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REVIEW ARTICLE

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PROTEINURIA – SELECTED ISSUES

Wiesław Skrzypczak

Department of Physiology, Cytobiology and Proteomics, West Pomeranian University of Technology Szczecin, Janickiego 29, 71-270 Szczecin, Poland

ABSTRACT

Proteins in the urine of healthy individuals of various species are present in trace, practically immeasurable amounts. Under physiological conditions, the renal glomeruli filter out proteins with a molecular weight below 69 kDa, which are then almost completely reabsorbed in the proximal tubules. Occasionally, as an effect of low temperature, physical exercise, rapid change of body position, high-protein diet, medications, or at the end of pregnancy and in the postnatal period etc., proteins may be present in the urine of healthy individuals in higher amounts. This condition is referred to as physiological proteinuria. Most often, however, proteinuria is a symptom of a kidney disorder and may lead to further damage, eventually to renal failure. Proteinuria may be a result of: (a) increased penetration of proteins, mainly of low molecular weight, through the normal filtration membrane and the inability to absorb the increased amount of proteins in the proximal tubules – overflow proteinuria, (b) increased permeability of the glomerular filtration barrier, most often as a result of its damage – glomerular proteinuria, (c) damage to the renal tubules due to failure of reabsorption mechanisms – tubular proteinuria. Excretion of larger amounts of protein in the urine is always indicative of dysfunction of the kidneys and/or of the urinary tract. Having knowledge on the kind of excreted proteins (in terms of weight/size of the molecules) is very useful in medical and veterinary practice, as it enables early identification of the causes of proteinuria and distinguishing its etiology. In recent years, much attention has been paid to the role of uromodulin as a diagnostic marker of an early phase of renal dysfunction, especially of the tubules. The observations on the interaction of the digestive and excretory systems in the regulation of proteonemia in the postnatal period also seem to be important.

Key words: kidney, proteinuria, low-molecular-weight proteins, high-molecular-weight proteins, uromodulin, zonulin

INTRODUCTION

Protein in the urine of healthy individuals of various animal species is present in trace, practically immeasurable amounts. Large amounts of protein discharged with the urine is always indicative of renal and/or urinary tract dysfunction. Proteinuria may not only be a symptom of one of numerous renal diseases, but also a factor contributing to progressive renal impairment. It is also an important risk factor of other diseases, including cardiovascular disorders. Protein may occasionally occur in higher amounts in the urine of healthy animals, e.g. healthy newborns [Becker 2004, Gudehithlu et al. 2004, Ożgo et al. 2009, Topham 2009, Joseph and Gattineni 2016, Viteri and Reid-Adam 2018].

The amount of protein carried with the urine strongly depends on the glomerular filtration (especially permeability to proteins of the glomerular capillaries) and protein reabsorption in the proximal tubules. The amount of filtered proteins is influenced by blood concentration of proteins, hydrostatic and oncotic pressure on both sides of the filtration barrier, size, shape and electrostatic charge of proteins and the properties of the filtration barrier [D'Amico and Bazzi 2003, Schäfer-Somi et al. 2005, Joseph and Gattineni 2016, Viteri and Reid-Adam 2018].

Due to the structure of the glomerular filter, low-molecular-weight (LMW) proteins, i.e. those below 69 kDa, penetrate to the primary urine (filtrate to the glomerular capsule) to be next nearly entirely reabsorbed in the proximal tubules. Under physiological conditions, protein reabsorption in nephrons takes place by endocytosis and occurs mainly in the convoluted segment and the initial part of the straight segment of the proximal tubules [Dickson et al. 2014].

Proteins involved in the reabsorption mechanism are receptor proteins present on the surface of tubu-

wieslaw.skrzypczak@zut.edu.pl

lar cells (including megalin and cubilin). Competition between proteins for nephron reabsorption systems has been demonstrated, and positively charged proteins are more readily reabsorbed [Birn et al. 2000, Zhai et al. 2000, Verroust et al. 2002, Baran et al. 2003a, Baran et al. 2003b, D'Amico and Bazzi 2003]. Reabsorbed proteins undergo proteolysis, and the resulting peptides and amino acids are removed from cells through exocytosis and absorbed into the blood. Fragments of hydrolyzed proteins may end up in the urine [Gudehithlu et al. 2004].

The daily protein content in the final urine should not exceed 150 mg (100 mg · m^{-2} body surface area, BSA). In children, newborns and infants, a daily discharge of up to 300 mg · m^{-2} BSA is acceptable [Viteri and Reid-Adam 2018]. Increased protein levels in the urine is known as proteinuria. Protein content in the daily urine exceeding 3.5 g indicates a severe kidney damage.

Pathophysiology of proteinuria

The types and causes of proteinuria may vary. It may be a transient functional proteinuria, occurring e.g. after exercise, at a fever, or on changing body position. Haemodynamic changes in the glomerulus are the main cause. Most often, however, proteinuria is a symptom of a kidney disease and cause further damage of the kidneys, ultimately leading to renal failure. Glomerular proteinuria may be developed as a result of the increased permeability of the glomerular endothelium, most often due to its damage. Increased filtration of proteins, mainly LMW proteins, through a normal filter membrane may result in overflow proteinuria. This is due to the inability to absorb the increased amount of proteins in the proximal tubules. When the renal tubules are damaged, due to the failure of the reabsorption mechanisms, unreabsorbed proteins and proteins of damaged cells reach the urine. This is referred to as tubular proteinuria [Sapierzyński et al. 2018, Viteri and Reid-Adam 2018].

Damage to the structure of the kidney may result from non-inflammatory or inflammatory processes in response to a variety of factors. It may occur in the glomeruli, in the tubules, or in the interstitial tissue. The damage to the glomeruli is most often of immunological nature. Schneider et al. [2013] demonstrated in 501 dogs that the damage to the glomeruli is in 48% of cases caused by immune-mediated glomerulonephritis. In addition, as a result of infections (viral or bacterial), immune complexes may accumulate in the glomeruli in amounts exceeding the removal ability, which, by intensifying inflammatory processes, leads to morphological changes in the glomeruli. These result in an increase in the permeability to proteins of the capillaries, including albumin, leading to their loss in the urine. As the permeability of the glomerular vessicles increases, not only does the amount of filtered proteins increase, but the content of proteins with higher molecular weights and a larger molecular radius increases too. For example, from the group of low-molecular-weight proteins (LMW), α1-microglobulin, β2-microglobulin appear in urine, and among high molecular weight (HMW) proteins, immunoglobulins M and G, lipoproteins, some complement components, ferritin, and growth factors (e.g. TGF-β). Albumin (69 kDa, molecular radius 36 Å) is a border protein between LMW and HMW proteins [Skrzypczak et al. 2005, Topham 2009, Viteri and Reid-Adam 2018].

Proteinuria is considered to be a strong nephrotoxin that destroys mesangial cells and glomerular epithelial cells releasing, inter alia, pro-inflammatory cytokines, which by positive feedback cause further kidney damage [Noronha et al. 2002].

Also, the increased protein load reaching the renal tubules may cause inflammation with the participation of proinflammatory cytokines (e.g. monocyte chemoattractant protein 1, MCP1) or growth factors (e.g. transforming growth factor β, TGF-β). The developing inflammatory process leads to further damage of the interstitial tissue and significant proteinuria [Jepson et al. 2009]. It has been shown that albumin, by binding free fatty acids, becomes toxic to the tubules [Tang et al. 2001]. These changes also lead to a gradual loss of the integrity of the proximal tubular cells and morphological changes, e.g. the disappearance of the brush border.

Proteinuria is considered not only a key factor of chronic kidney disease, but also the cause of cardiovascular complications, including arterial hypertension [Walls 2001, Stelloh et al. 2012]. Proteinuria has been demonstrated to be accompanied by generalized vascular endothelial dysfunction, which is an early symptom of the development of atherosclerotic lesions. Jepson et al. [2009] proved that the combined proteinuria and arterial hypertension significantly shortened the life span of cats.

Transitional proteinuria is usually asymptomatic. Also, morphological damage to the glomeruli and tubules, especially in the initial period, does not reveal clear clinical symptoms, which appear only as a result of renal failure. This, however, due to the large "functional reserve" of the kidney, occurs with a delay in relation to protein in the urine [Jepson et al. 2009, Sapierzyński et al. 2018]. The main effect of proteinuria is hypoalbuminemia. In response, the liver increases synthesis of lipoproteins, which leads to hyperlipidemia. As a result of the reduction of oncotic blood pressure, generalized edema may occur, which, however, in animals is observed sporadically. Hypertension and haematuria may appear.

Diagnose of proteinuria

If proteinuria persists, we may expect further damage to the glomeruli, renal tubules, and interstitial tissue, as

well as progressive loss of nephrons, as has been demonstrated, inter alia, in dogs and cats [Lees et al. 2005]. Therefore, the procedure should first identify the cause of proteinuria followed by aiming to reduce protein excretion. An important goal in the treatment of proteinuria is to control arterial hypertension (most often by inhibiting the Renin-Angiotensin-Aldosteron system).

The commonly used methods of in vivo assessment of kidney morphology include ultrasound examination, which allows evaluating the size and shape of the organ, and detect changes in renal echogenicity (this issue will be addressed later in this paper); this examination, however, does not allow for an unequivocal determination of the nature of the pathological process.

Innovative laboratory techniques (e.g. proteomics) enable precise, qualitative anaysis of the composition of the protein possibly present in the urine. The advances observed in proteomics makes urine useful in the evaluation of the functional efficiency of not only the excretory system, but also of other organs of the body. Protein maps and expression analysis of individual proteins, which are involved in specific metabolic processes, enable qualitative evaluation of urine and may reveal markers of specific processes [Dratwa-Chałupnik et al. 2020].

Undoubtedly, the results of these analyzes bring much information to the knowledge about the excretory system and its functioning. Nevertheless, it is believed that in the veterinary practice, the knowledge on excreted proteins (in terms of mass/molecule size) is more useful, as it allows early identification of proteinuria causes and enables differentiation of its etiology [Donderski et al. 2006]. Proteins with a molecular weight below 69 kDa (LMW), which under physiological conditions are subject to glomerular filtration, indicate a reduced resorptive efficiency in the proximal part of the nephrons (selective proteinuria), while proteins with a higher molecular weight (HMW) imply damage and/or immaturity of the filtration barrier (non-selective proteinuria).

SDS-PAGE, which reveals the type of urine proteins and their molecular weight by means of electrophoretic separation, is a valuable diagnostic tool. Using SDS-PAGE Molecular Weight Standards, proteins in the urine can be classified as LMW or HMW. Based on the optical density, the concentration of selected protein fractions and their percentage share in the total urine proteins can be calculated. The limitations of this method include the need to measure diuresis (urine output per unit time), e.g. by bladder catheterization or a daily urine collection.

Another, simpler method of urine proteins quantification, additionally eliminating the effect of urine concentration on test results, is the determination of the ratio: urine concentration of protein or albumin to urine concentration of creatinine (PCR, protein to creatinine ratio; ACR, albumin to creatinine ratio). Determination of PCR or ACR in a single urine test facilitates diagnosis, as it does not require catheterization or daily urine volume measurements [Vilhena et al. 2015]. The PCR is correlated with the health status: the higher the value of this indicator, the worse the prognosis. The PCR under normal conditions in dogs and cats is <0.2. Values between 0.2 and 0.4, in cats, and 0.2 and 0.5, in dogs, are considered borderline levels, while values >0.4, in cats, and >0.5, in dogs, give rise to diagnosing proteinuria. [Lees et al. 2005].

While diagnosing proteinuria, serum creatinine concentration should be analyzed along with calculating the estimated gromelural filtration rate (eGFR). Namely, the severity of proteinuria may decrease with the progression of kidney disease, since the number of active nephrons will be reduced (e.g. decreasing proteinuria with constant serum creatinine levels suggests an improvement in the renal function) [Lees et al. 2005].

The strip test is used for initial qualitative diagnostics. It is a less sensitive and a less specific method of detecting protein in urine. It is often used as a proteinuria screening tool. A color change of the strip with variable pH may reveal the presence of protein in the urine. The strip test detects primarily albumin (LMW proteins).

Uromodulin

In 1950, Igor Tamm and Frank Horsfall for the first time isolated and described the protein capable of inhibiting virus-induced hemagglutination [Tamm and Horsfall 1950]. The Tamm-Horsfall protein (THP) was named after its discoverers. In 1985, a glycoprotein with immunosuppressive abilities, called uromodulin (UM), was isolated from the urine of pregnant women. Two years later, it was demonstrated that THP and uromodulin are the same proteins [Fugiel et al. 2013, Wójtowicz et al. 2018]. THP is a physiological component of urine produced in mammalian kidneys and represents the main component of normal urine in newborns [Olczak 1999, Serafini-Cessi et al. 2003, Jędrasiak et al. 2006]. Uromodulin is expressed in the thick segment of the ascending limb of the nephron loop and in the initial segment of the distal tubule of the kidney. The molecular weight of its monomer is approximately 68 kDa.

In recent years, uromodulin has been facing a growing interest as a potential diagnostic marker of the early-stage renal dysfunction. Research using innovative analytical techniques aims at determining the exact role of uromodulin, especially in the thick segment of the ascending limb of the nephron loop. Moreover, molecular mechanisms regulating its expression and secretion are being searched for. The functions of this protein are still a subject of investigation, however it has been found, for example, that uromodulin is an element of the immune defense of the organism against bacterial pathogens colonizing the urinary tract, increases the activity of lym-

phocytes and stimulates phagocytosis in the local defense against pathogenic bacteria, acts against formation of renal stones through hindering calcium oxalate crystallization. Uromodulin acts as an antioxidant and protects the kidneys against ischemic damage. It probably plays a role in regulating the water and electrolyte balance in the thick segment of the ascending limb of the nephron loop, regulating water permeability [Devuyst et al. 2017, Wójtowicz et al. 2018].

A number of relationships between uromodulin excretion in urine and various forms of kidney diseases, also genetically determined, have also been demonstrated [Fugiel et al. 2013, Troyanov et al. 2016] . Mutations in the genes responsible for uromodulin encoding lead to rare autosomal dominant kidney diseases, which are characterized by progressive damage to the tubulointerstitial system, impaired urine concentrating processes, renal cysts, hyperuricemia, and progressive renal failure. Recent in vivo studies indicate the intracellular accumulation of the mutant form of uromodulin as the main pathogenetic factor of these diseases. Extensive genetic studies of the human genome have confirmed the role of uromodulin in the development of chronic kidney disease and hypertension. It seems that the analysis of uromodulin concentrations in blood serum and urine can help answer the question of how uromodulin affects the incidence and course of chronic kidney disease (CKD) [Serafini-Cessi et al. 2003, Fugiel et al. 2013].

A certain amount of uromodulin enters the bloodstream, although the mechanism of this remains unclear. Its concentration in the blood depends only on the efficiency of the kidney function. Unlike creatinine, blood levels of uromodulin are not influenced by body weight, muscle mass or diet. Scherberich et al. [2017] showed that both in children and in adults free of renal disease, uromodulin concentration in the serum is constant. The concentration of this protein in the blood decreases with the deterioration of kidney function, unlike other renal parameters, such as creatinine or urea [Tan et al. 2017]. According to Wójtowicz et al. [2018], changes in uromodulin concentration may be useful in the diagnosis of early-stage renal dysfunction. The authors showed that the concentration of uromodulin in the blood serum may be a marker of renal tubular function in healthy patients and in various stages of renal failure. They suggest that a reduction in serum uromodulin concentration could be used in the extended monitoring of patients with chronic renal failure.

Uromodulin, due to its production site, can be used primarily to assess the function of the renal tubules. Many reports indicate that it may be a marker of early renal failure, while other parameters, such as blood creatinine or urea concentration, do not show changes in concentration [Risch et al. 2014, Christensen et al. 2018, Wójtowicz et al. 2018]. This would indicate that the first stage of kidney damage, for whatever reason, begins with damage to the renal tubules in the ascending limb, resulting in a reduction in serum uromodulin levels.

Low serum uromodulin concentration (below 100 ng/ml) may indicate worsening of renal function and, as a prognostic factor, may indicate a possible deterioration of renal function in the future. On the other hand, a high concentration of uromodulin is associated with a lower risk of decreased glomerular filtration and acute kidney injury, as well as a reduced risk of urinary tract infections [Garimella and Sarnak 2017].

Tamm-Horsfall phenomenon in neonates

Ultrasonography is the least invasive imaging examination tool of the kidneys. In ultrasound imaging, based on the brightness of the image, the echogenicity of the tissue is assessed, i.e. the ability to reflect sound waves. The hyperechoic areas are brighter, and the hypoechoic areas are darker than the surrounding area. In neonates, the ultrasound image of a normal kidney is significantly different from that of an older child and an adult, the renal cortex is hyperechoic and the core is hypoechoic. With age, the echogenicity of the renal cortex gradually decreases. The higher echogenicity of the kidney cortex of newborns is due to the same number of glomeruli located in the narrower layer of the cortex compared to older children. It has been shown that the echogenicity of the renal cortex is inversely proportional to the gestational age, hence it may have even higher echogenicity in premature babies [Fugiel et al. 2013].

The Tamm-Horsfall phenomenon affects some newborns. It is a transient hyperechoic activity of the medullary part of the kidney in healthy full-term infants without accompanying clinical symptoms, observed in ultrasound in the first days of life [Starinsky et al. 1995]. The increase in echogenicity of the medullary part of the kidney is due to precipitation of Tamm-Horsfall protein in the renal tubules. Jędrasiak et al. [2006] demonstrated that the syndrome occurs in 24.6% full-term and 8.6% premature infants. In neonates, hyperechogenicity may affect all renal pyramids in both kidneys, but may occur in one kidney and/or in several pyramids.

This information, and the fact that also physiological proteinuria shows strong individual variability and does not occur in all neonates, may indicate a linkage between the two processes. Jędrasiak et al. [2006] observed a statistically significant relationship between the Tamm-Horsfall phenomenon and urine concentration of protein. In neonates with hyperechogenicity of the medullary part of the kidneys, the protein concentration was almost twice as high as in those who did not undergo this condition. However, not all authors confirmed the correlation of the Tamm-Horsfall phenomenon with the physiological proteinuria. As a rule, no significant differences in

uromodulin concentration in the urine of children with or without this syndrome were observed.

The Tamm-Horsfall phenomenon is more common in babies of higher birth weights, as well as in male neonates. No correlation with hypotrophy, asphyxia and intrauterine infections has been found. Also, no other ultrasound-detectable changes in the kidneys and no correlation with the size of this organ were found [Jędrasiak et al. 2006].

Neonatal proteinuria

Proteinuria occurs in healthy neonates of many species of animals and humans; however, a strong specific and individual variability in the frequency of occurence, duration and daily load of excreted proteins is observed, especially in the first days after birth [Drzeżdżon et al. 2004, Schäfer-Somi et al. 2005, Ożgo et al. 2009, Falakaflaki et al. 2011, Stelloh et al. 2012, Saxena et al. 2016, de Winter et al. 2020, Melandri et al. 2020, Skrzypczak et al. 2021].

The main causes of neonatal proteinuria include: morphological immaturity of the kidneys and dynamic adaptation processes occurring especially in the first days after birth, related to changes in renal hemodynamics and nephron function. In the postnatal period, an increase in the volume of renal bodies, changes in the structure of the layers forming the filtration barrier, elongation of the convulous segment of the proximal tubules and the nephron loop are observed. The morphological changes triger functional changes in nephrons, including an increase in blood flow, the size of glomerular filtration, resorptive and secretory efficiency of the renal tubules and the ability to concentrate the urine [Skrzypczak and Drzeżdżon 2001, Bauer et al. 2002, Faulks and Lane 2003, Skrzypczak et al. 2005, Falakaflaki et al. 2011, Stelloh et al. 2012, Joseph and Gattineni 2016, de Winter et al. 2020, Skrzypczak et al. 2021].

Proteinuria in healthy neonates is transient in character. Numerous studies reveal the presence of neonatal proteinuria, dynamic changes in the proportion of specific fractions of proteins in the urine, and a tendency to reduce the amount of proteins in urine excretion with age, in human babies and various animal species, including calves [Skrzypczak et al. 2021], kids [Drzeżdżon et al. 2003, Drzeżdżon et al. 2004, Ożgo et al. 2009], children [Hogg et al. 2000, Joseph and Gattineni 2016, Viteri and Reid-Adam 2018], puppies [Schäfer-Somi et al. 2005], baby rats [Calzada-Garcia et al. 1996, Gudehithlu et al. 2004, de Winter et al. 2020], foals [Jeffecott and Jeffecott 1974] and piglets [Bergelin and Karlsson 1975, Baintner et al. 1989, Bauer et al. 2002]. It should be noted, however, that the values of parameters obtained in the studies of these authors vary, which may be an indirect proof of the existence of specific and individual differences in the occurrence of neonatal proteinuria.

The results of many studies indicate an increased permeability (immaturity) of the filtration barrier in the kidneys of neonates and its effective sealing, and an increase in the efficiency of protein absorption in nephrons [Drzeżdżon et al. 2003, Drzeżdżon et al. 2004, Skrzypczak et al. 2005, Ożgo et al. 2009, Joseph and Gattineni 2016, Viteri and Reid-Adam 2018, Skrzypczak et al. 2021].

In our studies carried out on young ruminants (calves and billy goats), we have shown the presence of significant proteinuria of a selective character. The daily excretion of protein in the urine of calves ranged from 5.7 to 8.91 g · m^{-2} BSA, and the share of the LMW protein fraction in the urine on the first day after birth was 84.46% and decreased to 64.02% on day 7 of age. In the studies carried out on billy goats, we have also demonstrated selective proteinuria; the share of LMW proteins was 87.4% (on day 1 of age), 80.9% (on day 7) and 74.8 (on day 30). The daily amount of protein excreted ranged from 2.38 to 5.50 g · m^{-2} BSA and decreased with age. A detailed analysis of the occurrence of proteinuria in these animals has been described in a number of articles [Drzeżdżon et al. 2003, Drzeżdżon et al. 2004, Ożgo et al. 2009, Skrzypczak et al. 2021].

The intestinal barrier and proteinuria

The intestinal barrier is a physiological functional unit which is formed mainly by enterocytes and the tight junctions (TJ) between them. Small molecules below 300 Da can freely cross the intestinal barrier, otherwise impermeable to larger molecules, which could activate the immune system. The permeability of the barrier is regulated by a number of physiological as well as pathological factors. In 2000, Fasano et al. [2000] were the first to describe the potential role of zonulin in this process.

Zonulin is a protein included in the tight junctions (TJ), whose function is to modulate the permeability of the intestinal barrier. Increased expression of this protein causes the loosening of tight junctions between enterocytes, and increased permeability of the intestinal barrier means the possibility of macromolecules, e.g. proteins, penetrating into the blood (the so-called Leaky Gut Syndrome) [Sturgeon and Fasano 2016, Esnafoglu et al. 2017, Karabin 2018].

The expression of zonulin is regulated by the expression of pro-inflammatory cytokines (e.g. interleukin 6), therefore it is postulated that the tightness between enterocytes is reduced during inflammatory conditions of the bowel. Zonulin is secreted by enterocytes, but also by hepatic cells, adipose tissue, brain, heart, lungs, skin and kidneys.

Blood level of protein is influenced not only by its dietary supply and metabolism, but also by renal protein excretion. The results of our studies on calves and newborn

goats, showing the leakage of the glomerular filtration barrier in the kidneys and the limited ability of nephrons to reabsorb proteins, combined with the leaking intestinal barrier enabling the penetration of proteins with high molecular weights into the blood, may indicate the cooperation of the digestive system and excretory system in the regulation of proteinemia in neonates.

In this context, neonatal proteinuria does not necessarily mean that the kidneys are immature at birth, but may indicate that the organs are adapted to remove excess proteins from the body. Perhaps it is a process regulated by proteins, e.g. unsealing intercellular junctions. The relationship between the occurrence of proteinuria and the time of intestinal barrier closure was suggested by Jeffecott and Jeffecott [1974]. The authors observed proteinuria in colostrum-fed foals, especially in the first twelve hours of life, and found a positive correlation between the amount of colostrum fed and the intensity of proteinuria. However, they did not observe an increase in urinary protein excretion on the second day of life, after stimulation with a high-protein diet.

REFERENCES

Baintner, K., Kerenyi, T., Cseplo, A. (1989). Tubular reabsorption of protein by porcine kidneys during neonatal alimentary proteinuria. Acta Vet. Hung., 37, 69–74.

Baran, D., Tenstad, O., Aukland, K. (2003a). Aprotinin uptake in the proximal tubules in the rat kidney. I. Length of proximal tubular uptake segment. J. Struct. Biol., 142, 402–408. DOI: 10.1016/S1047-8477(03)00070-4.

Baran, D., Tenstad, O., Aukland, K. (2003b). Aprotinin uptake in the proximal tubules in the rat kidney. II. Uptake site relative to glomerulus. J. Struct. Biol., 142, 409–415. DOI: 10.1016/S1047-8477(03)00071-6.

Bauer, R., Walter, B., Bauer, K., Klupsch, R., Patt, S., Zwiener, U. (2002). Intrauterine growth restriction reduces nephron number and renal excretory function in newborn piglets. Acta Physiol. Scand., 176, 83–89. DOI: 10.1046/j.1365-201X.2002.01027.x.

Becker, G.J. (2004). Which albumin should we measure? Kidney Int., 66 (92), 16–17. DOI: 10.1111/j.1523-1755.2004.09204.x.

Bergelin, S.S., Karlsson, B.W. (1975). Functional structure of glomerular filtration barrier and proximal tubuli in the developing foetal and neonatal pig kidney. Anat. Embryol., 148, 223–234. DOI: 10.1007/BF00319845.

Birn, H., Fyfe, J.C., Jacobson, C., Mounier, F., Verroust, P.J., Ørskov, H., Willnow, T.E., Moestrup, S.K., Christensen, E.I. (2000). Cubilin is an albumin binding protein important for renal tubular albumin reabsorption. J. Clin. Invest., 105, 1353–1361. DOI: 10.1172/JCI8862.

Calzada-Garcia, J.A., Gonzales, M.N.P., Benito-Andres, F.J., Galcia, L.J.M., Cabezas, J.A., Sanchez-Bernal, C. (1996). Evaluation of patterns of urinary proteins by SDS-PAGE in rats of different ages. Mech. Ageing. Dev., 87, 1–13. DOI: 10.1016/0047-6374(96)01693-4.

Christensen, E.I., Schmitt, H., Herbst, V., Block, M., Kaden, J., Schlumberger, W. (2018). Serum uromodulin-a marker of kidney function and renal parenchymal integrity. Nephrol Dial Transplant., 33(2), 284–295. DOI: 10.1093/ndt/gfw422.

D'Amico, B., Bazzi, C. (2003). Pathophysiology of proteinuria. Kidney Int. 63, 809–825. DOI: 10.1046/j.1523-1755.2003.00840.x.

de Winter, D., Salaets, T., Gie A., Deprest, J., Levtchenko, E., Toelen, J. (2020). Glomerular developmental delay and proteinuria in the preterm neonatal rabbit. PLoS One, 15(11) DOI: 10.1371/journal.pone.0241384.

Devuyst, O., Olinger, E., Rampoldi, L. (2017). Uromodulin: from physiology to rare and complex kidney disorders. Nat Rev Nephrol., 13(9), 525–544. DOI: 10.1038/nrneph.2017.101.

Dickson, L.E., Wagner, M.C., Sandoval, R.M., Molitoris, B.A. (2014). The Proximal Tubule and Albuminuria: Really! J Am Soc Nephrol., 25, 443–453. DOI: 10.1681/ASN.2013090950.

Donderski, R., Bednarski, K., Manitius, J. (2006). Białkomocz a postęp przewlekłej choroby nerek. Czy rodzaj wydalanych białek może wpływać na przebieg przewlekłej choroby nerek? [Proteinuria and progression of chronic kidney disease. Does the kind of excreted protein affect progression of renal disease?] Diabetologia Praktyczna, 7(3), 194–199 [in Polish].

Dratwa-Chałupnik, A., Wojdyła, K., Ożgo, M., Lepczyński, A., Michałek, K., Herosimczyk, A., Rogowska-Wrzesińska, A. (2020). Urinary Proteome of Newborn Calves-New Potential in Non-Invasive Neonatal Diagnostic. Animals (Basel), 10(8), 1257. DOI: 10.3390/ani10081257.

Drzeżdżon, D., Skrzypczak, W.F., Ożgo, M. (2003). Wstępne badania nad proteinurią w okresie neonatalnym u koźląt [Introductory research on neonatal proteinuria in kids]. Folia Univ. Agric. Stetin., Zootechnica, 233, 93–102 [in Polish].

Drzeżdżon, D., Skrzypczak, W.F., Ziemak, J. (2004). Proteinuria neonatalna u koźląt [Neonatal proteinuria in kids]. In: Noworodek a środowisko, W. Skrzypczak, T. Stefaniak, R. Zabielski (eds.), Univ. Agric. Wrocław, 21–28 [in Polish].

Esnafoglu, E., Cırrık, S., Ayyıldız, S.N., Erdil, A., Ertürk, E.Y., Daglı, A., Noyan, T. (2017). Increased Serum Zonulin Levels as an Intestinal Permeability Marker in Autistic Subjects. J. Pediatr., 188, 240–244. DOI: 10.1016/j.jpeds.2017.04.004.

Falakaflaki, B., Mousavinasab, S.N., Mazloomzadeh, S. (2011). Dipstick Urinalysis Screening of Healthy Neonates. Pediatr. Neonatol., 52, 161–164. DOI: 10.1016/j.pedneo.2011.03.012.

Fasano, A., Not, T., Wang, W., Uzzau, S., Berti, I., Tommasini, A., Goldblum, S.E. (2000). Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. Lancet, 29, 355(9214), 1518–1519. DOI: 10.1016/S0140-6736(00)02169-3.

Faulks, R.D., Lane, I.F. (2003). Qualitative urinalyses in puppies 0 to 24 weeks of age. J. Am. Anim. Hosp. Assoc., 39(4), 369–378. DOI: 10.5326/0390369.

Fugiel, A., Kuźniewski, M., Fedak, D. (2013). Uromodulina – czy może być nowym wskaźnikiem uszkodzenia nerek? [Uromodulin – can it be a new marker of kidney damage?] Przegl. Lek., 70(11), 976–982. PMID: 24697042 [in Polish].

Garimella, P.S., Sarnak, M.J. (2017). Uromodulin in kidney health and disease. Curr. Opin. Nephrol. Hypertens., 26(2), 136–142.

Gudehithlu, K.P., Pegovavo, A.A., Dunea, G., Arruda, J.A.L., Singh, A.K. (2004). Degradation of albumin by the renal proximal tubule cells and subsequent fate of its fragments. Kidney Int., 2004, 65, 2113–2122. DOI: 10.1111/j.1523-1755.2004.00633.x.

Hogg, R.J., Portman, R.J., Milliner, D., Lemleg, K.V., Eddy, A., Ingelfinger, J. (2000). Evaluation and management of proteinuria and nephrotic syndrome in children: recommendation from a peditric nephrology panel established at the National Kidney Fundation conference on proteinuria, albuminuria, risk assessment, detection and elimination (PARADE). Pediatrics, 105, 1242–1249. DOI: 10.1542/peds.105.6.1242.

Jędrasiak, U., Brzewski, M., Roszkowska-Blaim, M., Turzańska, A., Wyględowska, G. (2006). Zjawisko Tamm-Horsfalla u noworodków [Tamm-Horsfall phenomenon in neonates]. Pol. J. Radiol., 71(2), 53–57 [in Polish].

Jeffecott, L.B., Jeffecott, T.J. (1974). Studies on passive immunity in the foal. III The characterization and significance of neonatal proteinuria. J. Comp. Path., 84, 455–465. DOI: 10.1016/0021-9975(74)90038-3.

Jepson, R.E., Brodbelt, D., Vallance, C., Syme, H.M., Elliott, J. (2009). Evaluation of predictors of the development of azotemia in cats. J. Vet. Intern. Med., 23(4), 806–813. DOI: 10.1111/j.1939-1676.2009.0339.x.

Joseph, C., Gattineni, J. (2016). Proteinuria and Hematuria in the Neonate. Curr. Opin. Pediatr., 28(2), 202–208. DOI: 10.1097/MOP.0000000000000323.

Karabin, K. (2018). Zaburzenia przepuszczalności bariery jelitowej i antygenów pokarmowych na rozwój chorób przewlekłych [Disturbances in the permeability of the intestinal barrier and food antigens to the development of chronic diseases]. Klin. Pediatr., 26, 6107–6110 [in Polish].

Lees, G.E., Brown, S.A., Elliott, J., Grauer, G.E., Vaden, S.L. (2005). American College of Veterinary Internal Medicine. 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: 10.1111/j.1939-1676.2005.tb02713.x.

Melandri, M., Veronesi, M.C., Alonge, S. (2020). Urinalysis in Great Dane Puppies from Birth to 28 Days of Age. Animals (Basel), 10(4), 636. DOI: 10.3390/ani10040636.

Noronha, I.L., Fujihara, C.K., Zatz, R. (2002). The inflammatory component in progressive renal disease-are interventions possible? Neph. Dial. Transp., 17, 363–368. DOI: 10.1093/ndt/17.3.363.

Olczak, T. (1999). Struktura i funkcja białka Tamm-Horsfalla w stanach fizjologicznych i patologicznych człowieka [Structure and function of Tamm-Horsfall protein in human physiologic and pathologic states]. Post. Hig. Med. Dośw., 53(5), 717–732 [in Polish].

Ożgo, M., Skrzypczak, W., Drzeżdżon, D., Lepczyński, A., Dratwa-Chalupnik, A., Michałek, K., Herosimczyk, A. (2009). Urinary excretion of low molecular weight proteins in goats during the neonatal period. J. Physiol. Pharmacol., 60, 119–125.

Risch, L., Lhotta, K., Meier, W.D., Medina-Escobar, P., Nydegger, U.E., Risch, M. (2014). The serum uromodulin level is associated with kidney function. Clin. Chem. Lab. Med., 52(12), 1755–1761. DOI: 10.1515/cclm-2014-0505.

Sapierzyński, R., Jońska, I., Ostrzeszewicz, M. (2018). Obraz morfologiczny zapalenia nerek u zwierząt [Morphological presentation of nephritis in animals]. Życie Weter., 93(10), 700–711 [in Polish].

Saxena, I., Shivankur, V., Kumar, M. (2016). Urinary Protein Creatinine Ratio in Normal Zero to Three-Day-Old Indian Neonates. J. Clin. Diag. Res., 10(3), 21–23. DOI: 10.7860/JCDR/2016/18651.7442.

Schäfer-Somi, S., Bär-Schadler, S., Aurich, J.E. (2005). Proteinuria and immunoglobulinuria in neonatal dogs. Vet. Record, 157(13), 378–382. DOI: 10.1136/vr.157.13.378.

Scherberich, J.E., Gruber, R., Nockher, W.A., Christensen E.I., Schmitt H., Herbst V., Block M., Kaden J., Schlumberger W. (2017). Serum uromodulin – a marker of kidney function and renal parenchymal integrity. Nephrol. Dial. Transplant.,16, 1–12. DOI: 10.1093/ndt/gfw422.

Schneider, S.M., Cianciolo, R.E., Nabity, Jr M.B., Clubb, F.J., Brown, C.A., Lees, G.E. (2013). Prevalence of immune-complex glomerulonephritides in dogs biopsied for suspected glomerular disease: 501 cases (2007-2012). J. Vet. Intern. Med., 27, 67–75. DOI: 10.1111/jvim.12247.

Serafini-Cessi, F., Malagolini, N., Cavallone, D. (2003). Tamm-Horsfall glicoprotein: biology and clinical relevance. Am J Kidney Dis., 42(4), 658–676. DOI: 10.1016/S0272-6386(03)00829-1.

Skrzypczak, W., Dratwa-Chałupnik, A., Ożgo, M., Boniecka, K. (2021). Neonatal proteinuria in calves – a quantitative aspect [in preparation].

Skrzypczak, W.F., Drzeżdżon, D. (2001). Kidney adaptation of kids and calves newborns to natrmia regulation. EJPAU, vol.4, Iss.2, #02.

Skrzypczak, W.F., Drzeżdżon, D., Ożgo, M., Michałek, K., Dratwa, A. (2005). Wstępna badania nad szczelnością nerkowej bariery filtracyjnej w okresie neonatalnym u kożląt [Introductory research on renal filtration barrier tightness in kids in neonatal period]. Folia Univ. Agric. Stetin., Zootechnica, 243(47), 153–160 [in Polish].

Starinsky, R., Vardi, O., Batasch, D., Goldberg, M. (1995). Increased renal medullary echogenicity in neonates. Pediatr. Radiol., 25(1), 43–45. DOI: 10.1007/BF03545580.

Stelloh, C., Allen, K.P., Mattson, D.L., Lerch-Gaggl, A., Reddy, S., El-Meanawy, A. (2012). Prematurity in mice leads to reduction in nephron number, hypertension, and proteinuria. Transl. Res., 159(2), 80–89. DOI: 10.1016/j.trsl.2011.10.004.

Sturgeon, C., Fasano, A. (2016). Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases, Tissue Barriers, 4(4), 125–138. DOI: 10.1080/21688370.2016.1251384.

Tamm, I., Horsfall, F.L. (1950). Characterization and separation of an inhibitor of viral hemagglutination present in

urine. Proc. Soc. Exp. Biol. Med., 74(1), 106–108. DOI: 10.3181/00379727-74-17825.

Tan, F., Zeng, Y., Yan, L., Zhang, D. (2017). Low plasma uromoduln is a predictor of early stagechronic kidney disease progression. Int. J. Clin. Exp. Med., 10(5), 8055–8059.

Tang, S., Lai, K.N., Chan, T.M., Lan, Y., Ho, S.K., Sack, S. (2001). Transferrin but not albumin mediates stimulation of complement C3 biosynthesis in human proximal tubular epithelial cells. Am. J. Kid. Diseases,37(1), 94–103. DOI: 10.1053/ajkd.2001.20593.

Topham, P. (2009). Proteinuric Renal Disease. Clini. Med., 9(3), 284–287. DOI: 10.7861/clinmedicine.9-3-284.

Troyanov, S., Delmas-Frenette, C., Bollée, G., Youhanna, S., Bruat, V., Awadalla, P., Devuyst, O., Madore, F. (2016). Clinical, Genetic, and Urinary Factors Associated with Uromodulin Excretion. Clin. J. Am. Soc. Nephrol., 11(1), 62–69. DOI: 10.2215/CJN.04770415.

Verroust, P.J., Birn, H., Nielsen, R., Kozyraki, R., Christensen E.J. (2002). The tandem endocytic receptors megalin and cubilin are important proteins in renal pathology. Kidney Int., 62, 745–756. DOI: 10.1046/j.1523-1755.2002.00501.x.

Vilhena, H.C.R., Santos, R.R., Sargo, T.J., Lima, T.B., Dias, S.S., Pastorinho, M.R., Queiroga, F.L., Silvestre-Ferreira, A.C. (2015). Urine protein-to-creatinine concentration ratio in samples collected by means of cystocentesis versus manual compression in cats. J. Am. Vet. Med. Assoc., 246(8), 862–867. DOI: 10.2460/javma.246.8.862.

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

Walls, J. (2001). Relationship between proteinuria and progressive renal disease. Am. J. Kidney Dis., 37(2), 13–16. DOI: 10.1053/ajkd.2001.20732.

Wójtowicz, M., Piechota, W., Rączka, A., Galas, K., Podstawka, I., Literacki, S., Woźniak-Kosek, A. (2018). Uromodulin serum concentration in patients with chronic kidney disease stages III-V. Correlations with markers of glomerular filtration rate and markers of calcium-phosphate and bone metabolism. Military Physician, 96(3), 213–220.

Zhai, X.Y., Nielsen, R., Birn, H., Drumm, K., Mildenberger, E., Freudinger, R., Moestrup, S.K., Verroust, P.J., Christensen, E.J., Gekle, M. (2000). Cubulin – and Megalin – mediated uptake of albumin in cultured proximal tubule cells of opposum kidney. Kidney Int. 58, 1523–1533. DOI: 10.1046/j.1523-1755.2000.00314.x.

PROTEINURIA – WYBRANE ZAGADNIENIA

STRESZCZENIE

Białko w moczu zdrowych osobników różnych gatunków występuje w śladowych, praktycznie niemierzalnych ilościach. W warunkach fizjologicznych w kłębkach nerkowych filtrują się białka o masie cząsteczkowej poniżej 69 kDa, które następnie są prawie w całości są resorbowane w kanalikach proksymalnych. Niekiedy, pod wpływem np. niskiej temperatury, wysiłku fizycznego, gwałtownej zmiany pozycji ciała, diety wysokobiałkowej, leków czy w końcowym okresie ciąży oraz w okresie pourodzeniowym białko może być obecne w moczu zdrowych osobników większych ilościach. Ten rodzaj białkomoczu nazywany jest fizjologicznym. Najczęściej jednak białkomocz jest objawem chorób nerek i przyczyną dalszego ich uszkadzania prowadzącą do niewydolności. Powstaje na skutek: (a) zwiększonego przesączania białek, głównie o niskiej masie, przez prawidłową błonę filtracyjną i niemożności wchłonięcia zwiększonej ilości białek w kanalikach proksymalnych, tzw. białkomocz z przeładowania, (b) zwiększonej przepuszczalności kłębkowej bariery filtracyjnej, najczęściej w wyniku jej uszkodzenia, tzw. białkomocz kłębuszkowy, (c) uszkodzenia kanalików nerkowych, na skutek niewydolności mechanizmów resorpcyjnych, tzw. białkomocz kanalikowy. Wydalanie większych ilości białka z moczem zawsze świadczy o dysfunkcji nerek i/lub dróg wyprowadzających. Znajomość rodzaju wydalanych białek (pod względem masy/wielkości cząsteczki) jest bardzo przydatna w praktyce lekarsko-wetwrynaryjnej, gdyż umożliwia wczesną identyfikację przyczyn białkomoczu i rozróżnienie jego etiologii. W ostatnich latach ponownie dużą uwagę zwraca się na rolę uromoduliny, jako wskaźnika diagnostycznego wczesnej fazy zaburzenia czynności nerek, zwłaszcza kanalików. Istotne wydają się również spostrzeżenia o współdziałaniu układu pokarmowego i wydalniczego w regulacji proteonemii w okresie pourodzeniowym.

Słowa kluczowe: nerki, proteinuria, frakcje białek LMW i HMW, uromodulina, zonulina

Wiesław Skrzypczak https://orcid.org/0000-0002-0483-3136