Proteinuria: Measurement and Interpretation

Gregory F. Grauer, DVM, MS, DACVIM

Proteinuria is a general term that describes the presence of any type of protein in the urine (e.g., albumin, globulins, mucoproteins, and Bence-Jones proteins); however, albumin is the predominate protein in urine in healthy dogs and cats as well as dogs and cats with renal disease. Proteinuria can arise from several different physiologic and pathologic causes, but persistent proteinuria associated with normal urine sediment is consistent with kidney disease. The urine dipstick colorimetric test is the usual first-line screening test for the detection of proteinuria, but false-positive reactions are common. When proteinuria of renal origin is suspected, the next diagnostic steps are quantitation and longitudinal monitoring via the urine protein/creatinine ratio. The recent availability of a species-specific albumin enzyme-linked immunosorbent assay technology that enables detection of low concentrations of canine and feline albuminuria has both increased diagnostic capability and stimulated discussion about what level of proteinuria/albuminuria is normal. Beyond being an important diagnostic marker, proteinuria is associated with kidney disease progression in both dogs and cats: the greater the magnitude of the proteinuria, the greater the risk of renal disease progression and mortality. Treatments that have attenuated proteinuria in dogs and cats have also been associated with slowed kidney disease progression and/or improved survival. For these reasons, screening for renal proteinuria and longitudinal assessment of renal proteinuria has recently received renewed interest.

Keywords: proteinuria, albuminuria, localization, screening, quantitation, monitoring

Type IV collagen within the basement membrane of the glomerular capillary wall restricts the filtration of most plasma proteins, primarily on the basis of molecular weight and size. Albumin (molecular weight of 69,000 D) and larger proteins are normally not present in large quantities in glomerular filtrate because of this glomerular selective permeability. The glomerular capillary wall is also negatively charged, which further impedes the passage of negatively charged proteins like albumin. The glomerular filtrate of healthy dogs and cats contains only 2 to 3 mg/dL of albumin compared with about 4 g/dL found in the plasma. Smaller-molecular-weight proteins, as well as those positively charged larger proteins that do pass through the glomerular capillary wall, are almost completely reabsorbed by tubular epithelial cells. Such reabsorbed proteins may be broken down and used by the epithelial cells or returned to the plasma. This reabsorption occurs primarily in proximal convoluted tubules and reduces the concentration of albumin in normal urine to <1 mg/dL. This tubular reabsorptive process has a transport maximum and tubular proteinuria may occur if that maximum is exceeded. Examples of tubular proteinuria include excessive production and filtration of small-molecular-weight proteins like Bence Jones proteins and damage to the tubular epithelial cells, which may occur with nephrotoxic injury or chronic tubulointerstitial disease.

From the Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS USA.
Address reprint requests to: Gregory F. Grauer, DVM, MS, (Small Animal Internal Medicine), Professor and Jarvis Chair of Medicine, Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, 1800 Denison Ave, Manhattan, KS 66506. E-mail: ggrauer@vet.ksu.edu.

1527-3369/06/0604-0171\.00/0
doi:10.1053/j.tcam.2011.04.002

Detection of Proteinuria

The urine dipstick colorimetric test is the most common first-line screening test for the detection of proteinuria/albuminuria; however, false-positive reactions are common and limit the test's utility. Because of these specificity issues, many laboratories confirm positive reactions for protein on the dipstick test with the sulfosalicylic acid (SSA) turbidimetric test. When proteinuria detected by dipstick and/or SSA screening tests is thought to be of renal origin, it is often confirmed and quantitated using the urine protein/creatinine ratio (UP/C). The dipstick, SSA, and UP/C tests are more sensitive for albumin than for other proteins; however, there are also albumin and species-specific tests that are capable of detecting albumin concentrations as low as 1 mg/dL in canine and feline urine (the Heska ERD test is semiquantitative and the Antech Diagnostics and Heska Corporation microalbuminuria tests are quantitative).

The dipstick colormetric test is easy to use and primarily measures albumin, but sensitivity and specificity are relatively low with this methodology (Fig 1). False-negative results (decreased sensitivity) may occur with Bence Jones proteinuria, low concentrations of albuminuria, and/or

Figure 1. Conventional dipstick test for assessment of proteinuria

dilute or acidic urine. The lower limit of protein detection for the conventional dipstick test is approximately 30 mg/dL. False-positive results (decreased specificity) are also common in both species with the dipstick but occur more frequently in cats than in dogs. For example, when 599 canine and 347 feline urine samples were analyzed by conventional urine protein test strip method (Multistix Reagent Strips; Bayer Corporation, or Roche Chemstrip 9; Roche Diagnostic Corporation) and a canine or feline albumin-specific quantitative enzyme-linked immunosorbence assay (ELISA) (Heska Corporation) there were disparate results.[1] The sensitivity (≥ to a trace positive reaction) for conventional urine protein test strips for albuminuria in canine and feline urine was 81% and 90%, respectively, but the specificity was only 48% and 11%, respectively[1] (Tables 1 and 2).

The SSA test is performed by mixing equal quantities of urine supernatant and 3% to 5% SSA in a glass test tube and grading the turbidity resulting from precipitation of protein on a 0 to 4+ scale (Fig 2). In addition to albumin, the SSA test can detect globulins and Bence Jones proteins to a greater extent than the dipstick test. False-positive results may occur if the urine contains radiographic contrast agents, penicillin, cephalosporins, sulfisoxazole, or thymol (a urine preservative), as well as for unknown reasons. The protein content may also be overestimated with the SSA test if uncentrifuged, turbid urine is analyzed. The reported sensitivity of the SSA test is approximately 5 mg/dL. Because of the relatively poor specificity of conventional dipstick analysis, many reference laboratories will confirm a positive dipstick test result for proteinuria using the SSA test. The sensitivity (≥ to a trace positive reaction) for the SSA test for albuminuria in canine and feline urine was 73% and 58%, respectively, but the specificity was only 64% and 25%, respectively[1] (Tables 1 and 2).

Based on the above study in canine urine, if the urine dipstick or SSA result is ≥2+ there is a high likelihood that the sample is positive for albumin.[1] However, if the dipstick analysis is trace or 1+ positive, a turbidimetric SSA analysis should be performed to confirm the diagnosis of proteinuria. When the dipstick and SSA tests are performed simultaneously they should be interpreted in series (both tests should be positive to consider the sample positive for albuminuria), rather than in parallel fashion, to increase specificity.[1] If dipstick and SSA results both fall into the trace to 1+ range, positive results should be confirmed with a more specific assay such the ELISA-based test.[1]

For feline urine samples, both routine-screening tests (dipstick and SSA) performed poorly and appear to be of minimal diagnostic value because of an unacceptable high number of false positives.[1] For both dipstick and SSA tests, the positive and negative likelihood ratios were close to 1 and the positive and negative predictive values were close to 50%, indicating that neither test provided useful information.[1] Based on these data, urine albumin detection in the feline patient should always be performed with a higher quality assay such as the species-specific ELISA.

It has long been recommended that proteinuria detected by these semiquantitative, screening methods be interpreted in light of the urine-specific gravity and urine sediment. For example, a positive dipstick reading of trace or 1+ proteinuria in hypersthenuric urine has often been attributed to urine concentration rather than abnormal proteinuria. In addition, a positive dipstick reading for protein in the presence of hematuria or pyuria was often

Table 1. Canine Urine Sample Results for Dipstick and SSA (599 Samples)

	Dipstick + if ≥ Tr	SSA + if ≥ Tr	Dipstick + if ≥ 2+	SSA+ if ≥ 2+
Sensitivity	81.2%	73.3%	32.9%	27.4%
Specificity	47.8%	63.9%	98.9%	99%
PPV*	34%	41.8%	90.7%	90.2%
NPV†	88.5%	87.1%	81.7%	79.4%

Abbreviations: SSA, Sulfosalicylic acid; Tr, trace; PPV, positive predictive value; NPV, negative predictive value.

*The animal is truly positive given a positive test.

†The animal is truly negative given a negative test.

Table 2. Feline Urine Sample Results for Dipstick and SSA (347 Samples)

	Dipstick + if ≥ Tr	SSA + if ≥ Tr	Dipstick + if ≥ 2+	SSA+ if ≥ 2+
Sensitivity	90.1%	58%	28.1%	9.6%
Specificity	11%	25.4%	80%	94.2%
PPV*	55.6%	46.9%	63.5%	65.2%
NPV†	47.2%	34.7%	47.3%	47.8%

Abbreviations: SSA, Sulfosalicylic acid; Tr, trace; PPV, positive predictive value; NPV, negative predictive value.

*The animal is truly positive given a positive test.

†The animal is truly negative given a negative test.

attributed to urinary tract hemorrhage or inflammation. However, in both situations, these interpretations may be inaccurate. Because of the limits of the conventional dipstick test sensitivity, any positive result for protein regardless of urine concentration may be abnormal (except in the case of false-positive results). Hematuria and pyuria have an inconsistent effect on urine albumin concentrations: not all dogs with microscopic hematuria and pyuria have albuminuria.[2] In patients with gross hematuria and/or microscopic pyuria, the source of the hemorrhage and/or inflammation should be diagnosed and treated before further assessment of the proteinuria.

Detection of Albuminuria

Albuminuria can be measured by a species-specific point-of-care, semiquantitative test (e.g., the Heska ERD-HealthScreen Urine test) and quantitative immunoassay at reference laboratories (Antech Diagnostics and Heska Corporation). Microalbuminuria (MA) is defined as concentrations of albumin in the urine that are greater than normal (> 1.0 mg/dL) but below the limit of detection using conventional dipstick urine protein screening methodology (i.e., ≤ 30 mg/dL). Urine albumin concentrations above 30 mg/dL are referred to as overt albuminuria. Urine albumin concentrations can be adjusted for differences in urine concentration by dividing by urine creatinine concentrations. For example, a urine albumin/creatinine ratio >30 mg/gm is considered abnormal in dogs.[3] Alternatively, urine can be diluted to a standard concentration, such as 1.010, before assay. In dogs, normalizing urine albumin concentrations to a 1.010 specific gravity yielded similar results to the urine albumin/creatinine ratio.[3]

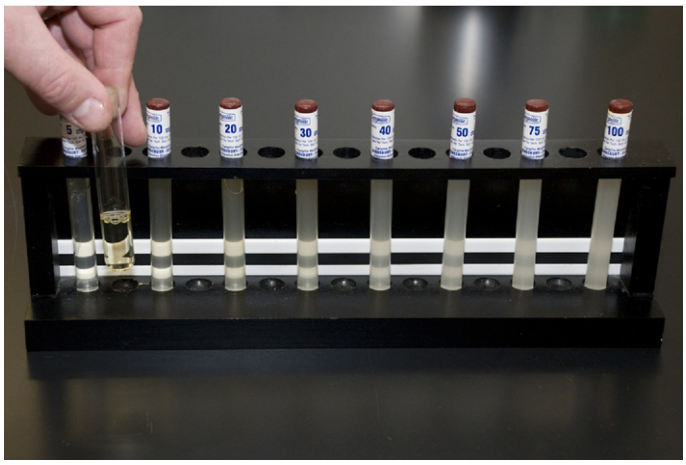

Figure 2. Comparison of a sulfosalicylic acid test sample to a set of standards. The sample shows no turbidity and would be read as negative or <5 mg/dL protein.

Indications for use of MA tests include:[4]

1 When equivocal or conflicting results or false-positive results are obtained/suspected with conventional screening tests for proteinuria;
2 When conventional screening tests for proteinuria are negative in apparently healthy, older dogs and cats and a more sensitive screening test is desired;
3 When conventional screening tests for proteinuria are negative in apparently healthy, young dogs and cats that have a familial risk for developing proteinuric renal disease and a more sensitive screening test is desired;
4 When conventional screening tests for proteinuria are negative in dogs and cats with chronic illnesses that are often associated with proteinuria renal disease and a more sensitive screening test is desired;
5 Confirmation/longitudinal monitoring of previously positive MA tests.

Interpretation and follow-up of MA testing is critical. Like other tests for proteinuria, MA tests can be affected by lower urinary tract inflammation and therefore assessment of patient history and urine sediment changes is important. A negative MA result is a useful finding because it obviates any concern about albuminuria until the next monitoring point. A positive test result is more complex and needs to be confirmed with follow-up testing approximately 7 to 10 days later. If the second test is negative, the initial positive test was likely due to transient, benign, or physiologic albuminuria that is unlikely to have any long-term consequence for the patient. If follow-up tests continue to be positive, more frequent monitoring and further investigation are indicated. Monitoring will verify persistence as well as changes in the

magnitude of the albuminuria. Increases in magnitude of MA are likely indicative of active, ongoing renal injury and should prompt further investigation to detect any neoplastic, infectious, or noninfectious inflammatory disease (see glomerular disease chapter) that might be the underlying cause of the animal's renal disease.

Causes of Albuminuria

Persistent renal albuminuria reflects the presence of intraglomerular hypertension and/or generalized vascular damage and endothelial cell dysfunction in humans.[5] Low-level albuminuria has been shown to be an accurate predictor of subsequent renal disease in human beings with both systemic hypertension and diabetes mellitus and has also been observed in human beings with systemic diseases that are associated with glomerulopathy.[6-10] Early detection of albuminuria and institution of appropriate treatment have slowed the progression of kidney disease in people.[11]

A limited number of studies in dogs suggest that low-level albuminuria is an accurate marker of early renal disease.[3,12,13] In addition to primary kidney disease, other conditions have been reported in dogs with albuminuria, including noninfectious inflammatory disease and metabolic and cardiovascular disease.[14,15] Results of a study of albuminuria in dogs with lymphosarcoma and osteosarcoma demonstrated that urine albumin concentrations were significantly increased in dogs with these tumors, even though the UP/C may not be increased above the reference range.[16] Albuminuria did not, however, consistently decrease with reduced tumor burden.

The prevalence of low-level albuminuria in dogs admitted for intensive care is higher than for normal canine populations and appears to vary with different classifications of disease.[14,15] As reported in people with acute inflammatory conditions, transient albuminuria occurred in some of these dogs. A large percentage of dogs that were euthanized or died had albuminuria, suggesting that, as in people, its presence may be a negative prognostic indicator. Short-term prednisone administration has been shown to cause a substantial but reversible increase in the magnitude of proteinuria/albuminuria in heterozygous, or carrier, female dogs with X-linked hereditary nephropathy.[17] Finally, a moderate amount of exercise in dogs (treadmill work for 20 minutes) does not appear to cause albuminuria.[18]

Table 3. Localization of Proteinuria

Type of Proteinuria		Diagnosis
Physiologic/Benign proteinuria		UP/C usually < 0.5 Compatible history Intermittent/transient
Examples include:	Change in exercise level Seizure activity Fever Exposure to temperature extremes Stress	
Pathologic Proteinuria		
Nonurinary:		Variable UP/C
Examples include:	Congestive heart failure	History/PE/Echo
	Hemoglobinuria/Myoglobinuria	Urine remains red after centrifugation
	Dysproteinemia/Dysprtoetinuria	Serum/Urine electrophoresis
	Genital tract inflammation/hemorrhage	PE/Imaging/Urine sediment
Urinary (Nonrenal):		
Examples include:	Lower urinary tract inflammation (e.g., bacterial cystitis, cystoliths, polyps, neoplasia)	UP/C not indicated History/PE Urine sediment Imaging
Urinary (Renal):		
Examples include:	Renal parenchymal inflammation (e.g., pyelonephritis, renoliths, neoplasia)	Variable UP/C Urine sediment Imaging
	Tubular proteinuria	UP/C usually = 0.5-1.0 May be accompanied by normoglycemic glucosuria and excessive urinary loss of electrolytes
	Glomerular proteinuria	Persistent UP/C ≥ 1.0 Inactive urine sediment with the exception of possible hyaline casts

Abbreviations: UP/C, Urine protein/creatinine ratio; PE, physical examination.

Localization of Proteinuria

When proteinuria/albuminuria is detected by screening tests, it is important to identify its source (Table 3). Proteinuria may be caused by physiologic or pathologic conditions. Physiologic or benign proteinuria is usually transient, of low magnitude, and abates when the underlying cause is corrected. Examples of conditions that may cause physiologic proteinuria are strenuous exercise, seizures, fever, exposure to extreme heat or cold, and stress. The mechanism of physiologic proteinuria is not completely understood, but may involve transient renal vasoconstriction, ischemia, and/or congestion. Decreased physical activity may also affect urine protein excretion in dogs: one study showed that urinary protein loss was higher in dogs confined to cages than in dogs with normal activity levels.[19]

Pathologic proteinuria may be caused by urinary or nonurinary abnormalities. Nonurinary disorders associated with proteinuria often involve the production of small-molecular-weight proteins (dysproteinemias) that are filtered by the glomeruli and subsequently overwhelm the reabsorptive capacity of proximal tubules. An example of this "prerenal" proteinuria is the production of immunoglobulin light chains (Bence Jones proteins) by neoplastic plasma cells. Genital tract inflammation (e.g., prostatitis or metritis) can also result in pathologic nonurinary proteinuria. Obtaining urine samples via cystocentesis reduces the potential for urine contamination with protein from the lower urinary tract. Note that inflammatory exudate from prostatic disease may reflux into the urinary bladder and cystocentesis should be avoided in cases of suspected pyometra.

Pathologic urinary proteinuria may be renal or nonrenal in origin. Nonrenal proteinuria most frequently occurs in association with lower urinary tract inflammation or hemorrhage (also referred to as postrenal proteinuria). Changes observed in the urine sediment are usually compatible with the underlying inflammation (e.g., pyuria, hematuria, bacteriuria, and increased numbers of transitional epithelial cells) and the patient history often includes pollakiuria, dysuria, stranguria, and/or hematuria. On the other hand, renal proteinuria is most often caused by increased glomerular filtration of plasma proteins associated with intraglomerular hypertension, the presence of immune complexes, vascular inflammation in glomerular capillaries, or structural defects in the glomerular basement membrane. Renal proteinuria may also be caused by decreased reabsorption of filtered plasma proteins due to tubulointerstitial disease. In some cases, tubulointerstitial proteinuria may be accompanied by normoglycemic glucosuria and increased excretion of electrolytes (e.g., Fanconi syndrome and acute tubular damage). Glomerular lesions usually result in more severe proteinuria than that associated with tubulointerstitial lesions. Renal proteinuria may also be caused by inflammatory or infiltrative disorders of the kidney (e.g., pyelonephritis, leptospirosis, neoplasia) which are often accompanied by an active urine sediment and ultrasonographic changes in the kidney.

Monitoring Renal Proteinuria

Transient renal proteinuria/albuminuria is likely of little consequence and does not warrant treatment. On the other hand, persistent proteinuria/albuminuria with an inactive sediment strongly suggests the presence of chronic kidney disease (CKD). Persistent proteinuria/albuminuria can be defined as positive test results on ≥3 occasions, ≥2 weeks apart. Because persistent proteinuria/albuminuria can be constant or increase or decrease in magnitude over time, monitoring should use quantitative methods (see below) to determine disease trends and/or response to treatment. Changes in the magnitude of proteinuria should always be interpreted in light of the patient's serum creatinine concentration because proteinuria may decrease in progressive renal disease as the number of functional nephrons decrease. Decreasing proteinuria in the face of a stable serum creatinine is a positive response to treatment, whereas decreasing proteinuria with an increasing serum creatinine suggests disease progression.

Quantitation of Proteinuria

If the results of the screening tests show persistent proteinuria associated with a normal urine sediment, urine protein excretion should be quantified. This helps to evaluate the severity of renal lesions and to assess the response to treatment or the progression of disease. Methods used to quantitate proteinuria include UP/C and immunoassays for albuminuria, the latter expressed as either urine albumin/creatinine ratio or as milligrams/deciliters in urine diluted to a standard specific gravity (e.g., 1.010). Albumin ≥30 mg/dL in 1.010 diluted urine will usually result in UP/C ≥0.4 in cats and 0.5 in dogs. The UP/Cs and urine albumin/creatinine ratios from spot urine samples accurately reflect the quantity of protein/albumin excreted in the urine over a 24-hour period,[20] but it is ideal to base clinical decisions on the average of more than one UP/C. Because 24-hour urine collection is difficult, spot sampling has greatly facilitated recognition of proteinuric renal diseases in veterinary medicine. Most studies have shown that normal urine protein excretion in dogs and cats is ≤10 mg/kg/24 hours and that normal UP/Cs are ≤0.2. (Previously suggested reference values for canine UP/Cs of < 1.0 have recently been lowered.) Today, UP/Cs of 0.2 to 0.5 in dogs and 0.2 to 0.4 in cats are considered borderline proteinuria.[4] Persistent proteinuria that results in UP/Cs >0.4 in cats and 0.5 in dogs, where prerenal and postrenal proteinuria have been ruled out, are consistent with glomerular or tubulointerstitial CKD, whereas UP/Cs >2.0 are strongly suggestive of glomerular disease.[4] It is likely that the definition of normal with the UP/C test will continue to change with additional research. It is interesting to note that, although the UP/C was a relatively specific test for canine and feline albuminuria when compared with the species-specific quantitative immunoassay, the cut-off value of 0.2 for UP/C resulted in an unacceptable number of false negatives[1] (Table 4). Therefore, the UP/C is not recommended as a routine screen-

Table 4. Canine and Feline Urine Sample Results for UP/C (390 Canine Samples, 217 Feline Samples)

	Canine UP/C ≥ 0.2	Canine UP/C ≥ 0.5	Feline UP/C ≥ 0.2	Feline UP/C ≥ 0.4
Sensitivity	47.9%	28.7%	32.7%	2.04%
Specificity	98.6%	99.7%	90.8%	99.2%
PPV*	91.8%	96.4%	74.4%	66.7%
NPV†	85.6%	81.5%	62.1%	55.1%

Abbreviations: UP/C, Urine protein/creatinine ratio; PPV, positive predictive value; NPV, negative predictive value.

*The animal is truly positive given a positive test.

†The animal is truly negative given a negative test.

ing test for urine albumin in dogs or cats, especially for low levels of albuminuria.[1]

Based on longitudinal testing results in dogs with X-linked hereditary nephropathy, the UP/C must change by at least 35% at high UP/C values (near 12) and 80% at low UP/C values (near 0.5) to demonstrate a significant difference between serial values.[21] One measurement was found to reliably estimate the UP/C when the values were <4, but 2 or more determinations were necessary to reliably estimate the UP/C when values were higher than 4.[21]

Implications of Proteinuria/Albuminuria

In addition to the classic complications of heavy proteinuria (hypoalbuminemia, edema, ascites, hypercholesterolemia, hypertension, and hypercoagulability), there is increasing evidence in laboratory animals and human beings that proteinuria can cause glomerular and tubulointerstitial damage and result in progressive nephron loss. Plasma proteins that have crossed the glomerular capillary wall can accumulate within the glomerular tuft and stimulate mesangial cell proliferation and increased production of mesangial matrix in human beings.[22] In addition, excessive amounts of protein in the glomerular filtrate can be toxic to human tubular epithelial cells and can lead to interstitial inflammation, fibrosis, and cell death by several mechanisms.[23-25] These mechanisms include tubular obstruction, lysosomal rupture, complement-mediated and peroxidative damage, and mesenchymal cell transformation, as well as increased production of cytokines and growth factors.

Evidence linking proteinuria to progression of renal disease is beginning to accumulate in dogs and cats. For example, in dogs with naturally occurring CKD, the relative risk of a uremic crisis or mortality was 3 times greater in dogs with UP/C >1.0 compared with dogs with UP/C <1.0.[26] Further, the risk of an adverse outcome was 1.5 times greater for every 1 unit increase in UP/C and the decline in renal function was greater in dogs with higher UP/C.[26] In cats with naturally occurring CKD, relatively mild proteinuria (UP/C >0.4) was a negative predictor of survival.[27] Increasing proteinuria was associated with increasing serum creatinine concentrations and increasing systolic blood pressure, and the UP/C was independently associated with mortality.[27] Individual nephron hyperfiltration and proteinuria have been documented in dogs with the remnant kidney model of renal failure[28]; however, treatments that have slowed the functional decline and/or histologic changes associated with this model have had variable effects on proteinuria. Angiotensin-converting enzyme inhibition and ω-3 fatty acid supplementation have decreased proteinuria and slowed progression[29,30]; however, calcium blockade treatment resulted in increased mesangial cell proliferation despite decreasing proteinuria.[29] Other treatments, such as reduction of dietary phosphorus, decreased renal disease progression in remnant kidney dogs but had no effect on proteinuria. In dogs with experimentally induced immune complex GN, treatment with a thromboxane synthetase inhibitor decreased proteinuria and attenuated the development of glomerular lesions but had no effect on established lesions.[31,32] More recently, reduction of proteinuria via ACE inhibition (enalapril) was associated with slowed progression of renal disease in dogs with 2 different types of naturally occurring glomerulopathies.[33,34]

Summary

Assessment of proteinuria is an important part of the complete urinalysis. Traditional screening tests for proteinuria (dipstick and SSA tests) lack sensitivity and have poor specificity, especially in cats. Species-specific urine albumin assays are quite sensitive and are appropriate for confirming and screening for proteinuria in dogs and cats, respectively. Proteinuria of renal origin is persistent and associated with a normal (noninflammatory, nonhemorrhagic) urine sediment. Proteinuria of suspected renal origin should be quantitated and monitored with the UP/C. Reducing renal proteinuria is an important treatment goal because of the association between proteinuria and progression of disease.

References

1. Lyon SD, Sanderson MW, Vaden SL, et al: Comparison of dipstick, sulfosalicylic acid, urine protein creatinine ratio, and

species-specific ELISA methodologies for detection of albumin in canine and feline urine samples. J Am Vet Med Assoc 236:874-879, 2010
2. Vaden SL, Pressler BM, Lappin MR, et al: Effects of urinary tract inflammation and sample blood contamination on urine albumin and total protein concentrations in canine urine samples. Vet Clin Pathol 33:14-19, 2004
3. Lees GE, Jensen WA, Simpson DF, Kashtan CE: Persistent albuminuria precedes onset of overt proteinuria in male dogs with X-linked hereditary nephropathy [abstract]. J Vet Intern Med 16:353, 2002
4. Lees GE, Brown SA, Elliott J, et al: Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (small animal). J Vet Intern Med 19:377-385, 2005
5. Kruger M, Gordjani N, Burghard R: Post exercise albuminuria in children with different duration of type-1 diabetes mellitus. Pediatr Nephrol 10:594-597, 1996
6. Hebert LA, Spetie DN, Keane WF: The urgent call of albuminuria/proteinuria: heeding its significance in early detection of kidney disease. Postgrad Med 110:79-96, 2001
7. Gerstein HC, Mann JF, Yi Q, et al: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. J Am Med Assoc 286:421-426, 2001
8. Osterby R, Hartmann A, Nyengaard JR, Bangstad HJ: Development of renal structural lesions in type-1 diabetic patients with microalbuminuria. Observations by light microscopy in 8-year follow-up biopsies. 440:94-101, 2002
9. Bakris GL: Microalbuminuria: what is it? Why is it important? What should be done about it? 3:99-102, 2001
10. Pinto-Sietsma SJ, Janssen WM, Hillege HL, et al: Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. J Am Soc Nephrol 10:1882-1888, 2000
11. Keane WF, Eknoyan G: Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis 33:1004-1010, 1999
12. Grauer GF, Oberhauser EB, Basaraba RJ, et al: Development of microalbuminuria in dogs with heartworm disease [abstract]. J Vet Intern Med 16:352, 2002
13. Vaden SL, Jensen WA, Longhofer SL, Simpson DF: Longitudinal study of microalbuminuria in soft-coated wheaten terriers [abstract]. J Vet Intern Med 15:300, 2001
14. Pressler BM, Vaden SL, Jensen WA: Prevalence of microalbuminuria in dogs evaluated at a referral veterinary hospital [abstract]. J Vet Intern Med 15:300, 2001
15. Whittemore JC, Jensen WA, Prause L, et al: Comparison of microalbuminuria, urine protein dipstick, and urine protein creatinine ratio results in clinically ill dogs [abstract]. J Vet Intern Med 17:437, 2003
16. Pressler BM, Proulx DA, Williams LE, et al: Urine albumin concentration is increased in dogs with lymphoma or osteosarcoma [abstract]. J Vet Intern Med 17:404, 2003
17. Lees GE, Willard MD, Dziezyc J: Glomerular proteinuria is rapidly but reversibly increased by short-term prednisone administration in heterozygous (carrier) female dogs with X-linked hereditary nephropathy [abstract]. J Vet Intern Med 16:352, 2002
18. Gary AT, Cohn LA, Kerl ME, Jensen WA: The effects of exercise on urinary albumin excretion in dogs. J Vet Intern Med 18:52-55, 2004
19. McCaw DL, Knapp DW, Hewett JE: Effect of collection time and exercise restriction on the prevention of urine protein excretion, using urine protein/creatinine ratio in dogs. Am J Vet Res 46:1665-1669, 1985
20. Grauer GF, Thomas CB, Eicker SW: Estimation of quantitative proteinuria in the dog, using the urine protein-to-creatinine ratio from a random, voided sample. Am J Vet Res 46:2116-2119, 1985
21. Nabity MB, Boggess MM, Kashten CE, et al: Day-to-day variation of the urine protein:creatinine ratio in female dogs with stable glomerular proteinuria caused by X-linked hereditary nephropathy. J Vet Intern Med 21:425-430, 2007
22. Jerums G, Panagiotopoulos S, Tsalamandris C, et al: Why is proteinuria such an important risk factor for progression in clinical trials? Kidney Int 52:S87-S92, 1997
23. Tang S, Sheerin NS, Zhou W, et al: Apical proteins stimulate complement synthesis by cultured human proximal tubular epithelial cells. J Am Soc Nephrol 10:69-76, 1999
24. Abrass CK: Clinical spectrum and complications of the nephrotic syndrome. J Investig Med 45:143-153, 1997
25. Eddy A: Role of cellular infiltrates in response to proteinuria. Am J Kidney Dis 37:S25-S29, 2001
26. Jacob F, Polzin DJ, Osborne CA, et al: 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 226:393-400, 2005
27. Syme HM, Markwell PJ, Pfeiffer D, et al: Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. J Vet Intern Med 20:528-535, 2006
28. Brown SA, Finco DR, Crowell WA, et al: Single-nephron adaptation to partial renal ablation in the dog. Am J Physiol 258: F495-F503, 1990
29. Brown SA, Walton CL, Crawford P, Bakris GL: Long-term effects of antihypertensive regimes on renal hemodynamics and proteinuria. Kidney Int 43:1210-1218, 1993
30. Brown SA, Brown CA, Crowell WA, et al: Beneficial effects of chronic administration of dietary ω-3 polyunsaturated fatty acids in dogs with renal insufficiency. J Lab Clin Med 131:447-455, 1998
31. Longhofer SL, Frisbie DD, Johnson HC, et al: Effects of thromboxane synthetase inhibition on immune complex glomerulonephritis. Am J Vet Res 52:480-487, 1991
32. Grauer GF, Frisbie DD, Longhofer SL, Cooley AJ: Effects of a thromboxane synthetase inhibitor on established immune complex glomerulonephritis in dogs. Am J Vet Res 53:808-813, 1992
33. Grodecki KM, Gains MJ, Baumal R, et al: Treatment of X-linked hereditary nephritis in Samoyed dogs with angiotensin converting enzyme (ACE) inhibitor. J Comp Path 117:209-225, 1997
34. Grauer GF, Greco DS, Getzy DM, et al: Effects of enalapril vs placebo as a treatment for canine idiopathic glomerulonephritis. J Vet Int Med 14:526-533, 2000