

# Clinical Significance of Low-Magnitude Proteinuria in the Cat

## IVMA CE Self-Study Offering

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### Abstract

*Within the last decade, proteinuria in cats has been established as a prognostic indicator in chronic kidney disease. Low levels of proteinuria have been shown to be predictive of a poorer prognosis when compared to non-proteinuric cats with a corresponding stage of renal insufficiency. As a result of these findings, there has been increasing attention directed at microalbuminuria. Although multiple tests have been developed for the detection of microalbuminuria in cats, the value of monitoring for microalbuminuria in this species remains unknown. This article reviews the methods of assessment of proteinuria as well as what is currently known about the prognostic and therapeutic significance of low magnitude proteinuria in cats.*

### Proteinuria: pathophysiology and classification

Proteinuria is classified by anatomic origin as pre-renal, renal, and post-renal. Pre-renal proteinuria is a result of excessive low molecular weight proteins in the circulation that are filtered by the glomerulus and exceed the reabsorptive capacity of the renal tubule. The classic example of pre-renal proteinuria in the cat is Bence-Jones proteinuria, caused by excess production of immunoglobulin light chains in multiple myeloma.<sup>1</sup> Post-renal proteinuria is the result of inflammation in the lower urinary tract which results in inflammatory proteins being added to the urine after it has been formed in the kidneys. With both pre-renal and post-renal causes, the proteinuria does not result from any abnormality of the kidney itself and these causes must be ruled out when considering the significance of proteinuria.

In contrast, renal proteinuria results from some change, either physiologic or pathologic, somewhere in the kidney. In the normal cat, the glomerular filtration barrier keeps the vast majority of plasma proteins in circulation. The proteins are prevented from passing through the

barrier because of their large size and negative charge. Small peptides and amino acids do pass through the glomerular filtration barrier and into the filtrate but are either reabsorbed or degraded in the proximal tubule. The resulting effect is that only a minimal amount of protein makes it into the urine of a healthy animal.

Renal proteinuria can be either physiologic (functional) or pathologic. Functional renal proteinuria, which can result from strenuous exercise or fever, is typically mild and results in transiently altered renal physiology.<sup>2</sup> This has not been well-studied in animals and is likely of minimal clinical significance in the feline patient. Pathologic proteinuria is the result of either primary or secondary renal dysfunction and is the primary focus of this article.

Since both the glomerular filtration barrier keeps proteins out of the filtrate and the renal tubules either absorb or degrade the amino acids and peptides that make it into the filtrate, renal proteinuria can result from glomerular dysfunction, tubular dysfunction, or both. Glomerular proteinuria can result from primary glomerular disease such as amyloidosis or glomerulonephritis, resulting in the classical high-magnitude proteinuria and protein-losing nephropathy but this is uncommon in cats, particularly when compared to dogs, and will not be discussed further.

In cats with chronic kidney disease (CKD), increased glomerular permeability can result from glomerular capillary hypertension. Glomerular hypertension may result as a maladaptive response to the loss of functioning nephrons in CKD. With nephron loss, there is a compensatory increase in the single-nephron glomerular filtration rate (GFR). This results in an increased transglomerular flux of proteins which then overwhelms the renal tubular reabsorptive capacity.<sup>3</sup> In addition, uncontrolled systemic hypertension can lead to glomerular hypertension through loss of renal autoregulatory mechanisms.<sup>3</sup>

Tubular dysfunction can also contribute to pathologic renal proteinuria. This can occur as part of a generalized renal tubular defect, with concurrent evidence of tubular dysfunction such as acid-base abnormalities and normoglycemic glucosuria.<sup>1</sup> What is more common is that this simply occurs as a result of a decrease in functioning nephrons in CKD.

## **Assessment of Proteinuria**

There are a number of diagnostic tests available for the detection and quantification of proteinuria in the cat. Semiquantitative tests will identify whether a urine sample is positive or negative for proteinuria and give a rough idea of the magnitude. The most commonly used and readily available semiquantitative test is the colorimetric urine dipstick test. The urine dipstick can detect urine protein concentrations greater than 30 mg/dl based on a color-change reaction on the reagent pad, with larger amounts of protein producing the greatest degree of color change. False positives are common, particularly in concentrated urine samples. The dipstick is more sensitive to albumin than other urine proteins, so false negatives can also occur, particularly when the primary urine protein is not albumin.<sup>4</sup>

The sulfosalicylic acid (SSA) turbidimetric test is another semiquantitative test involving the addition of SSA to a urine sample and assessing the resulting degree of turbidity, ranging from 0-4+. This test has a lower rate of false positives than the urine dipstick test.<sup>4</sup>

The gold standard for urine protein quantification involves 24-hour urine collection. The urine protein:creatinine ratio (UPC) has been shown to approximate 24-hour protein excretion and has become the standard test for urine protein quantification in a clinical setting.<sup>5</sup>

## **Microalbuminuria**

Microalbuminuria (MA) is defined as a urine protein concentration that is greater than normal but below the level of detection of the conventional urine dipstick test (30 mg/dl). The range of microalbuminuria has been described as 1-30 mg/dl in the cat.<sup>6</sup> Semiquantitative and quantitative tests also exist for microalbuminuria. The Early Renal Damage Test (ERD)<sup>®</sup> is available as a cage-side test.<sup>7</sup> It is an ELISA urine dipstick test using feline albumin antibodies to detect low levels of albumin in the urine. This semiquantitative test gives negative and low, medium, or high positive results. The reported sensitivity of the test is 95% and the specificity is >99%.<sup>6</sup> A quantitative feline-specific microalbuminuria ELISA is also available through some reference laboratories.

## **Prognostic Significance of Low-Magnitude Proteinuria**

There has been a lot of work done recently which has established low-magnitude proteinuria as a poor prognostic indicator in cats, particularly in cats with CKD. It is important to emphasize the fact noted earlier that cats, in general, do not frequently get primary glomerular disease, characterized by high-magnitude proteinuria (UPC > 2.0), resulting in protein-losing nephropathy and the nephrotic syndrome. In contrast, the majority of proteinuric cats have a UPC < 1.0, a value that was traditionally considered clinically insignificant.<sup>8</sup>

A number of studies have shown that proteinuria predicts a poor outcome in cats with CKD independent of the magnitude of azotemia.<sup>8,9,10</sup> While the degree of proteinuria is predictive of reduced survival, a survival disadvantage has even been shown in cats with a UPC of >0.2.<sup>8,9</sup> Proteinuria has also been shown to be predictive of the development of azotemia.<sup>11</sup>

While it is clear that proteinuria is a negative prognostic indicator, it is not clear whether or not proteinuria results in the progression of kidney dysfunction. Chronic kidney disease does not have a single, homogeneous pathogenesis and it is possible that proteinuria simply indicates a more aggressive disease process. In contrast, the presence of proteinuria, regardless of the cause, may play a role in accelerating renal damage. There is evidence that proteinuria is damaging to the renal tubular epithelium, but much of this evidence stems from experimental in vitro models in which the renal tubular epithelium is exposed to larger quantities of protein than would be expected in the actual disease process.<sup>12</sup> The ultimate goal in determining the true significance of proteinuria in feline CKD is to determine whether or not it warrants therapeutic intervention.

## **The Role of Therapeutic Intervention**

A number of studies have investigated the effect of different pharmacologic agents on proteinuria in cats. Angiotensin converting enzyme inhibitors (ACEIs) have been studied most frequently. Angiotensin converting enzyme inhibitors reduce glomerular hypertension through preferential dilation of the efferent arteriole. Cats with azotemic CKD treated with the ACEI benazepril at 0.5-1 mg/kg/day have been shown to experience a significant reduction in proteinuria compared with placebo-treated cats. Interestingly, while both of the benazepril studies showed significant reductions in proteinuria, neither demonstrated that benazepril had a significant effect on survival.<sup>9,13</sup>

Amlodipine is another pharmacologic agent that has been demonstrated to reduce proteinuria in cats. Amlodipine is a calcium-channel blocker that is used as an anti-hypertensive agent. Proteinuria has been considered a contraindication for amlodipine use in humans because amlodipine causes preferential dilation of the afferent arteriole, which will theoretically lead to an increase in glomerular capillary pressure and worsening of proteinuria. Systemic hypertension has been correlated with proteinuria in cats with similar levels of renal dysfunction.<sup>8</sup> In a study in which amlodipine was used to treat a group of client-owned hypertensive cats, amlodipine was shown to reduce proteinuria rather than exacerbate it, but again offered no survival advantage.<sup>14</sup>

### **The Significance of Microalbuminuria**

Microalbuminuria has been receiving increasing attention in veterinary medicine due to a screening test being readily available to practitioners. In humans, microalbuminuria has been shown to be an early predictor of nephropathy secondary to diabetes mellitus and hypertension and intervention to reduce proteinuria can prevent progression to end stage renal disease.<sup>15,16,17</sup>

In cats, the significance of microalbuminuria is less clear. Microalbuminuria has been shown to have a higher prevalence in cats with a wide variety of pre-existing diseases when compared to healthy cats.<sup>18</sup> The prevalence of microalbuminuria also has been shown to increase with age which may or may not be the result of an increasing prevalence of underlying disease.<sup>18,19</sup>

In both humans and dogs, microalbuminuria has been shown to be a negative prognostic indicator in critical illness.<sup>20,21</sup> While cats have also been shown to have a high prevalence of microalbuminuria in critical illness, a similar link to increased mortality has not been established but is suspected.<sup>21</sup> It is important to note that in this case microalbuminuria is a marker of systemic disease and not necessarily something that should be pursued as a therapeutic target. The glomerulus is a capillary bed and is uniquely capable of reflecting system-wide changes in vascular permeability. Increased mortality associated with microalbuminuria appears to be the result of microalbuminuria being reflective of a more severe systemic disease process.

### **Conclusions and Recommendations**

#### *Assessment of Proteinuria*

A urinalysis should be part of routine annual or semi-annual wellness screening in middle aged and elderly cats. The urinalysis includes a semi-quantitative assessment of proteinuria, which is typically the standard colorimetric dipstick test. Urine samples positive for proteinuria should be assessed further. This should always include a serum biochemical profile and urine sediment examination to rule out pre- and post-renal causes of proteinuria. This should be followed with a test to quantify the proteinuria, the most commonly used test being the UPC.

### *Treatment of Proteinuria*

It is becoming clear that low-magnitude proteinuria (UPC >0.4 and possibly >0.2) is significant in cats and has negative prognostic significance in cats with chronic kidney disease and may also have prognostic significance in non-azotemic cats. Recommendations for therapeutic intervention for proteinuria will likely continue to change over time as more is discovered about the clinical significance of varying magnitudes of proteinuria in groups of cats with and without different risk factors.

The ACVIM consensus statement on canine and feline proteinuria, published in 2005, advocates for therapeutic intervention when the UPC is  $\geq 0.4$  in cats with azotemic CKD.<sup>2</sup> The first line of therapy for proteinuria is dietary management with a therapeutic diet formulated for renal disease with reduced amounts of high quality protein; however, the reasons for instituting a renal therapeutic diet in cats extend well beyond the consideration of proteinuria as protein and phosphorus-restricted diets are important for management of azotemic CKD regardless of the presence of proteinuria.<sup>22</sup>

Pharmacologic intervention is more controversial. While studies have demonstrated that ACEIs can reduce proteinuria, they have not yet been shown to provide a survival advantage in CKD; however, Mizutani and others did find that cats not treated with benazepril were more likely to progress to a higher stage of CKD than those that were treated with placebo.<sup>13</sup>

Hypertension is a common complication of CKD in cats and can result in acute blindness, cardiovascular complications, and progression of renal damage.<sup>22</sup> Angiotensin-converting enzyme inhibitors, while they effectively reduce proteinuria, are minimally effective as anti-hypertensive agents in cats. Amlodipine is an effective anti-hypertensive agent in cats and also appears to reduce proteinuria.<sup>14</sup> Consequentially, amlodipine is recommended as the first line of

treatment for CKD cats with hypertension and the addition of an ACEI to improve control of hypertension and proteinuria logically may be optimal, although this strategy, too, has not been shown to provide a survival advantage.<sup>23</sup>

### *Microalbuminuria*

Microalbuminuria is common in cats with the presence of various diseases as well as with increasing age. Due to the high prevalence in the critically ill, it is likely that microalbuminuria is a marker of systemic vascular dysfunction associated with many serious illnesses. Because of the increasing prevalence with age in seemingly healthy cats, the range of microalbuminuria has been questioned, and it is not clear whether or not microalbuminuria is normal in older cats. A relationship between microalbuminuria and early renal injury has yet to be demonstrated in the cat but this topic warrants further investigation. Healthy cats that are found to be microalbuminuric without evidence of underlying disease should be monitored for progression to overt proteinuria as well as for evidence of loss of urine concentrating ability or azotemia. There is no evidence that supports the use of treatment for cats with microalbuminuria.

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1. Which of the following could result in pre-renal proteinuria?
  - a. Urinary tract infection
  - b. Hemolysis
  - c. Uroliths
  - d. Interstitial nephritis
2. Ace-inhibitors can reduce proteinuria through what mechanism?
  - a. Dilation of the afferent arteriole
  - b. Constriction of the efferent arteriole
  - c. Constriction of the afferent arteriole
  - d. Dilation of the efferent arteriole
3. One possible advantage of using the SSA turbidimetric test instead of the urine colorimetric dipstick test is:
  - a. It allows for quantification of urine protein.
  - b. It detects microalbuminuria
  - c. It is more sensitive (fewer false negatives).
  - d. It is more specific (fewer false positives).
4. The anti-hypertensive agent amlodipine has been shown to exacerbate proteinuria in cats with CKD.
  - a. True
  - b. False
5. When given to cats with CKD, benazepril has been shown to:
  - a. Reduce proteinuria and improve survival
  - b. Have no effect on proteinuria and improve survival
  - c. Reduce proteinuria and have no effect on survival
  - d. Reduce proteinuria and increase mortality
6. Microalbuminuria has been associated with increased mortality in cats with critical illness.

- a. True
  - b. False
7. ACEIs are ineffective first-line anti-hypertensive agents in cats.
- a. True
  - b. False
8. Which of the following statements about microalbuminuria is correct?
- a. Microalbuminuria is a negative prognostic indicator in feline CKD.
  - b. Therapeutic intervention to reduce microalbuminuria has been shown to prevent progression to end-stage renal disease in humans.
  - c. Treatment of microalbuminuria in critically ill dogs has been shown to improve outcome.
  - d. Microalbuminuria prevalence decreases with age in cats.
9. The urine protein:creatinine ratio cannot be interpreted without a urine sediment and biochemical profile.
- a. True
  - b. False
10. Urine protein concentration below \_\_\_\_ cannot be detected using the standard urine colorimetric dipstick test?
- a. 1 mg/dl
  - b. 50 mg/dl
  - c. 30 mg/dl
  - d. 2 mg/dl

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