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PROTEINURIA IN DOGS AND CATS – SELECTED ISSUES ON RENAL PHYSIOLOGY AND PATHOPHYSIOLOGY

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Abstract. Protein in the urine of healthy dogs and cats is present in trace amounts. It can occur in larger quantities in the urine of sick animals, as well as during certain physiological conditions. Routinely, proteinuria is assessed using the urine protein to creatinine ratio (UPC), which is a widely recognized prognostic indicator. Under normal conditions, its value is <0.2. Values ranging from 0.2 to 0.4 in cats and from 0.2 to 0.5 in dogs are considered upper limit of normal, whereas UPC values >0.4 in cats and >0.5 in dogs are indicative of proteinuria. When diagnosing the causes of proteinuria in dogs and cats, it is important to consider damage to the glomeruli, renal tubules, interstitial tissue, and progressive loss of nephrons. Protein fractions present in urine, which vary in molecular weight, are sensitive diagnostic indicators of kidney dysfunction. Increased excretion of high molecular weight proteins may indicate damage to the renal glomeruli, while loss of low molecular weight proteins may suggest dysfunction of the renal tubules. If proteinuria persists and/or does not resolve after treating the underlying disease, it is necessary to initiate treatment aimed at reducing proteinuria by >90% in cats and >50% in dogs. The most effective treatment method for reducing proteinuria, while also having nephroprotective and cardioprotective benefits, is the blockade of the renin-angiotensin-aldosterone system (at its different levels). It is also essential to implement a proper diet, particularly by restricting protein and sodium intake.

Key words: dogs, cats, glomerular proteinuria, tubular proteinuria, filtration membrane, podocytes, tubular protein resorption, urine protein to creatinine ratio (UPC), RAA system and proteinuria.

INTRODUCTION

Protein in the urine of healthy dogs and cats is present in trace amounts that are virtually unmeasurable. The presence of larger amounts of protein in urine typically indicates a pathological process and is defined as proteinuria. This condition can not only be a symptom of various kidney diseases, but also a factor contributing to the progressive impairment of its function. It is also an important risk factor for other diseases, especially cardiovascular disorders (Skrzypczak 2021; Skrzypczak et al. 2021). The risk of proteinuria in dogs and cats increases with chronic

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kidney diseases, as well as with the presence of diabetes and/or hypertension. O'Neill et al. (2014) have reported that the prevalence of chronic kidney disease (CKD) in young cats ranges from 2 to 4%, while in cats over 10 years old, it increases to 30–40%. Similar results were obtained by Hall et al. (2018) in a screening study involving dogs. In these animals, proteinuria often occurs in old age, without visible signs of disease. Persistent proteinuria increases the risk of mortality (Stompór 2009). The results of many studies indicate a relationship between the intensity of proteinuria and survival time (Syme 2009; Harley and Langston 2012). For the aforementioned reasons, the detection and quantitative as well as qualitative assessment of proteins excreted in urine are highly significant tests in the process of diagnosing and treating dogs and cats. Proteins present in urine can serve as diagnostic markers (allowing for the detection of disease at very early stages), prognostic markers (permitting assessment of disease severity and thus selection of appropriate treatment), and predictive markers (enabling prediction of disease occurrence) (Stompór 2009). Syme (2009) has argued that even minimal proteinuria, especially in cats, can be an important prognostic indicator.

PROTEINURIA TYPES

Three basic types of proteinuria can be distinguished based on the "origin" of the proteins present in the urine: prerenal, renal and atherosclerotic.

Prerenal proteinuria is caused by the passage into the urine of low molecular weight plasma proteins filtered through an intact filtration barrier, in quantities exceeding the tubular reabsorptive capacity, or proteins that do not normally occur in free form in the blood plasma, such as hemoglobin and myoglobin, or abnormal proteins, for example, immunoglobulin light chains (Bence-Jones proteins) (Lees et al. 2005; Stompór 2009; Syme 2009; Harley and Langston 2012).

Physiological renal proteinuria is not associated with morphological changes in the kidneys. It occurs, for example, during fever, exposure to very low or very high temperatures, intense physical exertion, stressful situations, or in the newborn period. It has a transient nature and resolves when the underlying cause subsides (Lees et al. 2005; Stompór 2009; Syme 2009; Skrzypczak 2021; Skrzypczak et al. 2021). The research concerning the causes of physiological proteinuria in dogs and cats is limited, but it has been shown that activities such as swimming in dogs or confinement in cages can lead to proteinuria, likely due to stress (Joles et al. 1984; Grauer 2007, 2011).

Pathological renal proteinuria is associated with morphological and functional changes, primarily alterations in the permeability of the filtration barrier (glomerular proteinuria) and/or changes in protein reabsorption in the proximal tubule cells (tubular proteinuria). Proteins can also pass into the urine from the interstitial tissue (from peritubular capillaries) during inflammation (interstitial proteinuria) (Lees et al. 2005; Stompór 2009).

Postrenal proteinuria is associated with the passage of proteins into the urine in the urinary tract (renal pelvis, ureters, urinary bladder, or urethra), for example, in infections or inflammatory conditions. Postrenal proteinuria resolves after the underlying disease is cured (Lees et al. 2005; Harley and Langston 2012).

GLOMERULAR PROTEINURIA DEVELOPMENT

Renal proteinuria resulting from glomerular dysfunction is most commonly associated with damage to the selective filtration barrier. In dogs, this is the predominant type of proteinuria.

The filtration barrier consists of 3 layers: the fenestrated endothelium of the glomerular capillaries, the basement membrane, and the slit membrane between the foot processes of podocytes.

The porous endothelium of the capillaries and the thin layer of mucopolysaccharides covering the cell membranes constitute the first layer of the glomerular filter for macromolecules.

The basement membrane of the glomeruli is located between the endothelial cells of the capillaries and the podocytes. It mainly consists of four macromolecules: laminin, collagen type IV, heparan sulfate (proteoglycan), and nidogen. They are synthesized by both podocytes and endothelial cells and secreted into the extracellular space, where they form an intertwining network with a thickness ranging from 250 to 400 nm. This layer provides structural support for the glomerular capillaries and contains ligands for receptors on endothelial cells, podocytes, and mesangial cells. It constitutes the second layer that is selective in terms of size and electrical charge of filtered particles (Yurchenco and Patton 2009; Miner 2011, 2012; Suh and Miner 2013; Skrzypczak 2021; de Souza et al. 2022). The porousness of the basement membrane is primarily conferred by cross-linked laminin and collagen (reducing the amount of these components increases its permeability by enlarging the pores), while the proteoglycan imparts a highly negative charge (known as anionic sites). Changes in the structure of the basement membrane, induced by mutations and/or environmental factors, lead to alterations in its structure, which can have a significant impact on the function of podocytes, endothelial, and mesangial cells (Eremina et al. 2003; Smithies 2003; Jefferson et al. 2008; Miner 2012; Suh and Miner 2013; Skrzypczak 2021; Skrzypczak et al. 2021).

However, podocytes play a crucial role in the filtration barrier. These are highly specialized cells with complex cytoarchitecture, characterized by their processes (major and foot processes). Foot processes contain a contractile apparatus composed of actin, myosin, actinin, talin, vinculin, and vimentin, which responds to changes in the cytoskeleton induced by various vasoactive substances. Therefore, podocytes regulate the size of glomerular filtration, stabilize the structure of the glomerulus, maintain physiological pressure within the glomerulus, but above all, they create a barrier for filtered proteins, thanks to the so-called slit membrane between foot processes. The slit membrane is composed of numerous proteins forming a functional complex. The main proteins are nephrin and podocin, belonging to signaling proteins, as well as: Neph1 (nephrin-like protein 1), α-actinin 4, CD2-associated protein (CD2AP), densin, and TRPC6 (canonical transient receptor potential 6). The slit membrane is covered with a surface coat rich in sialoglycoproteins, responsible for the high negative surface charge of podocytes (Rodewald and Karnovsky 1974; Pavenstädt et al. 2003; Neal 2015; de Souza et al. 2022). Characterization of the slit membrane and elucidating the role of the aforementioned proteins has greatly contributed to understanding the mechanism of proteinuria.

It should be noted that podocytes are fully differentiated cells and do not have the ability to regenerate. They cannot be replaced when damaged during the course of the disease. The factors that cause their damage can be, e.g., viruses, bacterial antigens, drugs, amyloid deposits of various types or immune complexes (Shackland 2006; Tryggvason et al. 2006; Stompór 2009; Littman 2011; Degenhardt et al. 2023). Changes in the glomerular environment, especially the presence of large amounts of proteins in the filtrate, also contribute to podocyte loss and changes in slit membrane protein expression. They act as chemotactic agents for mononuclear cells and pro-inflammatory cytokines, with TGF-beta being the most important one. It has been shown that podocytes secrete TGF-β in response to high levels of glucose, low-density lipoproteins or thrombin, which induces their apoptosis. Activation of

pro-inflammatory factors leads, among others, to detachment of podocytes from the basement membrane (Syme et al. 2006; Syme 2009; de Souza et al. 2022).

Another mechanism of podocyte damage leading to the development of proteinuria is hyperfiltration induced by disturbances in the autoregulation of renal microcirculation. It is most commonly caused by excessive dilation of the afferent arteriole, resulting in increased pulsation of the glomerulus (mesangial stretching). Under normal conditions, with preserved autoregulation of renal microcirculation, the glomerulus pulsates in rhythm with systolic-diastolic blood pressure fluctuations, with a volume change of less than 0.5%. However, with disrupted autoregulation, these changes can be as high as 10%. The increasing diameter of pores in endothelial cells facilitates the filtration of proteins. In stretched cells, genes are being activated leading to increased angiotensin II synthesis and release of growth factors. The pulsation of the renal glomerulus triggers the process of hypertrophy and apoptosis of podocytes, resulting in the loss of their anchorage in the basement membrane and podocytopenia (Brown and Brown 1995; Durvasula et al. 2004; Gruden et al. 2005; Syme et al. 2006; de Souza et al. 2022).

The consequence of podocyte loss is the direct contact of the basement membrane with the cells of the visceral layer of Bowman's capsule. Adhesions form and inflammatory processes intensify within the glomerular vascular loop, allowing the passage of macromolecules from the blood into the urine. A high correlation has been observed between podocytopenia and the extent of glomerulosclerosis, the magnitude of proteinuria, and the reduction in glomerular filtration.

Morphological changes in the filtration barrier, including podocyte loss, have been demonstrated in dogs with chronic kidney disease (CKD) (de Souza et al. 2022). The authors assessed the presence of mRNA for nephrin (NPHS1) and podocin (NPHS2) in urine sediments of dogs with chronic kidney disease (CKD) and healthy dogs. They demonstrated that physiological podocyturia occurred in healthy dogs, while in sick dogs, podocyturia varied depending on the stage of the disease, i.e., it was exacerbated in dogs in stages 1 or 2 and decreased in stages 3 or 4. Changes in the structure of the basement membrane were also observed in dogs with chronic kidney disease, primarily its thickening, loss of attachment between the membrane and podocytes, and gradual loss of foot processes. Specific glomerulopathies associated with abnormalities in the glomerular basement membrane and/or slit membrane have been described in dogs. As of now, they have not been documented in cats (Syme 2009).

TUBULAR PROTEINURIA DEVELOPMENT

The vast majority of proteins passing through the intact filtration barrier are captured by proximal tubule cells via endocytosis and subsequently undergo lysosomal degradation. This is a process mediated by receptors. In case of their saturation, an excess of proteins passes into the urine (Harley and Langston 2012; Skrzypczak 2021).

It should be noted that after reaching maximum reabsorptive capacity, proteins present in the lumen of the proximal tubules can cause damage to tubular cells (mainly through lysosomal enzymes) and additionally stimulate cells to release inflammatory mediators (e.g., monocyte chemotactic protein-1, vascular cell adhesion molecule, intercellular adhesion molecule-1 and TGF-β). The release of the aforementioned factors into the interstitium leads to the stimulation of fibroblasts and the process of interstitial fibrosis (Russo 2003; Langston and Reine 2006; Strutz 2009). It has been demonstrated that a key mediator activating tissue

fibrosis is TGF-β1, produced by mesangial and interstitial cells of the kidneys. Kongtasai et al. (2022) showed a significant correlation between the concentration of TGF-β in urine and the severity of interstitial fibrosis.

PROTEINURIA – QUANTITATIVE ASPECT

It should be assumed that a urine analysis for protein should be performed in any dog or cat reported for clinical evaluation where a routine blood test is indicated. A thorough examination of the quantity of proteins excreted in urine requires determining the volume of diuresis, as the concentration of a given substance in urine depends on its dilution/concentration. Measuring the concentration of protein in urine has very little diagnostic value without knowing the amount of urine produced by the kidneys over a unit of time.

Unfortunately, in practice, measuring diuresis is difficult or impossible, hence proteinuria is typically assessed based on the urine protein to creatinine ratio (UPC). This is considered a common prognostic indicator in dogs and cats. As part of the diagnostics of kidney disease, morning urine samples should be collected (fasting), and then the concentration of both parameters should be determined, and the protein/creatinine ratio calculated. Under normal conditions, this indicator in dogs and cats is <0.2. Values ranging from 0.2 to 0.4 in cats and from 0.2 to 0.5 in dogs are considered upper limit of normal, whereas UPC values >0.4 in cats and >0.5 in dogs are indicative of proteinuria (Lees et al. 2005; Whittemore et al. 2006; Harley and Langston 2012; Fidalgo et al. 2022; Mortier et al. 2023).

If the UPC value is higher than 0.4 and 0.5, respectively, the test should be repeated, at least three times, at an interval of 2 weeks (prerenal or postrenal proteinuria should be excluded). A UPC value above 1.0 in dogs, especially with confirmed kidney failure, is associated with an increased risk of developing uremia and mortality. A UPC ratio above 2.0 in cats and dogs likely indicates the presence of large molecular weight proteins in their urine (i.e., glomerular proteinuria) (Lees et al. 2005; Syme 2009; Smets et al. 2010; Harley and Langston 2012; Fidalgo et al. 2022; Mortier et al. 2023).

Lyon et al. (2010) have reported that the UPC ratio in dogs and cats exhibits high specificity in detecting albuminuria (99.7 and 99.2%, respectively), but low sensitivity (28.7 and 2.0%, respectively). Additionally, Mardell and Sparkes (2006) and Whittemore et al. (2007) have indicated that the UPC ratio is a nonspecific indicator, and the prevalence of proteinuria assessed using UPC measurement can vary significantly. The use of the UPC test in screenings to detect albumin in the urine of clinically healthy dogs and cats resulted in a high number of false-negative results.

In humans, the average urinary protein excretion is 80 mg/day (±24 mg d^{-1}). In this amount, approximately 50% consists of low molecular weight proteins that are filtered through the filtration barrier and not reabsorbed in the tubules, while the remaining 50% comprises proteins originating from kidney structures outside the glomerulus and from the urinary tract. In the excreted urine, albumin accounts for approximately 15% (from 2 to 25 mg d^{-1}). Excreting more than 150 mg of protein per day and more than 30 mg of albumin constitutes the threshold for proteinuria. Depending on the quantity of protein excreted in the urine over 24 hours, there are three categories of proteinuria: mild proteinuria, when the excretion of protein does not exceed 0.5 g per day; moderate proteinuria, when the amount of excreted protein ranges from 0.5 to 3.5 g per day; and severe proteinuria, when the daily urine contains more than 3.5 g of protein. In veterinary medicine, universally accepted values defining proteinuria have not been established (Stompór 2009; Syme 2009; Viteri and Reid-Adam 2018; Skrzypczak 2021; Skrzypczak et al. 2021).

It is important to interpret changes in the degree of proteinuria assessed based on the UPC ratio in combination with the results of serum creatinine measurements. For example, as kidney disease progresses and the number of functioning nephrons decreases, serum creatinine level may increase, resulting in a lower UPC ratio, falsely indicating proteinuria resolution.

KIDNEY DISEASE AND PROTEINURIA

When diagnosing proteinuria in dogs and cats, one must consider damage to the glomeruli, renal tubules, interstitial tissue, and progressive loss of nephrons (Lees et al. 2005; Grauer 2011).

Among the many kidney diseases leading to proteinuria, attention should be paid to acute glomerulonephritis (which can occur regardless of the age of the dog/cat) and chronic kidney disease (especially affecting older animals). They can develop, for example, on the basis of various infections, inflammatory conditions, neoplastic diseases, hypercalcemia, heart failure, and others.

For instance, primary glomerular disease occurs much more frequently in dogs than in cats (Littman 2011). The most indicative sign suggestive of glomerular disease in dogs is significant proteinuria (UPC >2). Cook and Cowgill (1996) showed that amyloidosis was the cause of 23% of glomerular diseases in dogs (UPC >10). High risk of this disease occurs in dog races such as beagles, collies or walkers (Cook and Cowgill 1996; Littman 2011). Littman (2011) demonstrated the occurrence of familial amyloidosis in shar pei dogs and amyloid deposition also in the renal medulla.

In cats, glomerular diseases that could lead to the development of nephrotic syndrome are rare. The main condition in these animals is chronic tubulointerstitial fibrosis. Littman (2011) has reported that Abyssinian and Siamese cats are predisposed to amyloidosis. The incidence of feline renal failure increases with age, with at least 15% of cats over the age of 15 being diagnosed with azotemia.

Animals with any form of kidney disease, who have proteinuria (cats with UPC >0.4 and dogs with UPC > 0.5), have a poorer prognosis and shorter long-term survival than animals with kidney disease but without proteinuria (Littman 2011; Harley and Langston 2012). Syme et al. (2006) demonstrated that protein excretion in cats (measured by the UPC ratio) was positively associated with shorter survival time. The average survival time for cats with chronic kidney disease was 281 days (UPC >0.4) compared to 766 days when UPC was <0.4. In cats that died within 1 month of being diagnosed with chronic kidney failure, the average UPC was 1.33 (0.50–6.47), which was significantly higher than in cats that lived longer (mean value was 0.22 and ranged from 0.01 to 1.44) (Kuwahara et al. 2006). Dogs with chronic kidney disease and the UPC ratio higher than 1.0, had a nearly threefold higher risk of death than dogs with the UPC ratios below 1.0 (Jacob et al. 2005; Lees et al. 2005; Syme et al. 2006; Wehner et al. 2008; Syme 2009).

In addition to kidney diseases, causes of proteinuria in both dogs and cats may include conditions such as arterial hypertension, heart failure, acute pancreatitis, hyperthyroidism, as well as heatstroke or extreme physical exertion (Jepson et al. 2007; Harley and Langston 2012). Excessive loss of protein in the urine is an independent prognostic indicator not only for the progression of kidney diseases but also for extrarenal complications (cardiovascular and cerebrovascular). Numerous studies have demonstrated that proteinuria is a factor that significantly increases the risk of acute coronary syndromes (2.5 times), cerebrovascular events, myocardial infarction, and death (Mann et al. 2003; Fortuna and Syme 2024).

Persistent proteinuria contributes to the occurrence of such conditions as alterations in blood lipid profile, hypercoagulability, impaired fibrinolysis, water retention, hypertension, anemia, decreased cellular immunity, and disturbances in hormonal and electrolyte balance (Stompór 2009; Littman 2011; Harley and Langston 2012). Therefore, treatment of animals should not be limited solely to the underlying disease but should also focus on reducing protein excretion in the urine (Ishani et al. 2006; Stompór 2009; Fortuna and Syme 2024).

REDUCING PROTEINURIA POSSIBILITY

If proteinuria persists or does not resolve after treating the underlying disease (UPC >0.4 in cats and >0.5 in dogs), detailed diagnostics and treatment are necessary. The goal should be to reduce proteinuria >90% in cats and > 50% in dogs (Lees et al. 2005; Harley and Langston 2012).

Diet has a significant impact on the magnitude of proteinuria; however, in animals with kidney disease and proteinuria, diet alone is not sufficient as a therapeutic measure (Burkholder et al. 2004; Littman 2011). First and foremost, it is necessary to restrict the amount of protein and sodium in the diet. Reduced protein levels in the blood decrease the risk of overloading the filtration barrier and facilitate protein reabsorption in the tubules. Littman (2011) showed that dogs with hereditary kidney inflammation lived 53% longer when fed a diet with reduced levels of protein, lipids, calcium, and phosphorus. Feeding cats with chronic kidney disease a diet low in protein and phosphates prolongs their survival, likely by alleviating the severity of secondary hyperparathyroidism and reducing the intensity of uremia (Elliott et al. 2000; Syme et al. 2006).

However, the blockade of the renin-angiotensin-aldosterone system (RAAS), with simultaneous nephroprotective and cardioprotective effects is the most effective method of reducing proteinuria. Drugs that block the RAA system lower peripheral arterial and intraglomerular pressure, restore impaired autoregulation of the renal circulation, inhibit interstitial fibrosis and glomerular sclerosis, and ultimately reduce urinary protein excretion. Studies in both humans and animal models have shown that the use of angiotensin converting enzyme inhibitors (ACE, angiotensin converting enzyme inhibitors) or sartans (angiotensin receptor blockers) in proteinuric nephropathies decrease the rate of progression of renal failure, with the effect being proportional to the degree of proteinuria reduction (Lees et al. 2005). Benazepril is an ACE inhibitor approved for use in cats in Europe and Japan, indicated for the treatment of chronic renal failure in these animals (it was shown to reduce glomerular capillary pressure in cats both experimentally and clinically) (Mizutani et al. 2006). Lees et al. (2005) and King et al. (2017) demonstrated reduced risk of progressive azotemia and increased survival in dogs after the application of RAA inhibitors. Angiotensin-converting enzyme inhibitors are contraindicated in dehydrated animals until hypovolemia is equalized.

There is limited data regarding the use of angiotensin receptor blockers in dogs and cats. In humans, sartans show nephroprotective effects and reduce proteinuria when used alone or in combination with ACE inhibitors (Galle 2008). In small animals, Losartan is the most commonly used angiotensin II receptor blocker.

There is also a lack of data regarding the use of aldosterone antagonists in the treatment of proteinuria in dogs and cats. Spironolactone is relatively well tolerated by animals and should be considered for use in animals not responding to ACE inhibitors. In humans, spironolactone was shown to reduce proteinuria by up to 34% and was more effective than sartans.

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REFERENCES

Bidani A.K., Griffin K.A. 2004. Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension 44(5), 599–601. DOI: 10.1161/01.HYP.0000145180.38707.84

Brown S.A., Brown C.A. 1995. Single-nephron adaptations to partial renal ablation in cats. Am. J. Physiol. 269, 1002–1008. DOI: 10.1152/ajpregu.1995.269.5.R1002.

Burkholder W.J., Lees G.E., LeBlanc A.K., Slater M.R., Bauer J.E., Kashtan C.E., McCracken B.A., Hannah S.S. 2004. Diet modulates proteinuria in heterozygous female dogs with X-linked hereditary nephropathy. J. Vet. Intern. Med. 18(2), 165–175. DOI: 10.1892/0891-6640(2004)18<165:dmpihf>2.0.co;2.

Cook A.K., Cowgill L.D. 1996. Clinical and pathologic features of protein-losing glomerular disease in the dog: A review of 137 cases (1985–1992). J. Am. Anim. Hosp. Assoc. 32(4), 313–322. DOI: 10.5326/15473317-32-4-313.

Degenhardt L., Dorsch R., Hartmann K., Dörfelt R. 2023. Serum amyloid A in cats with renal azotemia. Vet. World. 16(8), 1673–1681. DOI: 10.14202/vetworld.2023.1673-1681.

Durvasula R.V., Petermann A.T., Hiromura K., Blonski M., Pippin J., Mundel P., Pichler R., Griffin S., Couser W.G., Shankland S.J. 2004. Activation of a local tissue angiotensin system in podocytes by mechanical strain. Kidney Int. 65(1), 30–39. DOI: 10.1111/j.1523-1755.2004.00362.x.

Elliott J., Rawlings J.M., Markwell P.J., Barber P.J. 2000. Survival of cats with naturally occurring chronic renal failure: effect of dietary management. J. Small. Anim. Pract. 41(6), 235–242. DOI: 10.1111/j.1748-5827.2000.tb03932.x.

Eremina V., Sood M., Haigh J., Nagy A., Lajoie G., Ferrara N., Gerber H.P., Kikkawa Y., Miner J.H., Quaggin S.E. 2003. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. J. Clin. Invest. 111(5), 707–716. DOI: 10.1172/JCI17423.

Fidalgo M.A., Leal R.O., Duarte-Correia J.H. 2022. Urinary protein/creatinine ratio in feline medicine: reasons to perform it and its role in clinical practice – a retrospective study. Animals 12(12), 1575. DOI: 10.3390/ani12121575.

Fortuna L., Syme H.M. 2024. Factors associated with thrombotic disease in dogs with renal proteinuria: A retrospective of 150 cases. J. Vet. Intern. Med. 38(1), 228–237. DOI: 10.1111/jvim.16973.

Galle J. 2008. Reduction of proteinuria with angiotensin receptor blockers. Nat. Clin. Pract. Cardiovasc. Med. Suppl 1, 36–43. DOI: 10.1038/ncpcardio0806.

Grauer G.F. 2007. Measurement, interpretation, and implications of proteinuria and albuminuria. Vet. Clin. North Am. Small Anim. Pract. 37(2), 283–295. DOI: 10.1016/j.cvsm.2006.11.003.

Grauer G.F. 2011. Proteinuria: measurement and interpretation. Top. Companion Anim. Med. 26(3), 121–127. DOI: 10.1053/j.tcam.2011.04.002.

Gruden G., Setti G., Hayward A., Sugden D., Duggan S., Burt D., Buckingham R.E., Gnudi L., Viberti G. 2005. Mechanical stretch induces monocyte chemoattractant activity via an NF-kappaB-dependent monocyte chemoattractant protein-1-mediated pathway in human mesangial cells: inhibition by rosiglitazone. J. Am. Soc. Nephrol. 16(3), 688–696. DOI: 10.1681/ASN.2004030251.

Hall J.A., Fritsch D.A., Yerramilli M., Obare E., Yerramilli M., Jewell D.E. 2018. A longitudinal study on the acceptance and effects of a therapeutic renal food in pet dogs with IRIS-stage 1 chronic kidney disease. J. Anim. Physiol. Anim. Nutr. 102(1), 297–307. DOI: 10.1111/jpn.12692.

Harley L., Langston C. 2012. Proteinuria in dogs and cats. Can. Vet. J. 53(6), 631–638.

Ishani A., Grandits G.A., Grimm R.H., Svendsen K.H., Collins A.J., Prineas R.J., Neaton J.D. 2006. Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. J. Am. Soc. Nephrol. 17(5), 1444–1452. DOI: 10.1681/ASN.2005091012.

Jacob F., Polzin D.J., Osborne C.A., Neaton J.D., Kirk C.A., Allen T.A., Swanson L.L. 2005. Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure. J. Am. Vet. Med. Assoc. 226(3), 393–400. DOI: 10.2460/javma.2005.226.393.

Jefferson J.A., Shankland S.J., Pichler R.H. 2008. Proteinuria in diabetic kidney disease: a mechanistic viewpoint. Kidney Int. 74(1), 22–36. DOI: 10.1038/ki.2008.128.

Jepson R.E., Elliott J., Brodbelt D., Syme H.M. 2007. Effect of control of systolic blood pressure on survival in cats with systemic hypertension. J. Vet. Intern. Med. 21(3), 402–409. DOI: 10.1892/0891-6640(2007)21[402:eocosb]2.0.co;2.

Joles J.A., Sanders M., Velthuizen J., Den Hertog J.M., Van Dijk C. 1984. Proteinuria in intact and splenectomized dogs after running and swimming. Int. J. Sports Med. 5(6), 311–316. DOI: 10.1055/s-2008-1025923.

King J.N., Font A., Rousselot J.F., Ash R.A., Bonfanti U., Brovida C., Crowe I.D., Lanore D., Pechereau D., Seewald W., Strehlau G. 2017. Effects of benazepril on survival of dogs with chronic kidney disease: a multicenter, randomized, blinded, placebo-controlled clinical trial. J. Vet. Intern. Med. 31(4), 1113–1122. DOI: 10.1111/jvim.14726.

Kongtasai T., Paepe D., Meyer E., Mortier F., Marynissen S., Stammeleer L., Defauw P., Daminet S. 2022. Renal biomarkers in cats: A review of the current status in chronic kidney disease. J. Vet. Intern. Med. 36(2), 379–396. DOI: 10.1111/jvim.16377.

Kuwahara Y., Ohba Y., Kitoh K., Kuwahara N., Kitagawa H. 2006. Association of laboratory data and death within one month in cats with chronic renal failure. J. Small Anim. Pract. 47, 446–450.

Langston C.E., Reine N.J. 2006. Hyperthyroidism and the kidney. Clin. Tech. Small Anim. Pract. 21(1), 17–21. DOI: 10.1053/j.ctsap.2005.12.003.

Lees G.E., Brown S.A., Elliott J., Grauer G.E., Vaden S.L. 2005. Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (small animal). J. Vet. Intern. Med. 19(3), 377–385. DOI: 10.1892/0891-6640(2005)19[377:aamopi]2.0.co;2.

Littman M.P. 2011. Protein-losing nephropathy in small animals. Vet. Clin. Small Anim. 41(1), 31–62. DOI: 10.1016/j.cvsm.2010.09.006.

Lyon S.D., Sanderson M.W., Vaden S.L., Lappin M.R., Jensen W.A., Grauer G.F. 2010. Comparison of urine dipstick, sulfosalicylic acid, urine protein-to-creatinine ratio, and species-specific ELISA methods for detection of albumin in urine samples of cats and dogs. J. Am. Vet. Med. Assoc. 15, 236(8), 874–879. DOI: 10.2460/javma.236.8.874.

Mann J.F., Gerstein H.C., Yi Q.L., Lonn E.M., Hoogwerf B.J., Rashkow A., Yusuf S. 2003. Development of renal disease in people at high cardiovascular risk: results of the HOPE randomized study. J. Am. Soc. Nephrol. 14(3), 641–647. DOI: 10.1097/01.asn.0000051594.21922.99.

Mardell E.J., Sparkes A.H. 2006. Evaluation of a commercial in-house test kit for the semi-quantitative assessment of microalbuminuria in cats. J. Feline Med. Surg. 8(4), 269–278. DOI: 10.1016/j.jfms.2006.02.003.

Miner J.H. 2011. Organogenesis of the kidney glomerulus: focus on the glomerular basement membrane. Organogenesis 7(2), 75–82. DOI: 10.4161/org.7.2.15275.

Miner J.H. 2012. The glomerular basement membrane. Exp. Cell Res. 318, 973–978. DOI: 10.1016/j.yexcr.2012.02.031.

Mizutani H., Koyama H., Watanabe T., Kitagawa H., Nakano M., Kajiwara K., King J.N. 2006. Evaluation of the clinical efficacy of benazepril in the treatment of chronic renal insufficiency in cats. J. Vet. Intern. Med. 20(5), 1074–1079. DOI: 10.1892/0891-6640(2006)20[1074:eotceo]2.0.co;2.

Mortier F., Daminet S., Duchateau L., Biscop A., Paepe D. 2023. Biological variation of urinary protein: Creatinine ratio and urine specific gravity in cats. J. Vet. Intern. Med. 37(6), 2261–2268. DOI: 10.1111/jvim.16881.

Neal C.R. 2015. Podocytes… What's under yours? (Podocytes and foot processes and how they change in nephropathy). Front Endocrinol (Lausanne). 23, 6–9. DOI: 10.3389/fendo.2015.00009.

O'Neill D.G., Church D.B., McGreevy P.D., Thomson P.C., Brodbelt D.C. 2014. Prevalence of disorders recorded in cats attending primary-care veterinary practices in England. Vet J. 202(2), 286–291. DOI: 10.1016/j.tvjl.2014.08.004.

Pavenstädt H., Kriz W., Kretzler M. 2003. Cell biology of the glomerular podocyte. Physiol. Rev. 83, 253–307. DOI: 10.1152/physrev.00020.2002.

Rodewald R., Karnovsky M.J. 1974. Porous substructure of the glomerular slit diaphragm in the rat and mouse. J. Cell. Biol. 60(2), 423–433. DOI: 10.1083/jcb.60.2.423.

Russo L.M., Osicka T.M., Brammar G.C., Candido R., Jerums G., Comper W.D. 2003. Renal processing of albumin in diabetes and hypertension in rats: possible role of TGF-beta 1. Am. J. Nephrol. 23(2), 61–70. DOI: 10.1159/000068039.

Shackland S.J. 2006. The podocyte's response to injury: role in proteinuria and glomerulosclerosis. Kidney Int. 69(12), 2131–2147. DOI: 10.1038/sj.ki.5000410.

Skrzypczak W. 2021. Proteinuria – selected issues. Acta Sci. Pol. Zootechnica, 20(3), 51–58. DOI: 10.21005/asp.2021.20.3.07.

Skrzypczak W., Dratwa-Chałupnik A., Ożgo M., Boniecka K. 2021. Neonatal proteinuria in calves – a quantitative approach. Animals 20, 11(12), 3602. DOI: 10.3390/ani11123602.

Smets P.M., Meyer E., Maddens B.E., Duchateau L., Daminet S. 2010. Urinary markers in healthy young and aged dogs and dogs with chronic kidney disease. J. Vet. Intern. Med. 24(1), 65–72. DOI: 10.1111/j.1939-1676.2009.0426.x.

Smithies O. 2003. Why the kidney glomerulus does not clog: A gel permeation/diffusion hypothesis of renal function. Proc. Natl. Acad. Sci USA. 100, 4108–4113. DOI: 10.1073/pnas.0730776100.

Souza C. de, Coelho M., Antonelo D.S., Passarelli D., Rochetti A.L., Fukumasu H., Leite-Dellova D.C. 2022. Nephrin and podocin mRNA detection in urine sediment of dogs with chronic kidney disease: preliminary observations. J. Vet. Res. 66(2), 281–288. DOI: 10.2478/jvetres-2022-0019.

Stompór T. 2009. Białkomocz [Proteinuria]. Forum Nefrol. 2(1), 50–59 [in Polish].

Strutz F.M. 2009. EMT and proteinuria as progression factors. Kidney Int. 75, 475–481. DOI: 10.1038/ki.2008.425.

Suh J., Miner J. 2013. The glomerular basement membrane as a barrier to albumin. Nat. Rev. Nephrol. 9, 470–477. DOI: 10.1038/nrneph.2013.109.

Syme H.M. 2009. Proteinuria in cats: prognostic marker or mediator? *J. Feline Med. Surg.* 11(3), 211–218. DOI: 10.1016/j.jfms.2009.01.003.

Syme H.M., Markwell P.J., Pfeiffer D., Elliott J. 2006. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. J. Vet. Intern. Med. 20(3), 528–535. DOI: 10.1892/0891-6640(2006)20[528:socwno]2.0.co;2.

Tryggvason K., Patrakka J., Wartiovaara J. 2006. Hereditary proteinuria syndromes and mechanisms of proteinuria. N. Engl. J. Med. 354, 1387–1401. DOI: 10.1056/NEJMra052131.

Viteri B., Reid-Adam J. 2018. Hematuria and proteinuria in children. Pediatr. Rev. 39(12), 573–587. DOI: 10.1542/pir.2017-0300.

Wehner A., Hartmann K., Hirschberger J. 2008. Associations between proteinuria, systemic hypertension and glomerular filtration rate in dogs with renal and non-renal diseases. Vet. Rec. 162(5), 141–147. DOI: 10.1136/vr.162.5.141.

Whittemore J.C., Gill V.L., Jensen W.A., Radecki S.V., Lappin M.R. 2006. Evaluation of the association between microalbuminuria and the urine albumin-creatinine ratio and systemic disease in dogs. J. Am. Vet. Med. Assoc. 15, 229(6), 958–963. DOI: 10.2460/javma.229.6.958.

Whittemore J.C., Miyoshi Z., Jensen W.A., Radecki S.V., Lappin M.R. 2007. Association of microalbuminuria and the urine albumin-to-creatinine ratio with systemic disease in cats. *J. Am. Vet. Med. Assoc.* 230, 1165–1169. DOI: 10.2460/javma.230.8.1165.

Yurchenco P.D., Patton B.L. 2009. Developmental and pathogenic mechanisms of basement membrane assembly. Curr. Pharm. Des. 15, 1277–1294. DOI: 10.2174/138161209-787846766.

BIAŁKOMOCZ PSÓW I KOTÓW – WYBRANE ZAGADNIENIA Z FIZJOLOGII I PATOFIZJOLOGII NEREK

Streszczenie. W moczu zdrowych psów i kotów białko jest obecne w śladowych ilościach. W większych ilościach może występować w moczu zwierząt chorych, a także w niektórych stanach fizjologicznych. Rutynowo białkomocz jest oceniany na podstawie stosunku stężenia białka w moczu do stężenia kreatyniny (wskaźnik UPC, *urine protein to creatinine ratio*). Jest to wskaźnik powszechnie uznany za prognostyczny. W warunkach prawidłowych wynosi <0,2. Wartości mieszczące się w granicach od 0,2 do 0,4 u kotów oraz od 0,2 do 0,5 u psów uważa się za graniczne, natomiast wartości UPC >0,4 u kotów i >0,5 u psów są uważane za potwierdzenie białkomoczu. W procesie diagnozowania przyczyn białkomoczu u psów i kotów należy rozważyć uszkodzenie kłębuszków, kanalików nerkowych, tkanki śródmiąższowej oraz postępującą utratę nefronów. Czułym wskaźnikiem diagnostycznym dysfunkcji nerek są frakcje białek obecne w moczu, różniące się masą cząsteczkową. Zwiększone wydalanie białek o dużej masie może wskazywać na uszkodzenie kłębuszków nerkowych, a utrata białek drobnocząsteczkowych na dysfunkcję kanalików nerkowych. Jeśli białkomocz utrzymuje się i/lub nie ustępuje po leczeniu choroby podstawowej, konieczne jest wdrożenie leczenia, którego celem powinna być redukcja białkomoczu >90% u kotów i >50% u psów. Najskuteczniejszą metodą leczenia obniżającą białkomocz i mającą jednocześnie walor terapii nefroprotekcyjnej i kardioprotekcyjnej jest blokada układu renina–angiotensyna–aldosteron (na różnych jego poziomach). Nieodzowne jest również stosowanie właściwej diety, zwłaszcza ograniczenie podaży białka i sodu.

Słowa kluczowe: psy, koty, białkomocz kłębkowy, białkomocz kanalikowy, błona filtracyjna, podocyty, resorpcja kanalikowa białek, wskaźnik UPC, układ RAA a białkomocz.