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Pathogenesis of calcium oxalate urinary stone disease: species comparison of humans, dogs, and cats

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Abstract

Idiopathic calcium oxalate nephrolithiasis is a highly recurrent disease that is increasing in prevalence. Decades of research have not identified effective methods to consistently prevent the formation of nephroliths or induce medical dissolution. Idiopathic calcium oxalate nephroliths form in association with renal papillary subepithelial calcium phosphate deposits called Randall’s plaques (RPs). Rodent models are commonly used to experimentally induce calcium oxalate crystal and stone formation, but a rodent model that conclusively forms RPs has not been identified. Both dogs and cats form calcium oxalate uroliths that can be recurrent, but the etiopathologic mechanisms of stone formation, especially renal pathologic findings, are a relatively unexploited area of study. A large animal model that shares a similar environment to humans, along with a shorter lifespan and thus shorter time to recurrence, might provide an excellent means to study preventative and therapeutic measures, along with enhancing the concepts of the One Health initiative. This review article summarizes and compares important known features of idiopathic calcium oxalate stone disease in humans, dogs, and cats, and emphasizes important knowledge gaps and areas for future study in the quest to discover a naturally occurring animal model of idiopathic calcium oxalate stone disease.

Keywords

kidney stone; nephrolithiasis; calcium oxalate; canine; feline

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Compliance with Ethical Standards

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Introduction

Urolithiasis (or formation of stones, generally in the kidneys or bladder) is an important medical problem in people, and prevalence of this condition in the United States is increasing [1]. The most common type of kidney stone is composed of calcium oxalate [2, 3] (Table 1). Calcium oxalate stones are often recurrent, with a 10 year recurrence rate of 30% in first time stone formers [2]. The relationship of calcium oxalate kidney stones to important co-morbidities such as chronic kidney disease and metabolic syndrome is currently unclear. Kidney stones have been associated with a higher risk of chronic kidney disease in some studies [4], although when stone composition was evaluated, patients with calcium containing stones had better renal function than patients with non-calcium containing stones [5]. While uric acid stones have been consistently associated with metabolic syndrome, calcium oxalate kidney stones have had more variable associations with the metabolic syndrome components [6–8]. Although a variety of underlying diseases can lead to calcium oxalate nephrolithiasis, most cases are idiopathic and are associated with Randall's plaques [9]. Randall's plaques are subepithelial calcium phosphate deposits that breach the renal papillary urothelium and lead to calcium oxalate crystallization and stone formation [10].

Animal models to study calcium oxalate kidney stone disease most commonly involve experimentally induced hyperoxaluria in rats [11]. While these models are successful at inducing intratubular calcium oxalate crystallization and nephrolithiasis, rodent models that form Randall's plaques similar to humans have not been identified [11]. Thus, a naturally occurring animal model of disease that forms calcium oxalate stones on Randall's plaques may be more useful to study treatment and prevention of the idiopathic form of this disease.

Both dogs and cats form calcium oxalate kidney stones. The prevalence is difficult to estimate due to lack of studies specifically investigating nephroliths, although one study did find a 10 fold increase in upper urinary tract stones (kidney/ureter) in cats over a 20 year period [12]. Calcium oxalate is the most common type of stone found in the upper urinary tract of both species [13–17]. The prevalence of the various stone types analyzed at a single center from the canine and feline upper urinary tract are presented in Table 1. Recurrence rates have been studied primarily for calcium oxalate urinary bladder stones in dogs, with 48–57% of cases recurring within 3 years [18, 19]. In cats, the reported recurrence rate for calcium oxalate urinary bladder stones, is lower at 6.8% after 2 years [20]. It is possible that recurrence is underestimated due to the retrospective or survey based methods in these studies. Kidney stones have been reported in 29% of cats with chronic kidney disease (Figure 1), although the presence of a cause/effect relationship has not been evaluated [21]. Similar data is not available for dogs.

To the authors' knowledge, only one unpublished report of a single cat with nephrolithiasis provides a detailed investigation into the pathology of feline calcium oxalate nephrolithiasis [22], while no similar reports have been identified in dogs. Given that most nephroliths in dogs and cats are not removed, many of the studies of urolithiasis involve a combination of upper and lower urinary tract stones, or are only focused on lower urinary tract stones. It is often assumed that similar factors are involved in the development of upper and lower

urinary tract stones, which may or may not be the case. Additional study of upper urinary tract stones in dogs and cats is indicated to further determine pathogenesis as well as the relevance of these species as models for human idiopathic calcium oxalate nephrolithiasis. In this review, we discuss and compare the known pathogenesis of calcium oxalate stone formation in humans, cats, and dogs with a focus on upper urinary tract stones.

Epidemiology and Risk Factors for Calcium Oxalate Stone Formation

Humans

With respect to any kidney stone type, white non-Hispanic individuals are more likely to have a history of kidney stone disease than black non-Hispanic or Hispanic individuals [1]. Calcium oxalate kidney stones are more common in men [2, 3], although this gender gap is declining as kidney stones are being diagnosed more often in women [10]. Higher ambient temperature and sunlight indices are independently related to stone prevalence, indicating that geography and environment play a role in kidney stone risk [23]. Additionally, calcium oxalate stones are more likely to be submitted for analysis in the months of July, August, and September in the United States [3].

The most common pathophysiologic abnormality detected in calcium kidney stone patients is hypercalciuria [9, 24–26]. This hypercalciuria is usually idiopathic, associated with normal serum calcium concentrations, and can be due to an increase in gastrointestinal calcium absorption, an increase in bone turnover, decreased renal tubular calcium uptake, or a combination of these [24]. Although there is a familial component to idiopathic hypercalciuria in many cases, the genetic causes are not straightforward suggesting that the environment likely plays an important role [26]. Other causes of hypercalciuria that are less common include primary hyperparathyroidism, hypercalcemia of malignancy, sarcoidosis, hyperthyroidism, and vitamin D toxicity [25]. Dietary excess of sodium, protein, or acid, can also lead to hypercalciuria, as can immobilization (due to bone resorption) [26].

Hyperoxaluria is another important risk factor and can be caused by primary or secondary hyperoxaluria [25, 27]. Primary hyperoxaluria has several forms caused by enzymatic deficiencies in oxalate metabolism; these have been reviewed elsewhere [27]. Secondary hyperoxaluria can be caused by excessive dietary intake of oxalate or excessive vitamin C supplementation [25, 27], although the latter is only associated with increased risk of kidney stones in men [28]. Other causes include gastrointestinal conditions, such as intestinal resection, gastric bypass surgery, and inflammatory bowel disease, leading to decreased calcium availability to complex with oxalate in the intestines [25, 27]. Dietary calcium restriction has also been linked to increased urinary oxalate excretion and increased calcium oxalate relative supersaturation (RSS) [29]. Several studies have found a reduction in risk for recurrent calcium oxalate kidney stones in patients with gastrointestinal colonization by the oxalate degrading bacterium *Oxalobacter formigenes* [30, 31]. The mechanism is still unclear, because although plasma oxalate concentrations and urinary oxalate excretion are higher (the latter under controlled dietary conditions only) in non-colonized stone formers, Siener *et al* report no difference in intestinal oxalate absorption when compared with colonized patients [31].

Other risk factors for calcium nephrolithiasis include hypocitraturia [32, 33], low urine volume [26, 33], and hyperuricosuria (due to heterogenous crystallization of calcium oxalate) [25, 26]. Too little vitamin D may also play a role in stone formation, as deficiency or insufficiency has been linked to increased risk of calcium nephrolithiasis [34, 35]. Other compounds that modulate urinary stone formation are glycosaminoglycans and proteins (including Tamm-Horsfall protein, nephrocalcin, osteopontin, inter- α -inhibitor, urinary prothrombin fragment-1, calgranulin) [36, 37]. While they are thought to be inhibitory, the true contribution of many of these compounds remains undetermined and in-depth reviews are available elsewhere [36, 37]. Patients with Cushing's disease are at risk for nephrolithiasis, particularly calcium nephroliths, likely due to multifactorial lithogenic risk factors detected in these patients [38].

Despite multiple possible underlying causes, most cases of calcium oxalate nephrolithiasis are idiopathic and patients may have one or more metabolic abnormality present (eg. hypercalciuria, hyperoxaluria, hypocitraturia) [9]. Select risk factors for idiopathic calcium oxalate stone formation in humans are presented in Table 2 and compared with those risk factors that have been investigated in cats and dogs.

Cats

With respect to calcium oxalate stones overall, several breeds are predisposed, including Persians, Himalayans, and Burmese [39–41]. Like humans, there is a gender predisposition toward males, although in cats these males are most often neutered [39, 41]. The only study evaluating nephroliths specifically also found that males more commonly had calcium oxalate nephroliths than other stone types [15]. Cats affected with calcium oxalate urolithiasis are typically older with a peak risk at 10–15 years of age [40].

Like humans, the most common pathophysiologic risk factor detected is hypercalciuria [42, 43], although this has only been reported in a small number of cats. While this hypercalciuria is not necessarily associated with hypercalcemia [42], idiopathic hypercalcemia does occur in cats and has been associated with calcium oxalate urolithiasis [44, 45]. Other potential causes of hypercalciuria may include treatment with loop diuretics or corticosteroids, excess vitamin C or D, and treatment with urinary acidifiers [46], although these are not well described in cats.

Primary hyperoxaluria has been reported sporadically in young cats [47, 48], but this is likely a rare condition. Experimentally induced vitamin B6 deficiency causes oxalate nephrocalcinosis in kittens [49, 50], but has not been reported outside of this setting. To the authors' knowledge, studies comparing urinary oxalate in cats with idiopathic calcium oxalate uroliths compared with healthy control cats have not been published.

A study evaluating dietary risk factors for calcium oxalate urolithiasis reported that cats consuming diets with lower protein, calcium, phosphorous, magnesium, sodium, potassium, and moisture, and those that were formulated to acidify urine had increased risk for calcium oxalate urolithiasis [51]. Although this study was questionnaire based and thus subject to bias, it does raise some interesting questions given that high sodium and protein diets are risk factors for calcium oxalate nephrolithiasis in people [26]. In healthy cats, increasing

sodium chloride in the diet caused increased urine volume, no change in urine calcium concentration or calcium oxalate RSS, and decreased urinary oxalate concentration [52]. With respect to protein, healthy cats fed higher protein diets had higher urine volume, but also increased urinary calcium concentration, increased renal calcium excretion, and increased calcium oxalate RSS compared with lower protein diets, although oxalate concentration in the urine was lowest with the highest protein diets [53]. Thus, caution is needed when extrapolating these findings in healthy cats to stone forming cats. At the same time, these studies highlight that differences appear to exist between cats and humans. Other risk factors in people such as hypocitraturia and hyperuricosuria have had little to no study in cats thus far, and their role in calcium oxalate urolithiasis is unknown.

Dogs

Like cats, several dog breeds are predisposed to the development of calcium oxalate uroliths (Figure 2), including the Miniature Schnauzer, Lhasa Apso, Yorkshire terrier, Bichon Frise, Keeshond, Pomeranian, Shih Tzu, Cairn terrier, Maltese, and Miniature and Toy Poodle [14, 54, 55]. Other characteristics that increase risk include age (often >5–8 years), male sex, and being overweight [14, 54–57]. Neutering has also been found to be a risk factor in several studies [54, 56–58].

Similar to cats and humans, hypercalciuria is the most commonly identified urinary abnormality detected in calcium oxalate stone forming dogs [43, 59–62]. The majority of cases have serum calcium within the reference range [60, 61], but in one study blood ionized calcium was higher in stone forming dogs than in non-stone forming controls while still within the reference interval [60]. The cause for this normocalcemic hypercalciuria is unknown, although one study of Miniature Schnauzers found a greater degree of hypercalciuria in the fed versus fasted state and the authors speculated that gastrointestinal hyperabsorption may be the cause in this breed [61]. A study by one of the authors (Grant) is ongoing to further investigate urine calcium excretion in this breed in relation to feeding. Overt hypercalcemia, such as with primary hyperparathyroidism, may cause calcium oxalate urolithiasis [63]. Additionally, hyperadrenocorticism is a risk factor [64], but the mechanism for this in dogs has not been directly studied.

Similar to cats, questionnaire based studies in dogs have evaluated dietary risk factors for calcium oxalate urolithiasis. These studies found that diets with lower protein, fat, calcium, phosphorous, sodium, chloride, potassium, magnesium, moisture or high carbohydrates or fiber increased risk [65, 66]. In healthy dogs, the addition of sodium chloride to the diet led to decreased urine calcium and oxalate concentrations [67] and calcium oxalate RSS [67, 68], which is similar to results in cats. A prospective study evaluating diet diaries in dogs with calcium oxalate urolithiasis found similar results, including lower intake of sodium, calcium, potassium, and phosphorous in case dogs compared with control dogs [69]. The effects of dietary calcium and oxalate have been studied in healthy dogs, and, similar to humans, dietary calcium restriction without concomitant oxalate restriction led to an increase in calcium oxalate RSS in some dogs [70]. Although individual results had high variability, dietary calcium levels had the most influence on RSS compared with dietary oxalate in that study [70].

Compared with hypercalciuria, hyperoxaluria does not seem to be as an important a factor. Most studies have found either similar or lower urinary oxalate excretion in stone forming dogs compared to controls [60–62], with the exception of Stevenson *et al* [59] who found both high urinary oxalate and calcium excretion in stone forming dogs compared to breed matched controls. Primary hyperoxaluria has been documented rarely in Tibetan Spaniel and Coton de Tuleur puppies [71, 72]. Similar to humans, a link between a lack of enteric colonization with *Oxalobacter formigenes* (measured via PCR detection of the oxalyl CoA decarboxylase (*Oxc*) gene) and a risk of calcium oxalate urolith formation has been detected in a single study [73]. Unfortunately, to the authors’ knowledge, no further studies to date have been published to confirm these findings or investigate the relationship of colonization with plasma or urinary oxalate concentration.

Other risk factors described in humans have received little study in dogs. Experimentally induced chronic metabolic acidosis leads to decreased tubular calcium reabsorption in healthy dogs [74]; however, these effects have not been studied in stone forming dogs. There are conflicting results regarding the role of acidic urine pH as a risk factor among two studies, both of which were retrospective in nature and thus subject to inherent bias and limitations [58, 75]. Two small studies have not detected a difference in urinary citrate excretion between calcium oxalate stone forming dogs and non-stone forming controls [59, 61]. When evaluating urinary nephrocalcin, a crystallization inhibitor, nephrocalcin from calcium oxalate stone forming Miniature Schnauzers was less inhibitory toward calcium oxalate crystallization than healthy Beagle control dogs and the nephrocalcin isoforms excreted differed [62]. While further studies are needed, findings suggest that abnormalities of some crystallization inhibitors may play a role.

Renal Pathology in Calcium Oxalate Nephrolithiasis

Humans

This section will focus on renal pathology associated with idiopathic calcium oxalate nephrolithiasis. The basic concepts involved in stone formation (ie. crystal nucleation, supersaturation) have been recently reviewed elsewhere [10]. In the 1930s, Randall discovered calcium deposits on the renal papilla of post-mortem kidney specimens, some with adhered renal calculi [76]. On microscopic examination, Randall also described calcium deposits in collecting tubule basement membranes and in the surrounding interstitium [76]. These deposits, now known as Randall’s plaques (RPs), are found in most patients with idiopathic calcium oxalate nephrolithiasis [77–80] and have been confirmed to be composed of calcium phosphate [77, 80]. They are thought by most investigators to originate in the basement membrane of the Loops of Henle as laminated, spherulitic structures [77, 80, 81]; however, an alternative theory proposes that this initial event occurs in the walls of the vasa recta at the papillary tips [82]. Based on finding conglomerates of these calcium phosphate spherules in the interstitium, it is theorized that the plaques spread from the basement membranes into the interstitium as aggregates [77, 80, 81], although the mechanism of this aggregation and migration remains unknown. Eventually, they breach the papillary epithelium where they are exposed to the urine and act as an encrustation platform for deposition of calcium oxalate crystals [83, 84]. Evan *et al* (2007) elegantly described the

papillary attachment point of a calcium oxalate stone to the plaque and determined the composition, which consists of apatite (both biological and amorphous form) in layers with organic matrix that includes osteopontin and Tamm Horsfall protein at the plaque-stone interface, finally culminating in calcium oxalate crystallization and stone formation [83]. Plaque surface area on the papilla of calcium stone formers has been positively correlated with urine calcium excretion and negatively correlated with urine volume and urine pH [85]. Although the definitive events leading to the breach of the papillary epithelium by RPs has not been proven, Khan and Canales (2015) theorize that the mechanical force of the underlying plaque and matrix metalloproteinase activity cause a loss of epithelial integrity [84].

Randall’s plaques are not unique to idiopathic calcium stone formers. Randall’s early work described plaques in 17% of random kidney pairs examined following patient death [76]. Subsequent studies have documented RPs in patients without kidney stones, but at a lower frequency [86] and with smaller affected papillary surface area [85]. Patients with brushite stones or with calcium containing stones secondary to other conditions, including primary hyperparathyroidism, ileostomy, and small bowel resection have RPs [79, 87, 88]. These patients also have Bellini duct crystal plugs, also known as yellow plaque [79, 87, 88], which are theorized to form an anchor point for stone formation [10]. Bellini duct plugs are present in patients with stones secondary to obesity bypass surgery, cystinuria, primary hyperoxaluria, and renal tubular acidosis; however, these patients lack RPs [79]. Idiopathic calcium stone formers do not have Bellini duct plugs [79, 88].

Dogs and Cats

To date, histopathologic descriptions of dogs and cats with calcium oxalate nephrolithiasis in the literature are limited to case reports or small case series. The report of a single cat with calcium oxalate nephrolithiasis describes von Kossa stained mineral material (likely calcium phosphate) adjacent to the renal tubules in tissue near the renal pelvis [22]. This suggests that parenchymal mineralization, possibly similar to Randall’s plaques in humans, may occur in this species. Evaluation of more cats is necessary to determine if these findings represent changes specific to nephrolithiasis versus changes associated with chronic kidney disease given that mineralization of tubular basement membranes and/or tubular epithelial cells has been reported in over 50% of cats with azotemic chronic kidney disease [89]. Histopathologic findings from another cat with chronic kidney disease and calcium oxalate nephrolithiasis noted interstitial fibrosis, glomerular sclerosis, and multifocal lymphocytic aggregates in the kidneys, with no further details reported [90]. Three Ragdoll cats with chronic kidney disease that had a large number of oxalate crystals in tubules but without evidence of primary hyperoxaluria have also been described; one cat had concurrent nephroliths [91]. Other histologic abnormalities described were interstitial fibrosis, mononuclear inflammation, and atrophy of the tubular epithelium [91]. Cats with primary hyperoxaluria have birefringent crystals in the tubules and renal fibrosis [47, 48], with one cat also noted to have some crystals located in the interstitium, as well as interstitial nephritis and glomerulosclerosis [47]. In dogs, renal histopathologic findings from Tibetan Spaniel and Coton de Tulear puppies with primary hyperoxaluria have been reported, with intratubular crystals in the renal cortical proximal tubules but no uroliths found [72, 92].

Detailed histopathologic reports of dogs with idiopathic calcium oxalate nephrolithiasis are to date not available in the literature. There is clearly an important knowledge gap in this area, and further studies are indicated to better characterize the pathology of calcium oxalate nephrolithiasis in dogs and cats.

Conclusions and Future Directions for Research

Calcium oxalate urolithiasis is an important medical condition in humans, cats, and dogs. The lack of a conclusive animal model with similar pathology to humans may be a limitation to the discovery and development of methods to prevent and effectively treat this disease. The pathologic and etiologic mechanisms surrounding calcium oxalate nephrolithiasis in dogs and cats have been incompletely described to date. Further investigation and microscopic analysis of the kidneys of calcium oxalate stone forming cats and dogs, as well as more in depth study of potential risk factors (including crystallization inhibitors) is indicated. Dogs and cats are an attractive model for preventative and therapeutic studies in people, given their similar living environments and shorter lifespan. The use of cats and/or dogs with naturally occurring calcium oxalate stone disease in preventative or therapeutic trials could lead to important medical breakthroughs for both human and veterinary medicine, but further study into the pathology and pathogenesis of this condition is necessary to determine the true potential for dogs and cats to fill this role.

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Fig. 1. Sagittally sectioned kidney from a cat with calcium oxalate nephrolithiasis and chronic kidney disease. Multiple nephroliths are present in the renal pelvis, and the kidney is small and irregular. (Ruler marks=1mm)

Fig. 2. Lateral radiographic image of a dog with bilateral nephrolithiasis (long arrows) and bladder stone (short arrow). The bladder stone was composed of calcium oxalate; the nephroliths are suspected to be the same, but were not removed

Table 1

Composition of Upper Urinary Tract Stones in Dogs and Cats (analyzed between 1981 and 2007 at a single center, adapted from [13]) and Nephroliths in Humans (analyzed during 2010 at a single center, adapted from [3])

Stone Composition	Cats	Dogs	Humans
Calcium oxalate	70.4%	43%	67.3%
Struvite	8%	26%	3%
Matrix	8%	0%	0%
Calcium phosphate/apatite	4%	1.5%	16%
Purine	2%	13%	8.6%
Compound	5%	12%	N/A
Mixed	2.6%	3%	N/A
Cystine	0%	1.5%	0.35%
Brushite	0%	0%	0.9%
Artifact	N/A	N/A	3.2%
Drug	0%	0%	0.1%
Other	0%	0%	0.4%

Table 2

Idiopathic Calcium Oxalate Urolithiasis: Select Risk Factor Comparison by Species

Risk factor	Humans	Cats	Dogs
Sex	Male	Male	Male
Season	Summer	Unknown	Unknown
Hypercalciuria	Yes	Yes	Yes
Hyperoxaluria	Yes	Unknown	Possible
Absence of <i>O. formigenes</i> gut colonization	Yes	Unknown	Possible
Hypocitraturia	Yes	Unknown	No
Hyperuricosuria	Yes	Unknown	Unknown
Vitamin D deficiency	Possible	Unknown	Unknown
Low dietary calcium	Yes	Yes	Yes
Dietary sodium excess	Yes	No	No