groups for statistical analysis.

The 26-year study was arbitrarily grouped into 5 intervals (1981 to 1986, 1987 to 1992, 1993 to 1998, 1999 to 2004, and 2005 to 2007) to determine whether risk or protective factors changed over time. The Breslow-Day statistic was computed to determine whether ORs were homogenous over the 5 time intervals. Odds ratios for age group, sex, and reproductive status were calculated for each interval. The Mantel-Haenszel summary of OR was computed when results of the Breslow-Day test were not significant. Values of $P < 0.05$ were considered significant.

Because of the absence of continuous variables, ORs and univariate logistic regression analyses were computed by use of a hierarchic well-formulated modeling method to find the best risk model for age group, sex, reproductive status, season, anatomic location, and geographic location. After adjustment for confounding factors and interactions was made, risk factors for developing uroliths were determined from the best model. Odds ratio estimates were considered to be significantly different from 1 if the 95% CI did not encompass 1.0. On the basis of recommendations by Lilienfeld and Stolley, we classified significant ORs between 1.1 and 1.9 and ORs between 0.5 and 0.9 as weak associations. Likewise, we interpreted significant ORs > 2 (ie, risk) and < 0.5 (ie, protective) as clinically (biologically) important. All analyses were performed with standard software. Results were considered significant at values of $P < 0.05$.

**Results**

**Urolith composition**—Between 1981 and 2007, uroliths retrieved from 408 ferrets were analyzed at the Minnesota Urolith Center of which 272 (67%) were composed of struvite, 61 (15%) were cystine, and 43 (11%) were calcium oxalate. The remaining 32 (8%) were composed of ammonium urate (n = 8), calcium carbonate (1), calcium hydrogen phosphate (3), magnesium hydrogen phosphate (1), mixed minerals (6), mixed minerals (4), silica (1), ≥ 2 minerals (compound; 4), and dried blood (4). Uric acid, sodium urate, and xanthine uroliths were not observed. Of 272 uroliths classified as struvite, 239 (88%) were composed of 100% struvite, 22 (8%) were composed of 90% to 99% struvite, and 11 (4%) were composed of 70% to 89% struvite.

**Urolith histologic examination and bacteriologic culture**—Bacteria were not detected by means of aerobic culture (n = 50) nor by histologic examination of Gram-stained uroliths (10). Likewise, bacteria were not detected in H&E-stained urolith sections (n = 10).

Age—Mean ± SD age of ferrets with struvite uroliths was 3.6 ± 1.9 years (range, 0.2 to 9.8 years; median, 4.5 years). For all 408 ferrets, age ranged from 0.2 to 10.3 years.
Struvite uroliths were found most commonly in the 2 to < 4 year (38%) age group, followed by the 4 to < 7 year (34%) age group (Figure 1; Table 1). A significant (P < 0.001) association was found between advancing age and the detection of struvite uroliths. From 1981 to 1986, the mean age was 2.5 ± 1.8 years. From 1987 to 1992, the mean age was 3.5 ± 0.7 years. From 1993 to 1998, the mean age was 3.5 ± 1.6 years. From 1999 to 2004, the mean age was 4.9 ± 1.6 years. From 2005 to 2007, the mean age was 5.5 ± 1.6 years.

Using 2- to 6-month-old ferrets as the baseline control group for comparison, 2- to 4-year-old ferrets were 8.8 times (95% CI, 4.2 to 18.5; P < 0.001) as likely to develop struvite uroliths as were ferrets in the control group. Ferrets 4 to < 7 years old were 6.7 times (95% CI, 3.1 to 13.9; P < 0.001) as likely to develop struvite uroliths, compared with 2- to 6-month-old ferrets (Figure 1; Table 1).

For the Breslow-Day test, it was necessary to divide ferrets into 2 age groups: those < 4 years old and those ≥ 4 years old. Ferrets ≥ 4 years old were 1.3 times as likely to develop struvite uroliths as were ferrets < 4 years old.

Sex—Of 260 ferrets with struvite uroliths for which sex was recorded, 73% (n = 189) were males and 27% (71) were females. Male ferrets were 3.6 (95% CI, 2.5 to 5.1; P < 0.001) times as likely to develop struvite uroliths as were females (Figure 2; Table 1).

Reproductive status—Of 263 ferrets with struvite uroliths for which reproductive status was recorded, 237 (90%) were neutered and 26 (10%) were sexually intact. Neutered ferrets were 2.3 times (95% CI, 1.5 to 3.5; P < 0.001) as likely to develop struvite uroliths as were sexually intact ferrets (Figure 3; Table 1).

Anatomic location—Of 258 struvite uroliths for which location was recorded, 198 (77%) were retrieved from the urinary bladder, 56 (22%) from the urethra, 1 (1%) from a kidney, and 3 (1%) from the ureters. Uroliths were voided by 14 (5%) ferrets. Struvite uroliths in ferrets were significantly (P < 0.001) more likely to be retrieved from the lower urinary tract (bladder and urethra; n = 254) than from the upper urinary tract (kidneys and ureters; 4) in both males and females (Figure 4; Table 1).

Geographic location—Of the 250 ferrets with struvite urolithiasis for which the geographic locations in the United States were recorded, 79 (32%) were from the Midwest, 54 (22%) were from the Northeast, 70 (28%) were from the Southeast, 24 (10%) were from the Southwest, and 23 (9%) were from the West (Figure 5; Table 1).

Table 1—Crude and adjusted ORs and logistic regression analysis of struvite uroliths in ferrets submitted to the Minnesota Urolith Center between 1981 and 2007 by age, sex, reproductive status, anatomic location, season, and geographic location (affected ferrets vs control ferrets from the Veterinary Medical Database).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P value</th>
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<tr>
<td>Age</td>
<td>6 mo to &lt; 1 y vs 2 to &lt; 6 mo</td>
<td>1.4</td>
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<td>0.7</td>
<td>0.2–2.2</td>
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<td></td>
<td>1 to &lt; 2 y vs 2 to &lt; 6 mo</td>
<td>3.4</td>
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<td>1.3–6.8</td>
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<tr>
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<td>4.0–14.3</td>
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<td>4 to &lt; 7 y vs 2 to &lt; 6 mo</td>
<td>6.9</td>
<td>3.8–13.1</td>
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<td>3.1–13.9</td>
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<tr>
<td></td>
<td>≥ 7 y vs 2 to &lt; 6 mo</td>
<td>4.5</td>
<td>1.9–10.6</td>
<td>4.4</td>
<td>1.8–12.1</td>
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<td>Sex</td>
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<td>2.5–4.9</td>
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<td>2.5–5.1</td>
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<td>0.2–0.5</td>
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<td>1.6–3.5</td>
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<td>0.2–0.5</td>
<td>2.3</td>
<td>1.6–3.5</td>
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<td>Anatomic location</td>
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<td>4.5–12.6</td>
<td>9.5</td>
<td>5.6–17.8</td>
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<td>5.5–16.1</td>
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4). Using the West as a reference point, a significantly ($P < 0.001$) greater number of ferrets with struvite uroliths resided in the Northeast (Figure 5; Table 1) at the time uroliths were retrieved.

**Seasonal distribution**—Of 272 ferrets with struvite uroliths for which the date was recorded at the time the uroliths were retrieved, 50 (18%) were recorded in winter, 60 (22%) were recorded in spring, 83 (31%) were recorded in summer, and 79 (29%) were recorded in fall (Figure 6). Using winter ($n = 60$ [22%]) as a reference season, probabilities observed for summer ($P = 0.43$), spring ($P = 0.98$), and fall ($P = 0.55$) were not significant.

**Struvite urolith changes over time**—The number of struvite uroliths ($n = 272$) submitted to the Minnesota Urolith Center increased from 3 (1%) between 1981 and 1992 to 47 (17%) between 2005 and 2007. The largest number ($n = 125$) of struvite uroliths submitted to the Minnesota Urolith Center was between 1999 and 2004. During the same time interval, the mean ± SD age of ferrets with struvite uroliths increased from 2.5 ± 1.8 years between 1981 and 1992 to 5.5 ± 1.6 years between 2005 and 2007 (median, 4 years; range, 0.2 to 9.8 years).

**ORs and logistic regression**—Age, sex, reproductive status, and geographic location were adjusted as potentially confounding variables. Neutered male ferrets ($P < 0.001$), ferrets 2 to 4 years of age ($P < 0.001$), ferrets 4 to 7 years of age ($P < 0.001$), ferrets with uroliths in the lower urinary tract ($P < 0.001$), and ferrets from the Northeast ($P < 0.001$) had increased risk for struvite urolithiasis (Table 1).

**Breed**—Unlike cats and dogs, ferrets are not classified according to breed. They are differentiated by their coat colors. Ferrets with different coat colors are often grouped together into 1 category designated as domestic ferrets. We were unable to classify ferrets by breed or coat color.

**Discussion**

The results of the present study support our hypothesis that struvite is the predominant mineral found in uroliths in ferrets. Other investigators have reported$^{13-16}$ that struvite is a common mineral in ferret uroliths, but we could not find any evidence-based studies identifying sterile struvite as the most common form of struvite in this species. In the present study, bacteria
were not detected via light microscopic examination of sections of a representative subset of struvite uroliths stained with H&E (n = 10) and Gram stain (10). Likewise, aerobic bacteria were not cultured from a different subset of struvite uroliths (n = 30).

In the present study, struvite uroliths were commonly retrieved from 2- to 7-year-old ferrets. In a study of cats with sterile struvite uroliths reported in 2000, a similar range of ages (4 to 7 years) were found to be most common. Data derived from studies in dogs, cats, and humans suggest increased age is a risk factor for urolithiasis. Results of the present study of 272 ferrets with sterile struvite uroliths indicated that they were detected in male ferrets (73%) more often than in females (27%). These results may be related to the observations that the os penis of male ferrets is J-shaped and also that the distal portion of the urethra of male ferrets is smaller in diameter than the proximal portion of the urethra. These anatomic characteristics likely predisposed them to partial or total obstruction of the urethral lumen with uroliths.20,21 Struvite uroliths have been reported to be equally common in female and male cats.17

A higher proportion of neutered male and female ferrets (79%) had sterile struvite uroliths, compared with the proportion for sexually intact ferrets (21%). However, there was no association between reproductive status and uroliths in that the same trend of association with neutering was observed in the control group. Of the 258 sterile struvite uroliths, 98% were retrieved from the bladder and urethra and < 2% were retrieved from the kidneys and ureters. The occurrence of struvite uroliths from the lower urinary tract of domestic cats has been documented.22,23 Ferrets, dogs, and cats are similar in that nephroliths are uncommon, whereas nephroliths are most common in humans.24

The results of the present study support the hypothesis that struvite uroliths may be influenced by region of submission because a significant (P < 0.001) number of ferret struvite uroliths were submitted to the Minnesota Urolith Center from the Northeast region, compared with the West. The present study was not designed to explore the reasons for this observation. Our study did not support the hypothesis that seasons of the year were associated with struvite submission. Because the population of ferrets with struvite uroliths involved in this study (n = 272) was small, this observation should be verified by evaluating a larger population of clinically affected animals.

Of 272 uroliths classified as struvite in the present study, 239 (88%) were composed of 100% struvite, 22 (8%) were composed of 90% to 99% struvite, and 11 (4%) were composed of 70% to 89% struvite. We interpret these data as evidence to support our conclusion that ferrets are similar to domestic cats in that struvite uroliths in both species are uncommonly associated with uroseal-producing microbial urinary tract infections.25 In contrast, struvite uroliths in dogs and humans typically form as a result of urinary tract infections with urease-producing microbes.13 Infection-induced struvite uroliths found in dogs and humans typically contain 10% to 15% carbonate-apatite and 5% to 10% ammonium urate in addition to struvite.18 In our experience with tens of thousands of canine and feline struvite uroliths, infection-induced uroliths commonly contain carbonate-apatite and ammonium urate.18 In contrast, sterile struvite uroliths typically do not contain other biogenic minerals such as calcium carbonate-apatite and ammonium urate.

Struvite uroliths were classified as sterile struvite in this study on the basis of mineral composition, light microscopic appearance, and sterile cultures. We studied the epidemiological features of ferrets with sterile struvite uroliths and compared them with the epidemiological features of sterile struvite uroliths retrieved from cats. There are many similarities. For example, both species are obligate carnivores.26-27 Both species form struvite uroliths that are sterile.19,20,22,23 In both species, infection-induced uroliths are uncommon.19,22,23 In both species, bacterial urinary tract infections also appear to be uncommon.24,28 In healthy ferrets and cats, the urine pH range is similar (pH, 5.5 to 7).29 Likewise, the urine specific gravity values in both are typical of carnivores (1.001 to 1.089).28 In both species, urine osmolality is similar (≥ 3,000 mOsm/L).28 Also, in both species, neutering (≥ 90%) and lower urinary tract anatomic location of struvite uroliths (≥ 93%) are common.11,21,22,23 Whereas the os penis in ferrets is J-shaped, the os penis is straight in cats. Both species have narrow lumens in the distal portion of the urethra.22,23

The advent of safe and effective diet treatment to induce dissolution of sterile struvite uroliths in cats30 and the parallels between struvite urolithiasis in ferrets and cats30 prompts questions as to the safety and efficacy of diet-induced dissolution and prevention of sterile struvite urolith formation in ferrets. One of the goals of the present study was to compare features of sterile struvite in ferrets with those in cats. In our opinion, the results of those comparisons provide an evidence-based rationale for clinical trials to determine the safety and efficacy of diet-induced dissolution of sterile struvite uroliths in ferrets.

References

Magnetic resonance imaging vertebral canal and body ratios in Doberman Pinschers with and without disk-associated cervical spondylomyelopathy and clinically normal English Foxhounds

Steven De Decker et al

Objective—To determine magnetic resonance imaging (MRI) vertebral ratio values representing vertebral canal height, vertebral canal shape, and vertebral body shape in Doberman Pinschers with and without disk-associated cervical spondylomyelopathy (DACSM) and clinically normal English Foxhounds.

Animals—Doberman Pinschers with (n = 18) and without (20) DACSM and clinically normal English Foxhounds (19).

Procedures—All dogs underwent low-field MRI of the cervical vertebra. From 5 specific measurements made at C3 through C7, 4 linear vertebral ratios were calculated and assessed for correlation: vertebral canal height-to-body height ratio (CBHR), vertebral canal height-to-body length ratio (CBLR), caudal canal height-to-canonical canal height ratio (CCHR), and vertebral body length-to-height ratio (BLHR). The CBHR and CBLR described vertebral canal height, CCHR described vertebral canal shape, and BLHR described vertebral body shape. A midvertebral canal-occupying ratio (mVCOR) for the spinal cord was calculated at C5.

Results—Compared with both groups of unaffected dogs, CBHR, CBLR, and BLHR for Doberman Pinschers with DACSM were significantly smaller. The C7 CCHR was significantly larger in DACSM-affected Doberman Pinschers, compared with clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds. Ratios did not differ significantly between unaffected Doberman Pinschers and clinically normal English Foxhounds.

Conclusions and Clinical Relevance—Doberman Pinschers with DACSM had significantly smaller vertebral canal heights and more square-shaped vertebral bodies, compared with unaffected Doberman Pinschers, combined with a funnel-shaped vertebral canal at C7. Breed-specific differences were not evident. Linear MRI vertebral canal-to-body ratios did not appear to predict relative vertebral canal stenosis. (Am J Vet Res 2011;72:1496–1504)