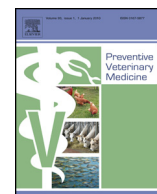




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# Risk factors associated with calcium oxalate urolithiasis in dogs evaluated at general care veterinary hospitals in the United States

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### ABSTRACT

Calcium oxalate urolithiasis results from the formation of aggregates of calcium salts in the urinary tract. Difficulties associated with effectively treating calcium oxalate urolithiasis and the proportional increase in the prevalence of calcium oxalate uroliths relative to other urolith types over the last 2 decades has increased the concern of clinicians about this disease. To determine factors associated with the development of calcium oxalate urolithiasis in dogs evaluated at general care veterinary hospitals in the United States, a retrospective case-control study was performed. A national electronic database of medical records of all dogs evaluated between October 1, 2007 and December 31, 2010 at 787 general care veterinary hospitals in the United States was reviewed. Dogs were selected as cases at the first-time diagnosis of a laboratory-confirmed urolith comprised of at least 70% calcium oxalate ( $n = 452$ ). Two sets of control dogs with no history of urolithiasis diagnosis were randomly selected after the medical records of all remaining dogs were reviewed: urinalysis examination was a requirement in the selection of one set ( $n = 1808$ ) but was not required in the other set ( $n = 1808$ ). Historical information extracted included urolith composition, dog's diet, age, sex, neuter status, breed size category, hospital location, date of diagnosis, and urinalysis results. Multivariable analysis showed that the odds of first-time diagnosis of calcium oxalate urolithiasis were significantly ( $P < 0.05$ ) greater for dogs  $< 7$  years, males (OR: 7.77, 95% CI: 4.93–12.26), neutered (OR: 2.58, 1.44–4.63), toy- vs. medium-sized breeds (OR: 3.15, 1.90–5.22), small- vs. medium-sized breeds (OR: 3.05, 1.83–5.08), large- vs. medium-sized breeds (OR: 0.05, 0.01–0.19), and those with a diagnosis of cystitis within the previous year (OR: 6.49, 4.14–10.16). Urinary factors significantly associated with first-time diagnosis of calcium oxalate urolithiasis were acidic vs. basic pH (OR: 1.94, 1.22–3.10), presence of RBCs (OR: 6.20, 3.91–9.83) or WBCs (OR: 1.62, 1.03–2.54), and protein concentration  $> 30$  mg/dL (OR: 1.55, 1.04–2.30). Patient demographics and urinalysis results are important factors that can support risk assessment and early identification of canine oxalate urolithiasis. Therefore, periodic urolith screening and monitoring of urine parameters should be encouraged for dogs at risk of developing these uroliths.

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**Abbreviations:** CaOx, calcium oxalate; CI, confidence interval; OR, odds ratio; Non-specific controls, control dogs with or without urinalysis results and no history of urolithiasis; RBC, red blood cell; SD, standard deviation; UTI, urinary tract infection; Urinalysis-specific controls, control dogs with urinalysis results and no history of urolithiasis; WBC, white blood cell.

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## 1. Introduction

Calcium oxalate (CaOx) and struvite (composed of magnesium ammonium phosphate hexahydrate) urolithiasis are the two most prevalent types of uroliths found in dogs (Adams and Syme, 2010). In the early 1980s, the proportion of CaOx uroliths relative to struvite uroliths was low (Bovee and McGuire, 1984; Osborne et al., 1986; Jones et al., 1998; Sosnar et al., 2005). Since 2001, however, submissions of CaOx uroliths to urolith laboratories has been increasing relative to struvite uroliths (Ling et al., 2003; Houston et al., 2004; Appel et al., 2008; Osborne et al., 2009; Low et al., 2010; Wisener et al., 2010a, 2010b). For example, a United States urolith laboratory reported 78% and 5% of canine uroliths were struvite and CaOx uroliths, respectively, in 1981 compared to 40% struvite uroliths and 41% CaOx uroliths in 2007 (Osborne et al., 2009). The recurrence of CaOx uroliths is not uncommon even after surgical removal of uroliths, suggesting that surgery may only provide short-term relief for some dogs (Lekcharoensuk et al., 2000). Effective medical protocols or special diets aimed at the dissolution of CaOx uroliths are currently unavailable, probably because of insufficient understanding of the factors involved in the pathogenesis of this urolith (Lulich et al., 1999a). Difficulties associated with an effective treatment for CaOx uroliths and its increase in proportional morbidity has increased the clinical concern about this disease.

Several hypotheses have been proposed to explain the change in the relative proportion of CaOx to struvite urolithiasis. The introduction in 1983 of calculolytic diets designed to dissolve struvite uroliths and the subsequent widespread use of these diets has been proposed to have reduced the submissions of struvite uroliths thus increasing the relative proportion of CaOx submissions (Osborne et al., 1999b; Ling et al., 2003; Osborne et al., 2009). However, the absence of a concomitant increase in the proportion of other urolith submissions such as calcium phosphate, silica, and cystine does not support this hypothesis (Lulich et al., 1999b; Low et al., 2010). Another hypothesis is that those calculolytic diets, in addition to preventing or decreasing the risk of struvite uroliths, could be increasing the risk of CaOx uroliths. This speculation was based on the widespread use of maintenance and prevention diets to minimize struvite uroliths in dogs (Osborne et al., 2009; Low et al., 2010). Nevertheless, neither of these hypotheses has been supported scientifically.

The risk factors for CaOx urolithiasis in dogs are complex because CaOx urolith formation depends on many factors, including the extent of urine saturation with CaOx and the balance between the promoters and inhibitors of urinary CaOx formation (Stevenson et al., 2003b). The promoters of CaOx formation are hypercalciuria and hyperoxaluria (Gisselman et al., 2009). Conditions associated with hypercalciuria in dogs include systemic hypercalcemia, diseases such as hyperadrenocorticism, certain medications (e.g., glucocorticoids), excessive dietary intake of calcium, protein, vitamin D or vitamin C intake, and acidifying diets (Hess et al., 1998; Bartges, 2004). Hyperoxaluria is associated with increased dietary oxalate precursors (Lulich et al., 1999b). On the other hand, inhibitors of CaOx formation

include substances such as pyrophosphate and nephrocalcin (Lulich et al., 1999b; Carvalho et al., 2006). As part of the complexity of the epidemiology of CaOx urolithiasis in dogs, signalment, environmental, and clinical factors are associated with the formation of these uroliths. These factors include dog age, sex, neuter status, breed, body condition score, geographic location, and diet (Ling et al., 1998a,c,d; Lulich et al., 1999a,b, 2001; Lekcharoensuk et al., 2000, 2002a,b; Wisener et al., 2010a). On average, CaOx urolithiasis are found in older dogs of either sex ranging from 8 to 10 years (Ling et al., 1998d). Male dogs are more commonly affected than females (Lulich et al., 1991; Weichselbaum et al., 1998; Ling et al., 1998a,c,d; Lulich et al., 1999a,b; Wisener et al., 2010a). Among canine uroliths submitted to laboratories for analysis, the most common breeds affected by CaOx uroliths are Miniature Schnauzers, Yorkshire Terriers and Pomeranians (Lulich et al., 1991; Weichselbaum et al., 1998; Ling et al., 1998c).

Most previous studies (Lulich et al., 1999b; Wisener et al., 2010a,b) evaluated the risk factors for CaOx urolithiasis in dogs using records from urolith laboratories and risk factors were derived from comparisons between urolith types or from registries without control subjects. The identification of controls can be a limitation of studies from diagnostic laboratories or referral clinics. Although two studies of risk factors for CaOx urolithiasis involved controls dogs that did not have urolithiasis, it is not clear whether the cases in these studies were first-time development only or a combination of first-time development and recurrent cases (Lekcharoensuk et al., 2000, 2002b). Because recurrence is known to occur among dogs with urolithiasis after surgical removal of the uroliths (Lekcharoensuk et al., 2000), the factors associated with first-time development of CaOx urolithiasis may differ from those associated with recurrence. Consequently, the objective of this retrospective case-control study was to identify dietary, signalment, temporal, and clinical factors associated with the first-time diagnosis of CaOx uroliths in a population of dogs that visit general care veterinary hospitals in the United States.

## 2. Materials and methods

### 2.1. Study population

All dogs in this study came from a population of dogs routinely seen from October 1, 2007 through December 31, 2010 at 787 general care veterinary hospitals located in 43 states of the United States. The 7 states without these hospitals were Hawaii, Alaska, Wyoming, North Dakota, West Virginia, Vermont, and Maine. These hospitals, managed and operated by Banfield Pet Hospital, used a uniform proprietary health data entry software program (PetWare, Banfield Pet Hospital, Portland, OR, USA). These electronic health records were uploaded nightly to a central database for storage. With the exception of medical notes and detailed compositions of uroliths, which had free text, the rest of information on patient's demographics, diets, ailments, urinary results, and diagnosis had preselected alternatives from drop-down menus with an extra option 'other' where free text could be entered for clarification,

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