Role of nutrition in endogenous oxalate metabolism in cats

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Introduction

Over the past 30 years, a progressive increase in calcium-oxalate (CaOx) urolith prevalence is seen in domestic cats diagnosed with urolithiasis.[1,2] This increase appears to have occurred since dietary modifications were introduced to address magnesium ammonium phosphate urolithiasis, although a solid scientific basis for this argument is lacking. Current non-invasive strategies based on nutrition are not able to reliably prevent CaOx urolithiasis and such strategies may partly be limited by incomplete knowledge regarding the pathogenesis of this multifactorial condition.

Several risk factors have been identified for CaOx urolithiasis in cats. As for animal related factors, cats with an increasing age (7–10 years) show the highest predisposition in developing CaOx uroliths.[3] Also, male cats seem to be more affected, and 95% of cats with CaOx urolithiasis are neutered.[3]

Hypercalcemia is thought to play an important role in the pathophysiology as well. In cats suffering from CaOx urolithiasis, mild hypercalcemia (11.1 to 13.5 mg/dl) was reported in 35% of the cases.[4] Although animal related factors may play a role in CaOx formation, the short time span in which the progressive increase in prevalence took place, may suggest a significant influence of nutritional factors. Any nutritional factor that is able to influence urinary concentrations of calcium (Ca) and oxalate may play a role in CaOx urolith formation.

Figure 1 displays a schematic model of dietary risk factors that are likely to increase urinary Ca or oxalate concentrations.

Dietary factors influencing urinary Ca concentration

For decades, the general consensus existed that a restricted dietary Ca intake would reduce the chance of CaOx urolith formation by reducing the urinary Ca excretion.[6] However, recent literature in humans and dogs indicate a possible advantage of an increased dietary Ca content.[7,8] This is thought to be related to complexation between dietary Ca and oxalate in the intestinal tract, making dietary oxalate less available for absorption. In support of this, a case control study by Lekcharoensuk et al[6] indicated that consuming diets with a

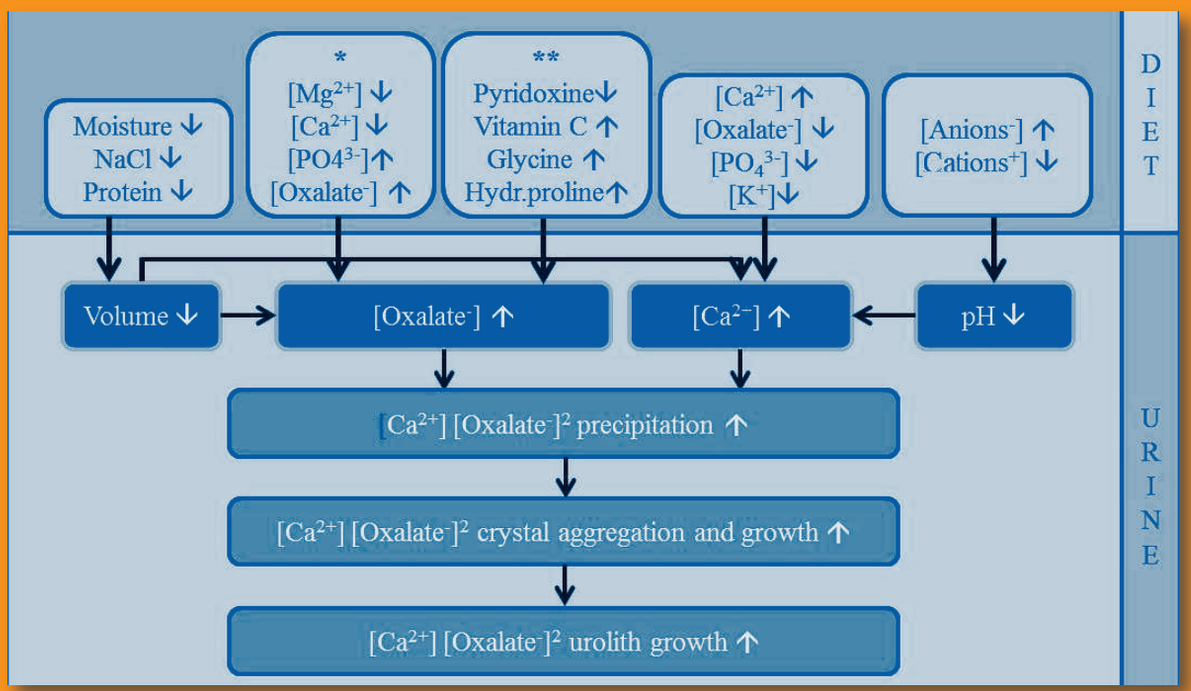

FIGURE 1 Schematic model of the influence of diet on urinary calcium and oxalate concentrations.
*** Dietary factors affecting exogenous oxalate.**
**** Dietary factors affecting endogenous oxalate synthesis.**
Modified from Dijcker et al[5]

relatively low amount of Ca (0.23–0.49 g/MJ) was associated with a higher risk for developing CaOx uroliths compared to diets with higher amounts of Ca (>0.49 g/MJ).

Low dietary intake of phosphate (P) may be related to an increased urinary Ca excretion in cats.[9] The rationale behind this finding may be a higher Ca availability in the gastrointestinal tract due to a reduced complexation with P. This is in agreement with the finding of Lekcharoensuk et al[6] that feeding diets with a low P content (0.2–0.4 g/MJ) showed an increased risk for CaOx urolithiasis compared to diets with a moderate P content (0.66–0.76 g/MJ). That same case-control study revealed that diets with a relatively high potassium (K) content (0.5–0.75 g/MJ) were less as half as likely (OR 0.45) to develop CaOx urolliths compared to cats that were fed diets with relatively low K content (0.23–0.38 g/MJ). A possible explanation for this effect may be the alkalizing effect of K salts, leading to a higher urinary pH, since a decrease in urinary pH is associated with an increase in urinary Ca excretion in cats.[10]

Dietary factors influencing exogenous urinary oxalate (Uox) concentration

Today's dry petfoods generally contain a relatively high amount of dietary oxalate, derived from bran concentrates and cereals. In 252 commercially available dry petfoods for cats the oxalate content was found to range between 3.1 and 117.9 mg/MJ, with a mean oxalate content of 27.2 mg/MJ.[11] The average daily intake of oxalate (7 mg/kg BW/day) compared to human daily oxalate intake (2—3 mg/kg BW/day)[12] can thus be considered high.

A high intake of dietary oxalate is a known factor that may increase Uox concentration. However, the amount of oxalate absorbed depends greatly on the availability of free oxalate in the gut. Research has shown that other dietary factors, like dietary Ca and magnesium content significantly affect the availability of oxalate for absorption. Both minerals can directly interact with oxalate, resulting in a lower free oxalate concentration in the gut.[13] The question remains whether dietary oxalate significantly contributes to Uox excretion in cats. In a recent study by Dijcker et al,[14] it was shown that increasing the oxalate intake from 13 to 93 mg/100g dry matter (corresponding with ± 15 mg/kg BW/day) did not affect Uox excretion. It was estimated that the intestinal absorption of supplemented oxalate was only 5.9 ± 5.24% and contributed for 0.78% to oxalates excreted in the urine. It was suggested that the relatively high Ca content of feline diets in general will lower the amount of free oxalate available for absorption, making the contribution of exogenous oxalate to Uox negligible.

Dietary factors influencing endogenous Uox concentration

Endogenous biosynthesis of oxalate mainly occurs in the liver, and is highly dependent on the glyoxylate content in the hepatocytes.[15] A schematic overview of the metabolic pathway of glyoxylate is given in Figure 2. Any glyoxylate that is not reduced to glycolate or transaminated to glycine is oxidized to oxalate, which is a metabolic 'end-waste product'. A key-enzyme in oxalate metabolism is alanine:glyoxylate aminotransferase 1 (AGT1), which converts glyoxylate into glycine. An essential co-factor for this enzyme is pyridoxine (Vitamin B6). A deficiency in pyridoxine has shown to significantly increase Uox excretion in kittens.[16]

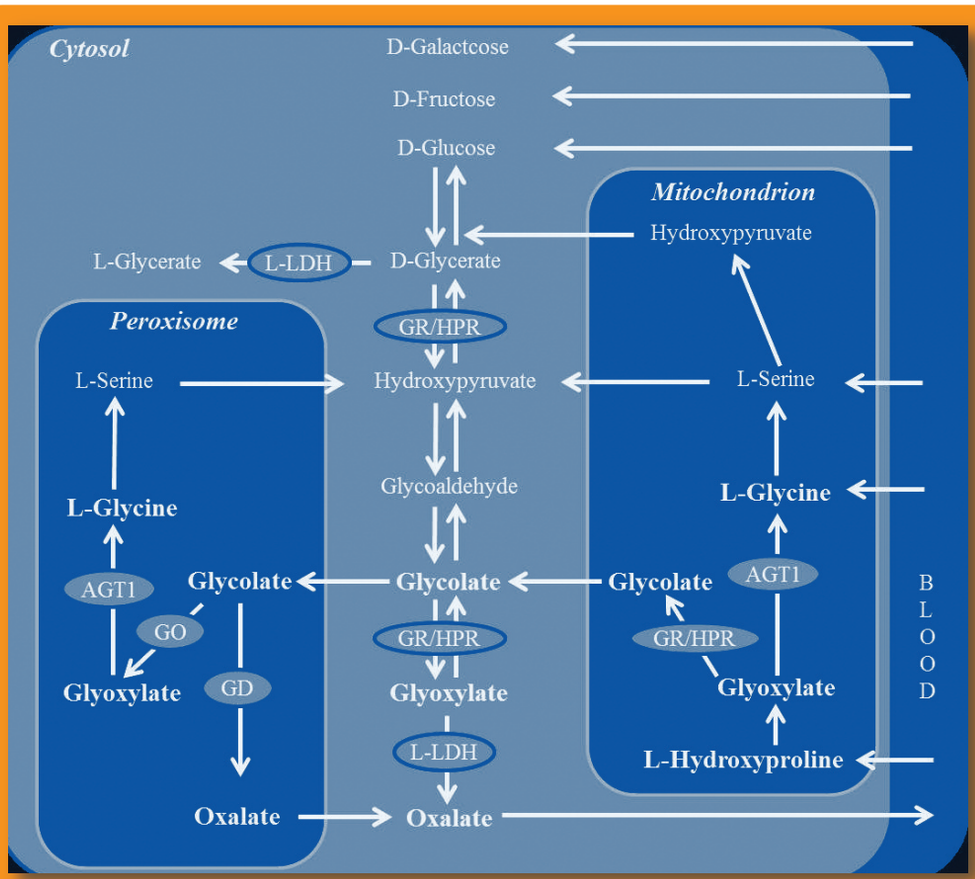

FIGURE 2 Schematic representation of de novo oxalate synthesis via glyoxylate metabolism in the hepatocyte. AGT-1 = alanine:glyoxylate aminotransferase; GD = glycolate dehydrogenase; GO = glycolate oxidase; GR/HPR = glyoxylate reductase/hydroxypyruvate reductase; L-LDH = L-lactate dehydrogenase. Modified from Dijcker et al[5]

AGT1 is both localized in mitochondrion and peroxisome, which reflects its dual physiological function, namely detoxification in peroxisomes and aiding gluconeogenesis in the mitochondrion.[17] Intra-peroxisomal detoxification of glyoxylate is essential in herbivores, since their diet is rich in glycolate and carbohydrates. To prevent oxidation of cytosolic glyoxylate to oxalate by L-lactate dehydrogenase (L-LDH, Figure 2), a high activity of AGT1 in the peroxisomes is needed. In contrast, carnivores naturally consume little glycolate and carbohydrates, which makes glyoxylate detoxification in the peroxisomes redundant. The high amount of animal protein in the natural diet of cats would clearly favor contribution of gluconeogenesis in the mitochondrion. This physiological difference between herbivores and carnivores is clearly expressed in the spatial localization between the different species. In carnivores AGT1 is mainly present in mitochondria, while in herbivores and humans AGT1 is predominantly located in the peroxisomes.[17]

The glyoxylate content in the hepatocyte is dependent in certain dietary precursors. In rats, it was shown that an increased intake of sugars (ie, glucose, fructose, galactose, xylose) and certain amino acids (hydroxyproline, glycine, serine) contributes to endogenous production of oxalate.[18–20] Based on the predominantly mitochondrial localization of AGT1 in cats, Dijcker et al[21] hypothesized that a high carbohydrate intake in this carnivorous species might induce endogenous oxalate synthesis and thereby affecting Uox excretion. To test their hypothesis, a randomized controlled trial was conducted in which 12 cats were fed three diets in a latin square design, only differing in macronutrient profile (high protein, high carbohydrate and high fat). It was found that, although the Uox concentration was significantly lower when the high protein diet was fed, net Uox excretion (mmol/kg BW0.75) was unaffected by a change in macronutrient profile. It was concluded that the activity of AGT1 in the peroxisomes was apparently sufficient for the removal of sugar-derived glyoxylate. Interestingly, Zentek et al,[22] in a study investigating the influence of dietary protein quality (horse meat, collagen tissue and soy isolate) and quantity (high or low protein) on Uox excretion, found the highest oxalate excretion when feeding the high and low protein diet formulated with collagen tissue, with an inverse relationship between Uox excretion and protein intake. The outcome of the Zentek's study is not in agreement with the data found by Dijcker.[21] This may be attributed to the protein sources used in the two

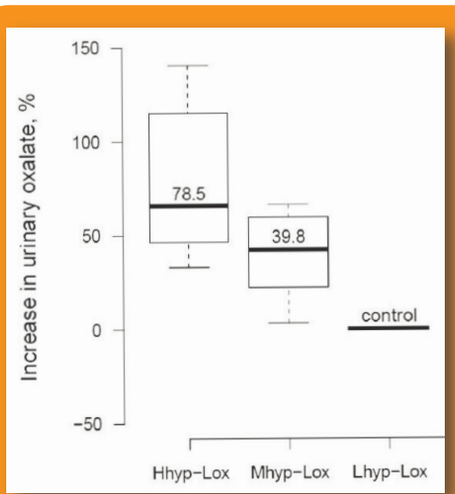

Figure 3 Box plot of the increase in urinary oxalate excretion in adult cats fed a low oxalate diet with low (Lhyp-Lox), moderate (Mhyp-Lox) and high (Hhyp-Lox) hydroxyproline. The box is representing values within 25th and 75th percentile. Whiskers extend to minimum and maximum values. Modified from Dijcker et al[14]

different studies. In the study of Dijcker, casein was used as a protein source, which is known to have no apparent effect on Uox excretion in cats. In the study of Zentek, collagen tissue was used as a protein source, generally rich in the amino acid hydroxyproline (hyp). In humans, rats and mice it was shown that significant amounts of endogenously synthesized oxalate is derived from hyp.[20,23,24] In another study by Dijcker et al[14] it was tested if hyp also influences endogenous oxalate metabolism in the carnivorous cat. For this purpose eight female cats were fed a diet low in oxalate (13 mg/100g DM) and low, medium or high in hyp (0.2, 2.0 and 3.8 g/100g DM, respectively) in a 48-day study with a latin square design. Increasing hyp intake resulted in an increased Uox excretion (P <0.0001) (Figure 3) and in a significant linear dose-response equation:

$$\text{Uox (mg/day)} = 5.622 + 2.097 * \text{hyp intake/day} \quad (r^2 = 0.56).$$

Based on the outcome of this study it was suggested by the authors that use of hyp-containing protein sources (like collagen tissue) should be minimized in CaOx preventative diets until their effect on Uox excretion is determined.

Conclusions

Nutrition seems to be able to influence formation of CaOx uroliths in cats, mainly by exerting an effect on Uox excretion. Urinary oxalate is largely derived from endogenous synthesis, as recent research has shown that exogenous oxalate marginally contributes to Uox excretion in cats. AGT1 is a key enzyme in endogenous oxalate metabolism. A nutritional deficiency in its co-factor vitamin B6 has shown to significantly increase Uox excretion. Protein source rather than protein content may be related to changes in endogenous oxalate synthesis, with hyp being a potent substrate in the formation of endogenous oxalate in cats.

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