L-methionine and struvite urolithiasis in dogs

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Struvite urolithiasis is a common problem in dogs. Predisposing factors for its development are bacterial infections of urinary tract, inadequate diet, as well as reduced uptake of water and fluids by the animal. Treatment of struvite urolithiasis requires multimodal management, including surgical treatment, antibacterial treatment, and acidification of urine. This article presents basic information about struvite urolithiasis in dogs and the role of methionine in the therapy and prevention of this disease.

Keywords: methionine, struvite urolithiasis, dogs

Struvite (infectious) urolithiasis, coexisting with urinary tract infection with urease-positive bacteria, has been a problem known in human and veterinary medicine for many years.

In 1817, Marcet observed the relationship between putrefaction, the presence of ammonia, the alkaline reaction of urine, and the formation of phosphate stones in the urinary tract (12). The basic condition for the formation of struvite stones (struvite – $MgNH_4PO_4x6H_2O$) in the urinary tract is the presence of bacteria producing urease, an enzyme that is not present in sterile urine. About 200 strains of microorganisms producing this enzyme have been described. These include both Gram-negative and Gram-positive bacteria, as well as yeasts. Urease-positive bacteria include *Proteus mirabilis*, *Proteus morganii*, *Proteus rettgeri*, *Providencia alcaliformis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Staphylococcus epidermidis*, *Ureaplasma urealyticum*. Thanks to urease, these microorganisms have the ability to produce amino acids from nitrogenous compounds (2). Under the influence of urease-positive bacteria,

the urine pH changes to alkaline. Urease is an amidohydrolase that decomposes urea into carbon dioxide (CO_2) and ammonium groups (NH_4) (1). Urea, excreted by the kidneys, stimulates the production of urease by bacteria, increasing its production by 5 to 25 times. This creates conditions for continuous production of urease in the infected urinary tract, e.g., by *Proteus bacteria* (1,3,8).

In addition to bacterial infections of the urinary tract, factors predisposing to the development of struvite urolithiasis include inappropriate diet (supersaturation of urine with minerals, excessive supply of protein and mineral salts in diet), reduced water and fluid intake by the animal, behavioral disorders, anatomical changes (bladder diverticulum), and the presence of crystalline core (exfoliated epithelium).

Struvite deposits in the urinary tract can grow very quickly (within a few weeks or months) and - if appropriate treatment is not implemented - fill, for example, the entire renal pelvis.

Symptoms and diagnosis

Struvite stones in dogs constitute 50-60% of all stones found in this species of animals. Its accompanying symptoms are a combination of symptoms of urolithiasis and urinary tract infection (fever, dysuria, pain in the lumbar region, urge to urinate, sometimes vomiting, loss of appetite, apathy) (6). Typical symptoms of renal colic are rare. Stones located in the urinary bladder may cause painful and frequent urination and hematuria. Sometimes their presence can be detected by palpating the bladder. When the urethra becomes obstructed, animals cannot urinate (anuria), and in severe cases, the urinary bladder may even rupture. The urine test shows its alkaline reaction and the presence of nitrites, and in the sediment - in addition to signs of infection (leukocyturia, sometimes leukocyte casts) - crystals of magnesium ammonium phosphate. These crystals usually take the shape of a coffin lid, less often – a fern leaf. Urine culture contains urease-producing bacteria. Imaging tests often reveal a large branching deposit. The most accurate method for detecting struvite deposits is computed tomography which can image deposits up to 1 mm in size. However, it has not been shown that it is possible to precisely assess the composition of the detected deposit (including the presence of magnesium ammonium phosphate) (13).

In veterinary medicine, the method of choice for diagnosing urinary tract stones is ultrasonography, which allows for the detection of all types of stones and, additionally, for the assessment of the thickness of the bladder wall (Fig. 1). Similarly to ultrasound, contrast X-ray (urography) allows one to detect stones and assess the patency of the urinary tract.

Treatment of patients with struvite stones

Treatment of urolithiasis requires multidirectional treatment, which includes surgical treatment, antibacterial treatment, and urine acidification (6).

In a situation where the patient has anuria, an attempt must be made to unblock the urinary tract and release the urine by catheterizing the urethra and pushing the stone into the bladder (the stones should then be removed during cystostomy). In some patients, urethrotomy is necessary.

A very important element of the treatment of struvite urolithiasis is antibiotic therapy carried out in accordance with urine culture and the results of antibiotic resistance testing of isolated strains of microorganisms. Antibacterial treatment may be used before and after surgical treatment. It should be long-term and periodically monitored with urine cultures. An unfavorable effect of long-term antibiotic therapy is the development of drug resistance in bacterial strains. Antibiotic therapy can be carried out for 3 or even 6 months (11).

Surgical intervention removes the cause of symptoms, but the only way to prevent recurrence of struvite urolithiasis is an appropriate diet and acidification of urine. Long-term and effective acidification of urine can be achieved by using urease inhibitors or by administering urine acidifying agents, such as vitamin C or L-methionine. Vitamin C causes a temporary decrease in urine pH as the body activates compensatory mechanisms, increasing the production of ammonia, which leads to a subsequent increase in urine pH. Additionally, vitamin C is considered a promoter of the urine alkalinization process by stimulating the secretion of citrates. Therefore, it seems that L-methionine has a better effect in this respect.

Properties of methionine

Methionine ($C_5H_{11}NO_2S$) belongs to the group of exogenous amino acids. Next to cysteine, it is one of two sulfur-containing amino acids. It is found in large amounts in lactic casein, and egg white. It is the first amino acid attached during the process of building a polypeptide chain. Methionine is essential in the methylation process which is important in the body's detoxification reactions, in the process of tissue growth and the formation of immune cells. This amino acid actively participates in all metabolic processes of the body. Methionine has detoxifying, lipotropic, anti-inflammatory, antiallergic, and choleretic properties, and prevents the formation of urinary tract stones (14).

It takes part in the synthesis of nucleic acids, choline, glycine betaine, creatine phosphate, and adrenaline. It increases the synthesis of glutathione, or gamma-Glutamyl-cysteinylglycine. Glutathione is an organic chemical compound that supports the reduction of peroxides by capturing reactive electrophilic factors, while protecting other cells from the harmful effects of toxins (9).

The following components participate in the metabolism of methionine: folic acid, trimethylglycine, vitamin B6, B12 and pyridoxal 5'-phosphate (active form of vitamin B6). Deficiency of vitamins B12, B6 or folic acid causes the level of homocysteine in the body to increase. If normal physiological processes occur, it remains biologically inactive. Otherwise, with impaired methionine transformation, the concentration of homocysteine in the blood increases (hyperhomocysteinemia). This may result in damage to vascular endothelium, disruption of blood coagulation processes (predisposition to atherosclerosis), increased risk of stroke, development of neurological diseases, and complications during pregnancy (7).

In veterinary medicine, methionine is used primarily in the supportive treatment of struvite urolithiasis and bacterial urinary tract inflammation. By acidifying urine and bile, it prevents the formation of deposits in the urinary

and biliary tracts and prevents their infection. Its mechanism of action is based on the fact that the sulfur contained in the molecule of this amino acid is oxidized to sulfates which are then excreted with the urine and lower its pH. Me-

thionine facilitates the dissolution of struvite stones if used long enough (8-12 weeks).

In one of the studies conducted on fourteen dogs with struvite urolithiasis, the animals were treated with antibiotics based on the results of urine culture and antibiotic sensitivity of isolated strains of microorganisms, as well as methionine to acidify the urine. Methionine was administered throughout the treatment period and an additional two weeks longer after the radiology examination confirmed the urinary bladder stones had been dissolved. The initial dose of the preparation was 100 mg/kg twice a day.

All animals used in the experiment underwent blood biochemistry tests, biochemical tests, and urine cultures, as well as blood gas analysis and radiological examinations at 4-week intervals, until no bladder stones could be detected radiologically.

If two subsequent radiological examinations showed no reduction in the size of struvite stones, the animals underwent surgery. Three dogs were removed from the experiment due to the difficulties in oral administration. In the case of the remaining 11 animals, in 8 individuals complete dissolution of struvite stones was observed on average after 2 months (1 to 4 months) of administration of methionine. The average final dose of L-methionine at which stone dissolution was observed was 97.3 +/- 25.6 mg/kg. In 3 dogs, despite long-term use of methionine preparations, the stones failed to dissolve, so they underwent surgery (10).

As a urine acidifying compound, methionine is recommended for use in dogs with struvite urolithiasis by the American College of Veterinary Internal Medicine (ACVIM) (5). Additionally, it should be noted that the use of methionine preparations shows to be significantly safe. According to Hickey's research (4), symptoms of intoxication with methionine contained in urine acidifying preparations occur when the recommended dose of the amino acid for representatives of this species is exceeded several times. Observations of 1,525 American dogs that consumed significant amounts of methionine confirmed the development of transient side effects (ataxia and vomiting) that spontaneously resolved within 48 hours in only 47% of dogs. No falls were recorded in any of the dogs. The results of the studies presented above, as well as our own observations, indicate that preparations containing L-methionine should constitute an important element of the therapy and prevention of struvite urolithiasis in dogs.

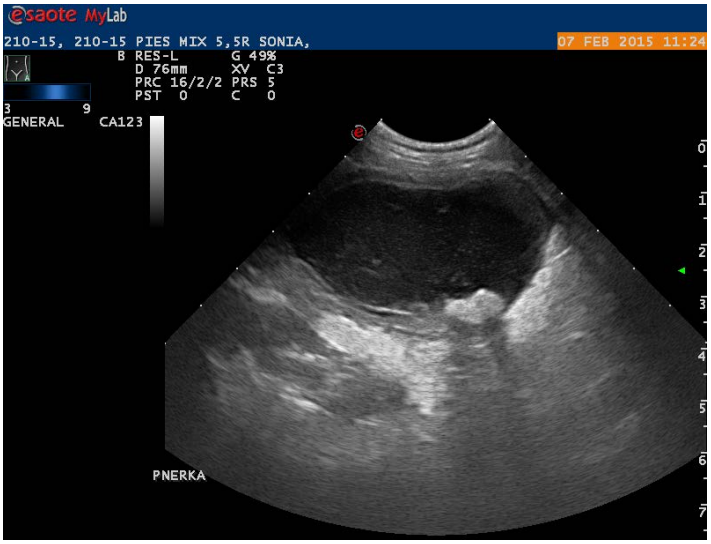

Fig.1. Ultrasound examination results in a dog with bladder stones.

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