Influence of nutrition on feline calcium oxalate urolithiasis with emphasis on endogenous oxalate synthesis

J. C. Dijcker¹, E. A. Plantinga¹*, J. van Baal² and W. H. Hendriks¹,²

¹Faculty of Veterinary Medicine, Utrecht University, Yalelaan 7, 3584 CL, Utrecht, The Netherlands
²Animal Nutrition Group, Wageningen University, PO Box 338, 6700 AH, Wageningen, The Netherlands

Abstract

The prevalence of calcium oxalate (CaOx) uroliths detected in cats with lower urinary tract disease has shown a sharp increase over the last decades with a concomitant reciprocal decrease in the occurrence of struvite (magnesium ammonium phosphate) uroliths. CaOx stone-preventative diets are available nowadays, but seem to be marginally effective, as CaOx urolith recurrence occurs in patients fed these diets. In order to improve the preventative measures against CaOx urolithiasis, it is important to understand its aetiopathogenesis. The main research focus in CaOx formation in cats has been on the role of Ca, whereas little research effort has been directed towards the role and origin of urinary oxalates. As in man, the exogenous origin of urinary oxalates in cats is thought to be of minor importance, although the precise contribution of dietary oxalates remains unclear. The generally accepted dietary risk factors for CaOx urolithiasis in cats are discussed and a model for the biosynthetic pathways of oxalate in feline liver is provided. Alanine:glyoxylate aminotransferase 1 (AGT1) in endogenous oxalate metabolism is a liver-specific enzyme targeted in the mitochondria in cats, and allows for efficient conversion of glyoxylate to glycine when fed a carnivorous diet. The low peroxisomal activity of AGT1 in cat liver is compatible with the view that felids utilised a low-carbohydrate diet throughout evolution. Future research should focus on understanding de novo biosynthesis of oxalate in cats and their adaptation(s) in oxalate metabolism, and on dietary oxalate intake and absorption by cats.

Key words: Urinary calcium oxalate; Urolithiasis; Oxalate biosynthesis; Cats; Diet

Introduction

Urolithiasis is the condition in which calculi are formed in the urinary tract from initially dissolved minerals and/or organic compounds. In domestic cats, the primary stones are composed of calcium oxalate (CaOx) monohydrate or dihydrate and struvite (magnesium ammonium phosphate hexahydrate). Less common stones are purines (i.e. ammonium urate, sodium (calcium) urate, potassium urate, uric acid dihydrate and xanthine), calcium phosphate, matrix, cystine and silica uroliths(1).

Urolithiasis in domestic cats is, after feline idiopathic cystitis (FIC), the second most common cause of lower urinary tract disease (LUTD)(2,3). Studies with the aim to determine the incidence rates for urolithiasis have not been conducted in cats. Estimates on incidence rates reported in the literature are largely based on morbidity rates seen in veterinary practices, with estimates varying between 0·2 and 0·7 %(4,5).

Over the past 30 years, a progressive increase in the prevalence of CaOx uroliths in cats diagnosed with LUTD has been reported in the USA(1), with a similar trend being observed in Western Europe(6). During the early 1980s, CaOx was detected in only 2 % of all feline uroliths submitted to the Minnesota Urolith Center, whereas struvite was detected in 78 % of the uroliths submitted (Fig. 1)(1). However, in the mid-1990s, together with a rapid increase in the total number of uroliths submitted for analysis, a notable shift in the submitted types of uroliths has been observed(7). In the mid-1980s, the submitted CaOx uroliths noticeably increased(8), reaching 55 % in 2002 in the USA(1) and 61 % in 2003 in Western Europe(6). Since 2003 a slight decline in the percentage of CaOx uroliths has been observed, reaching 41 % in 2007. This decline comes along with a reciprocal increase in the frequency of struvite uroliths, up to 49 % in 2007(1). The amount of less common uroliths (i.e. purines, calcium phosphate, etc) submitted for analysis has remained fairly constant at about 10 %(1).

Abbreviations: AGT1, alanine:glyoxylate aminotransferase 1; BW, body weight; CaOx, calcium oxalate; FIC, feline idiopathic cystitis; GAG, glycosaminoglycan; GR/HPR, glyoxylate reductase/hydroxypyruvate reductase; LUTD, lower urinary tract disease; ME, metabolisable energy; MTS, mitochondrial targeting sequence; PH, primary hyperoxaluria; RSS, relative supersaturation.

* Corresponding author: Dr Esther A. Plantinga, fax +31 30 253 7970, email E.A.Plantinga@uu.nl
The same general trend in urolith composition can be observed in dogs but is less extreme compared with cats\(^1,6\).

It is generally thought that the concomitant increase in the occurrence of CaOx uroliths with the reciprocal decrease in struvite until 2003 reflects the widespread use of struvite urolith-preventive diets since the mid-1980s\(^9,10\). These acidifying diets, often with reduced quantities of Mg, are believed to promote calciuria and reduce urinary Mg concentrations, both being risk factors for CaOx urolith formation\(^10,11\). The progressive decrease in occurrence of CaOx uroliths from 2003 until 2007 may be associated with the improvement of adult maintenance and therapeutic diets to minimise risks for CaOx crystalluria.

Despite the use of urolith-preventive diets over the past decades, the prevalence of CaOx uroliths in cats remains substantial. In order to further decrease the incidence of CaOx urolithiasis in cats, understanding of the aetiopathogenesis of CaOx urolithiasis is essential. The purpose of the present review is to discuss dietary risk factors for CaOx urolith formation in cats, with an emphasis on the origin of urinary oxalates. Endogenous biosynthesis of oxalate in the mammalian liver is reviewed and recommendations for research in order to reduce feline CaOx urolithiasis by dietary intervention are provided.

### Risk factors

Several risk factors have been identified for CaOx urolith formation in cats. The risk of developing CaOx uroliths appears to increase with age, with cats aged 7–10 years showing the highest predisposition\(^12\). Other predisposing factors seem to be sex and reproductive status, with male cats more commonly affected (59%)\(^12\), and 95% of cats with CaOx urolithiasis being neutered. However, the imbalance of reproductive status in the population of cats (for example, 78% of cats examined at primary veterinary practices in the USA were neutered\(^4\)) might be a confounding factor. In Burmese, Himalayan and Persian cats, a predisposition to develop CaOx uroliths has been observed, indicating that genetic background also contributes to CaOx urolithiasis\(^10,12,13\). Nevertheless, considering the short time span in which the types of feline uroliths have changed over the past three decades (Fig. 1), it is highly unlikely that animal-related factors have made a significant contribution to this observed trend, as opposed to nutritional and husbandry factors. Changes in nutrition are thought to be one of the main reasons for the epidemiologic shift in urolith type in cats\(^1\).

Urinary concentrations of Ca and oxalate play a key role in CaOx urolith formation. Factors indirectly influencing the formation of CaOx crystals are urinary volume, pH, citrate and glycosaminoglycans (GAG) concentration. The relationship between various dietary components and the risk factors for CaOx urolith formation are outlined in Fig. 2. Dietary components able to influence urine volume, urinary oxalate excretion, urinary Ca excretion, urine pH (acidosis) and urinary citrate and GAG levels (see Fig. 2) will be discussed in more detail.

### Urine volume

Theoretically, a high fluid intake could inhibit CaOx urolith formation since it dilutes the urine, thereby lowering the urinary concentrations of Ca and oxalate and, in turn, the crystallisation of CaOx in the urinary tract. Enhancing urine volume may also increase the frequency of urination, which would reduce crystalloid and crystal transit time along the urinary tract, thereby reducing the potential for crystal growth\(^14\). Therefore, measures to increase water intake to promote high urine volume can be considered.
as one of the best approaches to prevent urolith recurrence. A higher water intake can be achieved by feeding diets with high moisture and/or Na content.

**Dietary factors affecting urine volume.** Data in the literature indicate that feeding high-moisture diets to adult cats leads to a slightly higher total water intake leading to an increased urine volume\(^{(15,16)}\). When high (82\%)-moisture diets are fed, urine output is increased by 57·4\% compared with low (10\%)-moisture diets\(^{(15)}\). In a retrospective case–control study with 173 cats with CaOx uroliths, it was found that cats fed (canned) diets containing the highest moisture contents (77·4 to 81·2\%) were only about one-third as likely to develop CaOx uroliths compared with cats fed (dry kibble) diets low in moisture (7·0 to 7·9\%)\(^{(9)}\). The purpose of the latter study was to identify dietary factors associated with the increase in occurrence of CaOx uroliths. The dietary factors studied were moisture content, protein, carbohydrate, fat and fibre content, but also Ca, P, Mg, Na and chloride content and urine-acidifying potential. Of these factors, the moisture content of the diet seemed to have the strongest association with CaOx urolith formation in cats\(^{(9)}\). The favourable effect of a high water intake on LUTD in general was also reported by Markwell *et al.*\(^{(14)}\), who stated that recurrence rates of signs in cats classified as having idiopathic LUTD, or FIC, may be more than halved when affected animals are maintained on high-, rather than low-, moisture content diets. Gunn-Moore & Shenoy\(^{(17)}\) observed a significantly lower urine specific gravity in cats with FIC when they were fed more canned cat food as well.

The increased water intake when feeding moist diets might not only be due to its higher moisture content, but also because its higher mineral (ash) and protein content (evoking a higher renal solute load) may stimulate drinking\(^{(18,19)}\). This is in line with the finding that a high intake of animal protein is accompanied by increased water consumption and urine volume in cats\(^{(20)}\). Taking into account the overall beneficial effect of high-moisture diets by increasing urine volume, and therefore diluting all substances dissolved in the urine, feeding a high-moisture diet may be considered as one of the most effective measures to prevent CaOx formation.

Another way to increase urine volume is to stimulate drinking by increasing dietary Na intake\(^{(21,22)}\). This effect of a higher Na intake might not only be due to its higher moisture content, but also because its higher mineral (ash) and protein content (evoking a higher renal solute load) may stimulate drinking\(^{(18,19)}\). In humans, an increased salt intake has been associated with elevated urinary Ca excretion\(^{(23–25)}\). Salt-induced calcium is believed to result from Na–Ca interactions in the kidney, in both the proximal and distal tubule. Reabsorption of
Ca parallels the reabsorption of Na in the proximal tubule and loop of Henle. Na may influence renal reabsorption of Ca in the distal tubule by both a direct effect and indirectly through its effects on parathyroid hormone levels. In a study with healthy cats, the total daily amount of Ca excreted in urine was reported to be increased. Similar results were found in dogs. However, in two studies with healthy adult cats, dietary Na levels of up to 0.96 g/MJ ME did not increase urine Ca concentrations, but did increase the volume of water drunk, resulting in a larger urine volume and a concomitant decrease in urine specific gravity and CaOx relative supersaturation (RSS). A possible explanation for this discrepancy might be that an increased dietary Na intake enhances urinary total Ca excretion as seen in humans, but by augmenting urine volume, does not lead to substantially elevated urine Ca concentrations.

Overall, research indicates that the urine volume in cats can be increased successfully by feeding a high-moisture diet, as well as by increasing dietary Na intake. An increased Na intake might be used as a preventative measure for CaOx formation as there is no evidence that dietary Na induces elevated Ca concentrations in the urine of healthy cats, and there are no adverse long-term effects reported for this nutrient on, for example, blood pressure and kidney functioning as well. However, the effectiveness of increased dietary Na intake on reducing CaOx urolith formation in urolith-forming cats has not been tested.

### Urinary oxalate

Since oxalate forms a relatively insoluble salt with Ca ions at physiological pH, an increased urinary excretion of oxalate, i.e. hyperoxaluria, can promote CaOx formation. It has been argued that an increase in urinary oxalate concentration promotes CaOx urolith formation to a greater extent than comparable increases in Ca, as changes in urinary oxalate concentration are fifteen times as potent as equimolar changes in Ca concentration in effecting CaOx saturation. Therefore, hyperoxaluria is generally accepted as a critical factor of CaOx urolithiasis. To be able to reduce urinary oxalate excretion, it is essential to understand the origin of the oxalates excreted in the urine of cats. Both the intake of dietary oxalate (exogenous oxalate) and biosynthesis of oxalate (endogenous oxalate) contribute to the amount of oxalate excreted with the urine.

**Factors influencing urinary oxalate: exogenous urinary oxalates.** Intake of dietary oxalate is a known factor that increases urinary oxalate excretion. The amount of dietary oxalate available for absorption in the gastrointestinal tract is dependent on the amount of free oxalate present in the diet, dietary components which can form complexes with free oxalate (for example, Ca, Mg) and the activity of oxalate-degrading bacteria in the gastrointestinal tract of man and animals.

In general, large amounts of oxalate are present in green leafy vegetables and bran concentrates, moderate amounts in nuts and cereals, and low amounts in dairy products, meat and fish. The contribution of dietary oxalate intake to urinary oxalate excretion in free-roaming cats is unknown, but can be expected to be low, as the natural (carnivorous) diet of the cat is mainly composed of food prey items that contain low amounts of oxalate. In contrast, omnivorous diets (for example, for humans and rats) contain moderate to high levels of oxalate, which may result in a relatively high contribution of exogenous oxalate to total urinary oxalate excretion. In humans, contributions of dietary oxalate to urinary oxalates have been reported, with estimates ranging from 25 to 68 %.

Unfortunately, no such data are available in cats.

In thirty different dry pet foods for adult small breed dogs, the oxalate content was found to range between 9 and 60 mg/MJ ME (4–25 mg/100 kcal) with a mean of 26.3 g/MJ ME (11 mg/100 kcal). In a canned diet designed to assist in the management of LUTD in dogs, the oxalate content was 5.9 mg/MJ ME (2.5 mg/100 kcal). The average daily intake of oxalate (2.5–15.5 mg/kg body weight (BW) per day) in dogs fed these commercial dry diets can be considered to be relatively high compared with the average oxalate intake (2–3 mg/kg BW per day) by humans. Stevenson et al. studied the relative effects of dietary Ca and oxalate on the composition of urine by feeding healthy dogs a diet supplemented with 240 to 600 mg oxalate/MJ (10–25 mg/100 kcal) and varying the dietary Ca contents. These authors found that the oxalate excretion inconsistently increased with a higher oxalate intake only when dietary Ca intake was low (molar Ca:oxalate ratio < 18). With higher dietary Ca:oxalate ratios (> 25) the oxalate excretion remained low and stable, irrespective of dietary oxalate content. The variation between dogs when different oxalate levels were fed, in conjunction with a low dietary Ca content, was very high, with effects ranging from 0 to a 400 % increase in urinary oxalate excretion. These results indicate that the contribution of dietary oxalate to urinary oxalate excretion in dogs is dependent on the dietary Ca content, and is expected to be low with a high (> 40) molar Ca:oxalate ratio in the diet.

Other factors than dietary Ca are also known to influence intestinal oxalate absorption. A similar role for dietary Mg has been found. Both minerals can directly interact with oxalate to form an insoluble complex to lower the free oxalate concentration in the gastrointestinal tract, resulting in a reduction in the absorption of oxalate. Fat and phosphate can act as scavengers for Ca, thereby indirectly increasing the availability of oxalate for uptake by the intestine. In addition, oxalate-degrading bacteria, such as Oxalobacter formigenes present in the intestinal tract of man and rats, are known to reduce the
contribution of exogenous urinary oxalates to total urinary oxalates, as this bacterium uses oxalic acid (or its anion oxalate) as its sole energy source by degrading oxalic acid to formate\(^{50,51}\). *O. formigenes* has also been detected in the stool of cats and dogs\(^{52,53}\). Lactic acid bacteria have also been shown to degrade oxalates *in vitro*\(^{54}\). The impact of oxalate-degrading bacteria in the gastrointestinal tract of humans and animals on urinary oxalate excretion remains to be clarified.

Research in dogs indicates that, although canine foods contain relatively high levels of oxalate, the contribution of exogenous oxalates to the urinary oxalate excretion is expected to be of minor importance mainly due to the high molar Ca:oxalate ratio in commercial canine foods. The influence of factors other than dietary Ca that are known to affect intestinal oxalate absorption in humans is not known in dogs and cats, but is expected to be of minor importance in practice, as the dietary Mg content in the majority of commercial foods is approximately 10-fold lower than the Ca content, and dietary Ca and phosphate are normally balanced. Oxalate and Ca contents of dry commercial feline diets may be expected to be in the same range as canine foods, as similar ingredients are used. This would imply that the potential contribution of exogenous oxalates to total urinary oxalate excretion by domestic cats is expected to be marginal as well, as the Ca:oxalate ratio can be expected to be high. However, the oxalate content of commercial feline foods and its contribution to urinary oxalate excretion remains to be determined in order to ascertain its relative importance.

**Factors influencing urinary oxalate: endogenous urinary oxalates.** Since hyperoxaluria in humans is recognised as an important risk factor for CaOx urolith formation, many studies (mainly in rodents) have been conducted to unravel the aetiopathogenesis of hyperoxaluria. Studies in human subjects and rodents have revealed that the largest part of the endogenous oxalate formation originates from the conversion of sugars (including glucose and fructose), amino acids (including hydroxyproline, glycine, serine, phenylalanine, tyrosine and tryptophan) and/or glycolate, ending via the metabolism of glyoxylate to oxalate. Another precursor that can give rise to oxalate is ascorbic acid, which can break down non-enzymically in urine to produce oxalate, a reaction which is accelerated at alkaline pH. Originally it was thought that 40 to 50% of urinary oxalate was derived from the breakdown of ascorbic acid\(^{42,55–57}\). However, close scrutiny of the experimental procedures indicates that the breakdown occurred due to processing of urine at alkaline pH\(^{48}\). In cats, ascorbate has not been found to be an important dietary precursor of oxalate\(^{59}\), indicating that endogenous oxalate biosynthesis in cats relies predominantly on glyoxylate metabolism.

Endogenous biosynthesis of oxalate occurs mainly in the liver\(^{60}\) and is highly dependent on the glyoxylate content in the hepatocytes (Fig. 3). Any glyoxylate that is not reduced to glycolate or transaminated to glycine is oxidised to oxalate, a reaction catalysed by cytosolic l-lactate dehydrogenase\(^{61}\) (Fig. 3(a), step I). Since oxalate can be considered a metabolic ‘end-waste-product’ it will be quantitatively excreted in the urine, mainly via glomerular filtration. Oxalate excretion also occurs in the proximal tubule after a high oral oxalate load\(^{62,63}\). The most efficient way of reducing urinary endogenous oxalate excretion is to reduce the content of glyoxylate in the hepatocyte (Fig. 3). This can be achieved in two ways: by supplying less dietary precursors for glyoxylate production in the hepatocyte or by metabolic removal of glyoxylate from oxalate synthesis.

Glyoxylate removal can be achieved through the conversion into glycinuric, which is catalysed by serine: pyruvate aminotransferase/alanine-glyoxylate aminotransferase, also called alanine-glyoxylate aminotransferase 1 (AGT1)\(^{64}\) (Fig. 3(a), step II). This enzyme can also convert serine into hydroxypropyruvate. An essential cofactor for AGT1 is pyridoxine, or vitamin B\(_6\). A deficiency in pyridoxine can lead to a shift from glyoxylate removal through conversion into glycine, to glyoxylate oxidation to oxalate. This shift has been well documented in cats. In a study with kittens that were fed a pyridoxine-deficient diet, a significantly higher daily urinary oxalate excretion was observed\(^{65}\).

Glyoxylate can also be converted into glycolate (Fig. 3(a), step III) via the action of the enzyme glyoxylate reductase/hydroxypropyruvate reductase (GR/HPR), a 2-hydroxy-acid dehydrogenase. GR/HPR also catalyses the reduction of hydroxypropyruvate to d-glycerate (Fig. 3(a), step IV) and the oxidation of d-glycerate to hydroxypropyruvate\(^{66}\). In the human liver, GR/HPR is found predominantly in the cytosol (\(> 90\%\)), with a small portion in the mitochondria\(^{67}\). In cats, GR/HPR localisation has been reported to predominantly occur in the cytosol\(^{68}\).

The existence and importance of the conversions of glyoxylate into glycine and glycolate in the hepatocyte has been discovered as a result of extensive research into two severe autosomal-recessive disorders leading to mild to severe hyperoxaluria in humans. These disorders are termed primary hyperoxaluria (PH) and two types can be distinguished. PH type I is an inherited disorder of glyoxylate metabolism arising from a deficiency in AGT1, leading to a disrupted conversion of glyoxylate into glycine (Fig. 3(a), step II). PH type II is an inherited disease caused by mutations in GR/HPR, leading to a reduced conversion of glyoxylate into glycine (Fig. 3(a), step II). PH type II patients have a limited ability to convert d-glycerate into hydroxypropyruvate, resulting in most cases in an elevated concentration of l-glycerate in the urine, as metabolic removal of d-glycerate occurs via conversion into l-glycerate (Fig. 3). The reported cases of PH in cats\(^{71,72}\) reflect those of human PH type II\(^{68}\), while...
### Feline hepatocyte

**Situation A: high-protein, low-carbohydrate diet**

- Cytosol: L-Galactose → L-Glycerate
- Mitochondrion: Hydroxypropionate → L-Glycerate

**Situation B: low-protein, high-carbohydrate diet**

- Cytosol: D-Galactose → D-Glycerate
- Mitochondrion: Hydroxypropionate → D-Glycerate

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**Fig. 3. Proposed metabolic pathways of de novo oxalate synthesis via glyoxylate metabolism.** Major metabolic conversions that are considered prominent in the feline hepatocytes when precursors from a carnivorous and omnivorous diet are present are shown in panels A and B, respectively. Metabolic conversions expected to play a major role are indicated by thick arrows. Metabolic conversions expected to play a minor role are indicated by dashed arrows. Essential metabolic conversions in situation B are indicated with I, II, III or IV, meaning: I, conversion of glyoxylate into oxalate catalysed by cytosolic L-lactate dehydrogenase (L-LDH)[61,69]; II, conversion of glyoxylate into L-glycerate catalysed by alanyl:glyoxylate aminotransferase 1 (AGT1)[64,74,75,82,83,92,100,101,105]; III, conversion of glyoxylate into glycolate catalysed by glyoxylate reductase/hydroxypyruvate reductase (GR/HPR)[67,68,69,72,155,156]; IV, conversion of hydroxypyruvate into oxalate catalysed by glycolate dehydrogenase (GD)[97]; III, conversion of peroxisomal glycolate into glyoxylate catalysed by glycolate oxidase (GO)[97]; IV, conversion of hydroxypyruvate into glycolaldehyde catalysed by grx/hpr (67,68,69,72,155,156). Essential metabolic conversions in situation B are indicated with Ia–d, II, III and IV, meaning: Ia, conversion of cytosolic d-fructose, d-glucose and d-galactose into d-glycerate (86,87,89); Ib, conversion of d-glycerate into hydroxypropionate; Ic, conversion of hydroxypropionate into glycolaldehyde (80); Id, conversion of glycolaldehyde into glycolate (80); II, conversion of peroxisomal glycolate into oxalate catalysed by glycolate dehydrogenase (GD)[97]; III, conversion of peroxisomal glycolate into glyoxylate catalysed by glycolate oxidase (GO)[97]; IV, conversion of glycolate into L-glycerate catalysed by alanyl:glyoxylate aminotransferase 1[64,74,75,101,157].

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Highly notable is the observation that the spatial localisation of AGT1 seems to be species dependent. In carnivores and insectivores, AGT1 is mainly present in mitochondria[73,74], while in the human liver an almost exclusive peroxisomal localisation of this enzyme has been reported[75]. The mitochondrial localisation of AGT1 is seen in carnivorous and insectivorous species of different genera (mammals, birds, reptiles)[73], indicating that AGT1 localisation in the mitochondrion might be a necessity when consuming high-protein, low-carbohydrate diets. Interestingly, the Gly170Arg in combination with the Pro11Leu mutation in the gene AGXT, encoding for AGT1, which are commonly found in human patients with PH type I, targets AGT1 to mitochondria instead of to its normal location in peroxisomes[75], resembling the mitochondrial localisation of hepatic AGT1 in carnivores[74]. Herbivores, such as Old World monkeys (macaques and baboons), rabbits and guinea-pigs, have most, if not all of their AGT1 located in peroxisomes[74]. Rodents (rats, mice, hamsters) and marmosets (New World monkey) have AGT1 distributed approximately equally between both organelles. The interspecies difference in intracellular localisation of hepatic AGT1 may very well be the result of dietary selection pressure during evolution[74].

Genomic expression analyses have revealed that the adaptive shift in AGT1 targeting among species can be ascribed to the use of alternative transcription- and translation-initiation sites of the single-copy AGXT gene[76,77]. The longest transcript of AGXT, as found in cats, encodes a cleavable N-terminal mitochondrial targeting sequence (MTS) and C-terminal peroxisomal targeting sequences for peroxisomal uptake, in which MTS is dominant over peroxisomal targeting sequences in determining the final subcellular destination of AGT1[76,77]. Species such as man and rabbits expressing AGT1 almost exclusively in peroxisomes have lost the first translation start site during evolution resulting in an MTS-lacking protein. In cats and
other species expressing AGT1 almost exclusively in mitochondria, almost all encoded proteins contain the MTS due to the loss of the – more downstream – second transcription-initiation site\(^ {74,77}\). Species in which hepatic AGT1 is roughly equally distributed between both organelles utilise both translation-initiation sites\(^ {78}\).

It has been postulated that the dual localisation of AGT1 in the liver is a reflection of its dual physiological function: that is, its role in glyoxylate detoxification in peroxisomes and its role in gluconeogenesis in mitochondria\(^ {64,74}\). Intraperoxisomal glyoxylate detoxification is essential in herbivores, since their diet is rich in glycolate and carbohydrates. To prevent oxidation of cytosolic glyoxylate to oxalate by \( \alpha \)-lactate dehydrogenase (Fig. 3(a), step I), a high activity of intraperoxisomal AGT1 is required. High levels of glycolate and carbohydrates in combination with a scarcity of animal protein (containing L-hydroxyproline, glycine, serine), typically found in diets of herbivores, retard the need for directing hydroxyproline-derived glyoxylate into gluconeogenesis by conversions facilitated by AGT1 (Fig. 3(a), step II). In contrast, carnivores and insectivores are likely to have consumed a very low amount of glycolate and carbohydrates during evolution and these species have not required intensive detoxification of glyoxylate in the peroxisome. In contrast, the high animal protein and low carbohydrate content of the diet of carnivores and insectivores would clearly favour the contribution of gluconeogenesis in the mitochondrion\(^ {64}\).

As stated earlier, the glyoxylate content in the hepatocyte is also dependent on certain dietary precursors. In human medicine, it has been demonstrated that a high intake of amino acids (i.e. hydroxyproline, serine, glycine, phenylalanine, tyrosine and tryptophan)\(^ {78–83}\) or sugars (i.e. glucose, fructose, galactose, xylose)\(^ {84–89}\) stimulates oxalate synthesis from the intermediate product glycolate. Knight et al.\(^ {80,91}\) showed that hydroxyproline is a potent contributor to urinary oxalates, with glycine contributing little to the endogenous production of glycolate or oxalate. In cats, the endogenous synthesis of oxalate has not been widely studied. A study by Zentek & Schulz\(^ {92}\) describes the effects of various dietary protein sources (collagen tissue, horse meat and soya isolate) on urine composition, including urinary oxalate excretion. Uptake of the (high)-protein diet with collagen as the protein source resulted in an increase in urinary oxalate excretion (2.83 (SD 0.89) mg/kg BW per d) compared with the (high)-protein diets with horse meat and soya protein isolate as the protein source (0.94 (SD 0.29) mg/kg BW per d and 1.17 (SD 0.53) mg/kg BW per d, respectively). Since the hydroxyproline content of collagen tissue is high (about 10–13%), mitochondrial AGT1, which converts L-hydroxyproline-derived glyoxylate into glycine (Fig. 3(a), step II), might have been saturated in the cats fed the collagen protein, leading to undesirable conversions to oxalate by \( \alpha \)-lactate dehydrogenase (Fig. 3(a), step I), resulting in an increased urinary oxalate excretion\(^ {85}\).

Besides hydroxyproline, the amino acids glycine and serine are also present in relatively high concentrations in collagen tissue\(^ {83}\).

Zentek & Schulz\(^ {92}\) also investigated the effects of different dietary protein levels on daily urinary oxalate excretion. Of each protein source (collagen tissue, horse meat and soya isolate), two diets were fed, one containing a high and the other a low protein level. In the low-protein diets, protein was exchanged with rice (carbohydrate) and animal fat. Remarkably, all low-protein diets showed a consistently higher daily urinary oxalate excretion. The oxalate excretion increased approximately 5-fold (from 2.83 (SD 0.89) to 13.70 (SD 4.32) mg/kg BW per d) when fed the low-protein diet with collagen as the protein source compared with the high-protein diet. Urinary oxalate excretion increased 4-fold when changing from high- to low-protein diets using soya isolate and horse meat as a protein source (soya isolate diet from 1.17 (SD 0.53) to 4.79 (SD 2.73) mg/kg BW per d and the horse meat diet from 0.94 (SD 0.29) to 3.62 (SD 2.44) mg/kg BW per d). However, the observed increase in urinary oxalate excretion might have been the result of a concomitant high carbohydrate intake with the low-protein diets. As stated earlier, in humans sugars (i.e. glucose, fructose, galactose, xylose) are known to be a substrate for the peroxisomal glyoxylate pathway\(^ {84–89}\). It is conceivable that when fed a high-carbohydrate diet, cats suffer an overload of hepatic oxalate as a consequence of a deficiency in peroxisomal AGT1 and excrete more oxalate in their urine. Although the urinary oxalate excretion was found to be unaffected in a study feeding healthy cats a dry commercial diet with a low carbohydrate content (19.1 g/MJ ME) vs. a high carbohydrate content (34.7 g/MJ ME)\(^ {94}\), the carbohydrate content of the low-carbohydrate diet in this study can still be considered to be high compared with the carbohydrate content of the experimental diets in the study of Zentek & Schulz\(^ {92}\) (i.e. collagen tissue diets: 2.7 vs. 23.2 g/MJ ME; soya diets 7.1 vs. 22.3 g/MJ ME; horse meat diets 5.9 vs. 25.3 g/MJ ME).

A proposed metabolic pathway for the synthesis of the undesirable metabolite oxalate in cats from sugars is presented in Fig. 3(b). In this model, the sugars D-fructose, D-glucose and D-galactose are first converted to D-glycerate (Fig. 3(b), step 1a). Since the activity of fructokinase in feline liver is found to be relatively high and that of glucokinase to be low\(^ {95}\), the contribution of D-fructose compared with D-glucose is expected to be higher. D-Glycerate can subsequently be converted into glycolate via the intermediates hydroxypropionate and glycolaldehyde (Fig. 3(b), steps 1b, 1c and 1d). The sugar D-galactose\(^ {64}\) can also be converted to glycolate, with only glycolaldehyde as an intermediate. The sugar xylose enters the metabolic pathway to oxalate via glycolaldehyde as well\(^ {96}\). Cytosolic glycolate may partly be directed into the peroxisomes by diffusion where glycolate will be either oxidised directly to oxalate by the enzyme glycolate
dehydrogenase (Fig. 3(b), step II) or converted to glycolate by the enzyme glycolate oxidase (Fig. 3(b), step III). In most animals, the major part of this glycolate will be transaminated to glycine by AGT1 (Fig. 3(b), step IV) (i.e. peroxisomal glycolate detoxification), but in cats, and other carnivores, most of this glycolate will probably be converted back to glycolate due to a deficit of AGT1 activity in the peroxisome. This surplus in glycoglyceral will probably result in an increased conversion of glycolate to oxalate catalysed by glycolate dehydrogenase (Fig. 3(b), step II).

An additional explanation for the increase in oxalate synthesis upon feeding diets high in carbohydrate and low in protein content may be a reduction of gluconeogenesis in the liver, which results in a lower need for glycine and serine as a gluconeogenic precursor. It is conceivable that high concentrations of glycine and/or serine attenuate mitochondrial AGT1 in a negative feedback loop. This might result in an additional shift to oxalate synthesis. Collectively, it is possible that in cats a high carbohydrate intake is a potential risk factor for CaOx urolith formation by increasing endogenous oxalate synthesis.

The prevention of oxalate synthesis in cats by expressing AGT1 almost exclusively in the mitochondrion can be considered as one of the many enzymic adaptations as a result of their obligatory carnivorous lifestyle throughout evolution. By expressing AGT1 almost exclusively in the mitochondrion, the formed glycolate (mainly originating from hydroxyproline) is efficiently transaminated to glycine (Fig. 3(a), step II), which can directly be used for intramitochondrial gluconeogenesis. This enzymic adaptation appears to be part of a long list of adaptations in this species, such as cysteine dioxygenase and cysteinesulfinic carboxylase (taurine synthesis), pyrroline-5-carboxylase (taurine synthesis), pyrroline-5-decarboxylase and ornithine aminotransferase (citrulline synthesis), dioxgenase (retinol synthesis), glucokinase (glucose metabolism), 7-hydroxycholesterol-hydroxysteroid reductase (25-hydroxycholesterol synthesis) and picolinic carboxylase (nicotinic acid synthesis).

**Dietary factors influencing endogenous urinary oxalate synthesis**. In cats, urinary oxalate excretion has been found to be inversely correlated with protein intake and dependent on the protein source, although the inverse correlation with protein intake might be the result of a higher carbohydrate intake. In contrast, in human subjects some studies reported that urinary oxalate excretion increased with increased dietary protein intake and decreased with protein restriction. This might be explained by the distinct subcellular AGT1 distribution in humans and cats.

AGT1 catalyses the hepatic transamination of glyoxylate, being an important precursor of oxalate, to glycine. Pyridoxine, or vitamin B₆, is a known cofactor for AGT1 and, as such, pyridoxine deprivation could indirectly elevate endogenous oxalate biosynthesis and, in turn, its urinary excretion. Indeed, the daily urinary oxalate excretion was higher in kittens fed a pyridoxine-deficient diet compared with those receiving adequate amounts of pyridoxine. Moreover, pyridoxine can act as a cofactor for various enzymes in the tricarboxylic acid cycle as well, leading to a decreased synthesis of citrate. Thus, under the condition of pyridoxine deficiency, citrate metabolism may be impaired, leading to a lower urinary citrate concentration and increased risk of precipitation with CaOx. To the authors' knowledge, the effect of pyridoxine on urinary citrate excretion in cats has not been studied.

Although an excess consumption of ascorbate (i.e. vitamin C) has been associated with increased endogenous oxalate synthesis (by the non-enzymic oxidation of ascorbate to oxalate) in humans, in healthy cats dietary supplementation with ascorbate up to 193 mg/kg did not affect urinary oxalate concentrations. However, only the effect of a moderate and not a high amount of ascorbate on the urinary oxalate excretion has been tested. As cats, in contrast to man, can synthesise ascorbate in sufficient amounts de novo from glucose, ascorbate is not an essential nutrient. Although there is no evidence that dietary ascorbate can increase urinary oxalate levels in cats, it is generally recommended to avoid excessive amounts of dietary ascorbate. This recommendation is purely based on the results obtained in human subjects.

**Urinary calcium**

It goes without saying that an increase in urinary Ca excretion, as one of the constituents of CaOx uroliths, significantly contributes to CaOx formation. The question is whether hypercalciuria is indeed a causative factor in CaOx uroliths formation. In humans hypercalciuria is thought to be a risk factor for, but not necessarily the cause of, CaOx urolith formation.

One of the factors that can cause hypercalciuria is hypercalcaemia. Approximately 35% of the cats with CaOx uroliths also have evidence of an increase in total serum Ca concentrations. On the other hand, in a study which reported the laboratory findings, clinical course, and treatment of twenty cats with idiopathic hypercalcaemia, 35% (seven cats) had signs of urolithiasis, and in only two cats these uroliths were composed of CaOx. Although hypercalcaemia is frequently seen in cats with CaOx urolithiasis, hypercalcaemia in itself does not seem to be a causative factor in CaOx formation.

Another factor that is frequently indicated as a possible cause for hypercalciuria is feeding an acidified diet. In a case report of five cats with hypercalcaemia and CaOx urolithiasis, hypercalcaemia resolved after discontinuation of urinary acidifying therapy or dietary change, or both. Controlled studies in cats have confirmed that feeding acidifying diets to cats leads to increased urinary Ca excretion. In a long-term case-control study, feeding healthy adult cats an acidifying diet supplemented with 1-7% phosphoric
acid, a low urine pH ($\leq 6.4$) was found, together with an increase in urinary Ca excretion \cite{115}. Another study reported the same effect, with the exception that only after 1 month of feeding an acidifying diet (1.5% ammonium chloride added), the calciuric response declined gradually (during 4 months) \cite{116}.

**Dietary factors influencing urinary calcium excretion.** Conflicting results exist in the literature on the role of dietary Ca in inducing and resolving hypercalciuria. For decades, the prevailing consensus was that dietary Ca restriction would reduce urinary Ca excretion, and as such CaOx formation \cite{9}. However, recent literature in humans and dogs indicates that there might be an advantage of increased dietary Ca intake, which is thought to be related to interactions between Ca and oxalate in the intestinal lumen \cite{44,117}. When sufficient dietary Ca is available, complexation with oxalate occurs in the intestinal lumen, which in turn results in a reduction of intestinal absorption and renal excretion of both exogenous Ca and oxalate. Furthermore, a retrospective case–control study in cats revealed that consuming diets with a relatively low amount of Ca (0.23 to 0.49 g/MJ ME) had a significantly greater risk for CaOx urolith formation than cats that consumed higher dietary levels of Ca \cite{9}. This association may be explained by a higher oxalate absorption from the gastrointestinal tract.

Low dietary intake of P may be related to an increased urinary Ca excretion due to a lower binding of Ca by phosphate ions in the gastrointestinal tract resulting in an increased Ca absorption \cite{118}. An increase in urinary Ca excretion due to a low dietary P content could explain the increased risk for developing CaOx uroliths in cats fed diets containing a low P content (0.20 to 0.42 g/MJ ME) \cite{9}. On the other hand, the same study indicates that diets with a high P content (0.76 to 1.13 g/MJ ME) correlate with an increased risk of CaOx urolith formation compared with diets with moderate P content (0.66 to 0.76 g/MJ ME).

Excessive amounts of P present in the gastrointestinal tract could compete with oxalate, preventing intestinal Ca complexation with oxalate, which in turn could increase the availability of free oxalate for intestinal absorption and eventually renal excretion \cite{9,119,120}. The precise influence of dietary P on hypercalcaemia and CaOx formation in cats remains unclear and should be further studied.

Results of a retrospective case–control study revealed that cats fed diets with relatively high K contents (0.52 to 0.77 g/MJ ME) were less than half as likely (OR 0.45) to develop CaOx uroliths compared with cats fed diets with low K contents (0.23 to 0.38 g/MJ ME) \cite{9}. In cats, no studies have been conducted that may explain this relationship. However, in human subjects, studies have observed reduced Ca excretion after K supplementation \cite{121,122}. The authors of these studies suggested that the decrease in urinary Ca during K administration may be related to the natriuretic effects of K, resulting in extracellular fluid-volume contraction or to K-induced phosphate retention and/or suppression of 1,25-dihydroxyvitamin D$_3$ synthesis \cite{121}. Another explanation for the relationship of a higher K content with a decrease in CaOx formation is the alkalisating effect of K salts, leading to a higher urine pH and therefore a lower potential for Ca and oxalate to precipitate. Whether these suggested mechanisms are effective in cats should be investigated further.

**Urine pH**

Although the solubility of CaOx in urine is marginally influenced by pH of 4.5 to 7.5, several epidemiological studies have consistently identified acidifying diets (containing acidifying components such as phosphoric acid, ammonium chloride or D,L-methionine) as one of the most prominent risk factors for cats \cite{9,10,13}. The influence of urine pH on CaOx formation in cats was confirmed in a study feeding urine-acidifying, basal, and alkalinising diets to cats during 12 months (resulting in urine pH of 6.2 (SD 0.1), 6.8 (SD 0.2) and 7.2 (SD 0.3), respectively). Significant differences in urine saturation for CaOx were found: the highest saturation occurring in cats consuming the acidifying diet and the lowest saturation occurring in cats consuming the alkalinising diet \cite{129}. Compared with cats, a less prominent association with dietary acidifying potential was found in dogs, especially when fed canned diets \cite{124}. It has been suggested that urine pH may affect the potency of CaOx crystallisation inhibitors, such as chondroitin sulfate and citrate \cite{125}. Another possible explanation is that acidifying diets increase urinary Ca excretion. Since there is a correlation between the base excess in the food and the average urine pH \cite{126–128}, an acidified diet induces persistent aciduria which is associated with low-grade metabolic acidosis. This metabolic acidosis induces bone mobilisation, which results in an increased urinary Ca excretion \cite{115,116,129}. Another mechanism of acidified urine to result in elevated Ca excretion is by inhibition of Ca reabsorption in the distal renal tubule \cite{114}. Luminal protons directly inhibit transepithelial Ca reabsorption in the kidney by altering the conformation of the Ca-selective channel TRPV5 located in the apical membrane of the distal renal tubule \cite{130}.

Although the cause of acidosis-induced hypercalcaemia in cats has not been identified, it is possible that acidosis affects the activity of TRPV5 in osteoclasts as well, which plays a critical role in bone formation and maintenance of serum Ca \cite{131}. From the literature it appears that a dietary-induced decrease in urine pH affects the Ca excretion in the urine of cats, although the long-term effect remains questionable \cite{115,116}.

As an elevated Ca concentration in the urine can be considered as a risk factor for CaOx urolith formation, it might be reasonable to assume that a decrease in urine pH might affect the RSS of CaOx. However, some studies have claimed no correlation between urinary pH and CaOx RSS \cite{132,133}. Since the RSS is thought to serve as a
predictor of CaOx urolith formation\(^{(134)}\), these findings suggest that factors other than urine pH play a role in CaOx urolith formation as well. However, it is important to note that, although the value for urinary RSS with CaOx is higher in urolith-forming dogs and cats, no prospective studies are available to confirm that a high RSS value indeed correlates with increased frequency of CaOx urolith recurrence\(^{(28,135)}\).

**Dietary factors influencing urine pH.** Dietary protein of animal origin may decrease the base excess of the diet and increase the acid intake. As described above, a high acid intake can result in an increase in urinary Ca excretion. It can also reduce urinary citrate excretion since protons are able to associate with citrate in the intestine and kidney\(^{(136)}\). This mechanism might explain why humans do have a higher risk for CaOx formation following the consumption of high amounts of animal protein\(^{(99,137)}\). In cats, however, an opposite effect has been found. In a retrospective case–control study it was demonstrated that cats fed diets containing high amounts of protein (25.1 to 33.0 g/MJ ME) were less than half as likely (OR 0.44) to develop CaOx urolithiasis compared with cats receiving diets with a low protein content (12.4 to 18.9 g/MJ ME)\(^{(9)}\). An explanation might be that in cats the consumption of animal protein is often accompanied by stimulated water consumption, eventually resulting in an increase in urine volume, and an increased P excretion without altering Ca excretion\(^{(20)}\).

The observed lower oxalate excretion in healthy cats fed a high-protein diet compared with a low-protein diet\(^{(92)}\) might explain this association as well (Fig. 3).

The precise mechanism in which urinary Mg may influence CaOx formation is still largely unknown. Originally, Mg was thought to act as a mild inhibitor of CaOx crystallisation\(^{(138)}\). Another plausible explanation is that Mg, given as alkali salts, increase the urine pH, which in turn stimulates urinary citrate excretion by the kidney, which reduces the risk of CaOx crystal formation\(^{(139,140)}\).

A retrospective case–control study in cats revealed that diets with a low Mg content (22 to 43 mg/MJ ME) were associated with CaOx urolith formation\(^{(9)}\). Several studies (in other species) have reported an association between low dietary Mg and CaOx urolith formation as well\(^{(139,141–143)}\). In addition, in human medicine an increased dietary intake of Mg salts (containing citrate) is recommended in patients suffering from CaOx urolithiasis\(^{(139,144,145)}\). An additional mechanism of action is the formation of complexes between Mg and oxalate, thereby reducing the supersaturation with CaOx. However, in a study with cats fed a diet with a high Mg concentration, despite a significant increase in urinary Mg, no significant effect was observed regarding urinary CaOx crystal growth inhibition, agglomeration inhibition or solubility, compared with the base diet\(^{(140)}\). Interestingly, in the earlier mentioned retrospective case–control study, diets high in Mg content (86 to 336 mg/MJ ME) were associated with a higher risk for CaOx urolith formation compared with diets with a moderate Mg content (43–86 mg/MJ ME)\(^{(9)}\). An explanation might be that in cats the contribution of dietary oxalate to urinary oxalate excretion is less prominent and therefore complexation of oxalate in the gastrointestinal tract by Mg less effective. Moreover, in cats there is no evidence that hypocitruria is a risk factor for CaOx urolith formation.

**Urinary citrate**

Citrate synthesised by the kidney or derived from the diet is one of the most abundant organic anions in urine and has two main functions. First, it prevents alkaline-induced calcium phosphate stone formation by permitting base excretion without raising urine pH. Second, urinary citrate acts as a chelator of Ca and is therefore considered to be the best natural inhibitor of CaOx urolith formation\(^{(147)}\). The higher the citrate concentration in the urine, the less Ca is available to form CaOx crystals. As a consequence, a deficiency of urinary citrate caused by renal or gastrointestinal disorders is often seen in humans with CaOx stone disease\(^{(148,149)}\). However, there is no evidence that hypocitruria is a risk factor for CaOx urolith formation in cats. In dogs with CaOx urolithiasis, no hypocitruria was reported\(^{(150)}\).

In order to increase the citrate concentration in the urine, potassium or sodium citrate is added to the majority of the CaOx urolithiasis therapeutic diets. However, there have been no studies in cats investigating the effects of dietary citrate addition on citrate concentrations in the urine or the formation of CaOx. In healthy dogs, supplementation of dietary potassium citrate did not result in a consistent increase in urinary citrate excretion\(^{(151)}\). In this study, only a small, but not significant, increase in urine pH was observed. This increase in urine pH might be beneficial, although the influence of the urine acidity on CaOx formation remains questionable.

**Urinary glycosaminoglycans**

GAG comprise another class of components affecting stone formation. They can act in two ways: GAG, chondroitin sulfate and heparin sulfate are freely excreted in the urine and can inhibit the growth of CaOx crystals. Secondly, GAG are part of the extracellular matrix and can cover the inner wall of the bladder to form a defence against microbial and crystal adherence\(^{(152)}\). In cats with FIC, compared with healthy cats, a lower urinary GAG excretion has been detected, indicating that the defence against microbial and crystal adherence and inhibition of CaOx growth is decreased\(^{(153)}\). Oral supplementation of GAG in order to increase the free GAG concentration in urine has been shown to have a moderate to significant beneficial effect in humans with interstitial and radial cystitis\(^{(154)}\). In a study where oral glucosamine supplementation (i.e. 125 mg N-acetyl glucosamine) was compared with a
placebo control group in order to manage cats with FIC, no significant difference in urinary GAG concentration between the two groups was observed\(^\text{(17)}\). Surprisingly, no significant difference in urinary GAG concentration between the two groups. According to Gunn-Moore & Shenoy\(^\text{(17)}\), the improvement in both groups can be explained by the significant decrease in urine specific gravity that was found in about 90% of the subjects (of both treatment and placebo groups). It is likely that this positive effect was due to the fact that the owners decided to feed their cats more moist food during this study and not due to the N-acetyl glucosamine treatment.

Conclusions
Most of the dietary modifications to reduce CaOx urolith formation in cats and dogs are mainly based on data from epidemiological studies in these species and clinical studies in human subjects and rodents. Controlled studies designed to evaluate the efficacy of these dietary modifications in cats are scarce. To be able to improve the preventative measures (i.e. dietary modifications) against CaOx urolithiasis in cats, it is important to study the aetiopathogenesis of CaOx urolithiasis.

In contrast to human medicine, dietary modifications to decrease endogenous oxalate synthesis have hardly been studied in cats and future focus should examine the origin of urinary oxalate in cats, as a representative of the carnivores. The exclusive mitochondrial localisation of AGT1 in cats conforms to the notion that obligate carnivores, including domestic cats, are adapted to their natural diet, i.e. eating small mammals, containing high levels of animal protein, low levels of carbohydrate and glycolate. The observation that most commercial cat foods contain relatively high amounts of carbohydrates, often at the expense of animal protein, raises the question whether the consumption of these diets increases endogenous oxalate synthesis and in consequence the risk of CaOx urolithiasis. In addition, the contribution of exogenous oxalates to urinary oxalate excretion is unknown in cats as well. Knowledge about the dietary oxalate content in commercial feline diets, which is expected to be higher than in their natural diet, is essential in order to determine the contribution of exogenous oxalates in urinary oxalate excretion.

In-depth knowledge of feline endogenous oxalate metabolism and dietary oxalate absorption will provide a better understanding of the sharp increase in CaOx urolith prevalence in cats reported over the last few decades and provide new insights for preventative strategies. Also, based on the fact that in many human PH type I patients AGT1 is mistargeted to the mitochondria, mimicking the subcellular AGT1 distribution of cats, the cat might be a perfect research object to study endogenous oxalate synthesis in this genetic disorder.

Acknowledgements
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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All authors contributed fundamentally to the present study. J. C. D. contributed to all facets, including literature study, scientific interpretation and manuscript preparation. E. A. P. contributed to scientific interpretation and overall manuscript preparation. J. v. B. and W. H. H. both added valuable scientific knowledge to the present review, and contributed to improve readability and layout of the manuscript.

There are no conflicts of interest.

References


Feline endogenous oxalate synthesis


