



## STATE OF THE ART LECTURE

### THE IMPORTANCE OF PROTEINURIA AND MICROALBUMINURIA

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We now recognize that proteinuria is associated with increased risk of developing end-stage renal failure in cats and with an increased risk of mortality even in nonazotemic animals. Further, studies have shown that therapies that reduce the magnitude of proteinuria are often renoprotective.

Recent findings have suggested that renal protein leak is not only a marker of severity of renal disease but also potentially could be a cause of renal injury. While the role of this protein leak in producing renal damage has not been clearly established in cats, findings in cell culture studies and investigations of rodent models of renal failure raise our concerns for the importance of separately evaluating our patients for the presence or absence of proteinuria and for monitoring patients with proteinuria to determine its magnitude, location, persistence. We should investigate proteinuria in those cases where it is present and institute appropriate therapy, if indicated. It is critical, however, that veterinary clinicians develop an enlightened approach to the diagnosis and management of proteinuria.

Proper management of proteinuria mandates two initial steps. First, a finding of proteinuria should lead to characterization (confirmation by sulfosalicylic acid or Robert's reagent or urine protein/creatinine ratio; quantification by the urine protein/creatinine ratio) and if confirmed, it should be categorized.

#### **Categorizing Proteinuria - Prerenal Proteinuria**

*Prerenal proteinuria* is caused by the presence of proteins in the plasma that are filtered through a normal glomerulus with normal permeability to macromolecules (i.e., permselectivity). These proteins may be normal proteins (e.g., hemoglobin) or abnormal proteins such as immunoglobulin light chains (e.g., Bence-Jones proteins)

#### **Categorization of Proteinuria - Postrenal**

*Postrenal proteinuria* is due to plasma proteins from hemorrhage or inflammation in the urinary tract (kidneys, ureters, bladder, urethra, and/or accessory sex glands). Many would also include extra-urinary losses such as from the accessory glands or genital tract as a postrenal cause of proteinuria.

#### **Categorization of Proteinuria - Three Types of Renal Proteinuria**

Most, but not all, causes of renal proteinuria are abnormal. There are some functional causes of proteinuria (e.g., fever or exercise) that are transient, mild, and reversible and considered variants of normal.

Pathological renal proteinuria is due to a renal abnormality in protein handling. It may occur from increased leakage of protein across the glomerulus (permselectivity defect causing *glomerular proteinuria*) or abnormal tubular

handling of filtered protein (*tubular proteinuria*), or both. Tubular proteinuria occurs because small plasma proteins (<15,000 molecular weight) freely traverse the glomerular barrier. There are also small amounts of larger molecular weight proteins (e.g., albumin = 69,000 gm/mole) that are filtered through the normal filtration barrier. In a normal kidney, the tubules reabsorb practically all of this filtered protein. In some diseases (e.g., gentamicin nephrotoxicosis) the glomerulus is normal and permits filtering of only small molecular weight proteins and a minor amount of albumin. However, the diseased tubules are unable to metabolize these proteins and tubular proteinuria ensues.

Protein may also enter the tubular fluid from interstitial inflammation (e.g., pyelonephritis or renal neoplasia) and this is referred to as *interstitial proteinuria*.

### Proteinuria in cats

Once proteinuria is identified and categorized, it is critical to ascertain whether or not it is persistent. Generally, this means assessing the urine protein/creatinine ratio on 3 occasions at 2 week intervals. In cats with chronic kidney disease, urine protein/creatinine values  $\geq 0.4$  in cats are associated with an increased risk of mortality. A benefit of angiotensin converting enzyme inhibitor therapy has been shown for cats with a ratio of 1.0 or greater. Anti-proteinuric, renoprotective therapy is generally taken to be indicated in cats with kidney disease and a persistently elevated ratio which exceeds 0.5. In cats, this will initially be an angiotensin converting enzyme inhibitor (e.g., benazepril at 0.5 mg/kg once daily).

Results of recent studies suggest have heightened our concern about the importance of proteinuria in dogs and cats, as evidence suggests that persistent proteinuria is associated with progression of chronic kidney disease (CKD) and worsened mortality rates, perhaps even in animals without CKD. In veterinary medicine, we have traditionally relied upon the urine dipstick and more recently, the urine protein-to-creatinine ratio, to identify and characterize proteinuria. Now there is a renewed focus on proteinuria and more specifically on microalbuminuria as a screening test for our patients. It is altogether fitting and proper that we should do this.

It has long been known that in diabetic people, proteinuria is a hallmark of impending nephropathy. Studies to quantify protein in the urine of diabetic people demonstrated that even small quantities of albuminuria were predictive of subsequent renal disease. This small amount of albuminuria (30-300 mg albumin in a 24-hour urine collection) was less than that observed

in overt proteinuria (>300 mg/24 hrs) and it became known as microalbuminuria because it was a comparatively smaller ("micro") amount of albumin observed in the urine. A 24-hour urine collection test to detect for the presence microalbuminuria test has been used for decades as a screen in diabetic people. In this nomenclature, < 30mg albumin/day is normal in people, 30-300 mg/day is defined as microalbuminuria, and >300mg/day is proteinuria.

While we often think of proteinuria originating from the glomerulus as a sign of kidney disease, recently it has been shown that in people with endothelial dysfunction small amounts of albumin can leak through the glomeruli of an otherwise normal kidney, producing microalbuminuria. This led to a new hypothesis: generalized endothelial dysfunction is manifest in the renal microcirculation as glomerular capillary albumin leak, which the clinician (veterinarian and physician) can detect as the presence of microalbuminuria. These consequent small amounts of albumin may be detected only by sensitive tests, which may confirm the presence of microalbuminuria. Traditionally this would require a 24-hour urine collection as a screening test.

Tests for microalbuminuria became a focus in human medicine where microalbuminuria is an independent risk factor for death from cardiovascular disease and for the development of myocardial infarction and stroke in people with CKD. Indeed, these cardiovascular complications are more common end-points than uremic mortality for people with CKD. In the past decade it has become apparent that microalbuminuria is a marker for fairly common renal and cardiovascular problems, including systemic hypertension, neoplasia, and generalized inflammatory conditions in people. As the need for a more clinically useful microalbuminuria test arose, measurement of the urine albumin/creatinine ratio (> 30 mg/gm is abnormal) or the use of albumin dipsticks became commonplace in people as a screening test for the presence of microalbuminuria.

Veterinary medicine has historically utilized the routine (traditional) urine dipstick as a screening tool for identifying proteinuria and employed the urine protein-to-creatinine ratio to provide semi-quantitative information about the magnitude of proteinuria in positive cases. This back-up test is required because the dipstick is only qualitative and is fraught with problems, particularly in specificity. There is now a commercially available albumin-detecting dipstick test (E.R.D.-Screen™ Urine Test, Heska, Ft. Collins, CO) which is more sensitive and specific than the routine urine

dipstick and that could be used to confirm the presence of proteinuria in the face of a positive dipstick result. It is altogether fitting and proper that we should do this.

Critically, the traditional dipstick will generally detect urine albumin present at a concentration of >30 mg/dL, whereas the new albumin-specific dipstick can reportedly detect > 1 mg/dL. Because this microalbuminuria is thus reportedly more sensitive than the traditional urine dipstick, it has become possible to use this new dipstick as a test for the presence of microalbuminuria in dogs and cats. It can thus be employed as a screening test in dogs and cats, similar to the approach in people. By one method of classification in veterinary medicine, microalbuminuria is defined as a positive albumin-specific dipstick in the absence of a positive routine (traditional) urine dipstick. We could use this test to screen all dogs and cats for the presence of CKD or for the presence of endothelial dysfunction. Based on what we know today, we need to act cautiously in this regard as it is probably not altogether fitting and proper that we should do this.

First, transient microalbuminuria may be observed in a variety of transient conditions, some of which remain to be identified in dogs and cats. *Persistent microalbuminuria* is an important clinical finding. In dogs and cats, persistent microalbuminuria is defined by the ACVIM Proteinuria Consensus Panel as microalbuminuria found repeatedly in  $\geq 3$  specimens obtained  $\geq 2$  weeks apart which cannot be attributed to a postrenal cause. Persistent microalbuminuria is often due to altered glomerular permselectivity (CKD or endothelial dysfunction); but impaired tubular handling of the small amounts of albumin that traverses the normal glomerular filtration barrier can also cause microalbuminuria. There is no clinically applicable way to reliably determine the source of microalbuminuria (glomerular vs. tubular). Nonetheless, progressive increases in magnitude of microalbuminuria are likely to indicate significant renal injury.

Since *persistent microalbuminuria* may be a marker of either CKD or endothelial dysfunction in dogs and cats, a microalbuminuria screening test may lead to discovery of a treatable underlying CKD or an inflammatory, metabolic, or neoplastic condition in an apparently healthy animal.

Urine testing that for the presence of microalbuminuria should be considered for the following circumstances: animals with chronic illnesses that may be complicated by proteinuric nephropathies (e.g., systemic lupus), screening apparently healthy dogs that are  $\geq 6$  years old and cats that are  $\geq 8$  years old, animals with confirmed or suspected systemic hypertension,

screening dogs or cats to detect possible onset of a hereditary nephropathy as early as possible.

Much remains to be learned about this exciting and novel approach that utilizes of the presence of small amounts of protein in the urine as a potentially valuable early marker of CKD and other conditions of clinical importance in dogs and cats. As veterinarians, we should be open to adopting this approach as we carefully scrutinize the literature for developing new information. It is altogether fitting and proper that we should do this.

## References

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