Management of Proteinuria in Dogs and Cats with Chronic Kidney Disease

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KEYWORDS

• Urine protein:creatinine ratio • Proteinuria • Hypertension • Angiotensin
• Aldosterone • Glomerular • Chronic kidney disease

KEY POINTS

- Proteinuria is a negative prognostic for chronic kidney disease and is associated with degree of functional impairment, the risk of uremic crisis, progressive worsening of azotemia, or death.
- Normal dogs and most normal cats should have a urine protein:creatinine ratio that is less than 0.4 and less than 0.2, respectively; persistent proteinuria above this magnitude warrants attention.
- Administration of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers is considered a standard of care in dogs and cats with renal proteinuria.
- Blood pressure control and nutritional modification are important considerations and part of the standard of care for dogs and cats with renal proteinuria.
- Renal biopsy and administration of immunosuppressive agents should be considered in dogs with glomerular proteinuria that have not responded to standard therapy.

Dr S.L. Vaden has acted as a paid consultant for Heska Corporation and Idexx Ltd. She receives research grant funding from Morris Animal Foundation (D12CA-053) and the American Kennel Club Canine Health Foundation (01844). Dr J. Elliot has acted as a paid consultant for Bayer Animal Health, Boehringer Ingelheim, Elanco Animal Health, Idexx Ltd, CEVA Animal Health, Orion Inc, Nextvet Ltd, Waltham Centre for Pet Nutrition. He receives research grant funding from CEVA Animal Health, Elanco Animal Health, Zoetis Animal Health, Royal Canin and Waltham Centre for Pet Nutrition. Dr J. Elliot is also a member of the International Renal Interest Society, which receives financial support from Elanco Animal Health.
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Vet Clin Small Anim 46 (2016) 1115–1130
http://dx.doi.org/10.1016/j.cvsm.2016.06.009
vetsmall.theclinics.com

PROTEINURIA AS A PROGNOSTIC INDICATOR IN CHRONIC KIDNEY DISEASE

Proteinuria is a negative prognostic indicator for both dogs and cats with chronic kidney disease. In dogs with chronic kidney disease, an initial urine protein:creatinine ratio (UPC) of greater than 1.0 was associated with a threefold greater risk of developing a uremic crisis and death.[1] The relative risk of adverse outcomes increased 1.5 times for every increase in the UPC by 1. In another canine study, proteinuria correlated with the degree of functional impairment, as measured by glomerular filtration rate; dogs with a UPC of less than 1.0 lived 2.7 times longer on average than dogs with a UPC of greater than 1.0.[2]

When nonazotemic cats were evaluated prospectively and longitudinally, proteinuria was found to be associated significantly with the development of azotemia by 12 months.[3] Both proteinuria and serum creatinine were related to shortened survival in cats with chronic kidney disease.[4,5] This was true even when cats had UPC as low as 0.2 to 0.4.

Chronic proteinuria has been shown to be associated with interstitial fibrosis as well as tubular degeneration and atrophy, although the exact mechanisms of injury are a subject of debate.[6,7] There is some evidence that reabsorbed proteins and lipids are directly toxic to the tubular epithelial cells, triggering inflammation and apoptosis. In addition, excessive lysosomal processing of proteins leads to lysosomal rupture and the intracellular release of cytotoxic enzymes. Proteinuria may increase the workload of the tubular epithelial cell beyond its capabilities. Proteinacious casts cause tubular obstruction, which further injures the cells. Glomerular injury results in decreased perfusion of the tubulointerstitium, resulting in cellular hypoxia. Increased glomerular permselectivity increases the filtration of other substances, such as transferrin, that cause additional tubular injury.

Because proteinuria is associated with negative outcomes, it is imperative that the practicing veterinarian has a thorough understanding of appropriate assessment and management of proteinuria in dogs and cats with chronic kidney disease.

NORMAL RENAL HANDLING OF PROTEIN

The glomerulus is a complex structure that functions as a filter, across which an ultrafiltrate of the plasma is formed. This filtration system, made up of the fenestrated endothelium, glomerular basement membrane, and visceral epithelial cells (podocytes), is freely permeable to water and small dissolved solutes but retains cells and most macromolecules, such as proteins. The podocyte is the most differentiated cell in the glomerulus and is essential to the filtration unit.[6] In addition to these factors, glycocalyx has been found to play an important role in maintaining glomerular permselectivity by restricting the passage of proteins.[8] The major determinant restricting passage of proteins into the filtrate is molecular size. Low-molecular-weight proteins, such as insulin and immunoglobulin fragments, pass freely through the filter, but as molecules increase in size they are retained with increasing efficiency. Only small amounts of substances larger than 60,000 to 70,000 Da pass in to the filtrate. The podocyte foot processes, epithelial slits, basement membrane, and endothelium are all rich in negatively charged glycoproteins that create an ionic charge barrier and impede the passage of negatively charged molecules more than would be expected based on their size alone. Albumin, a negatively charged protein with a molecular weight of 69,000 Da, is normally largely excluded from the filtrate. Despite this complex filtration system, the glomerulus normally leaks small quantities of albumin. Rapid endocytosis and hydrolysis of these proteins by proximal tubular cells occurs. Filtered albumin and other proteins are ultimately released to the blood as amino