Microalbuminuria Positive Results – Causes and Intervention Points in Dogs and Cats

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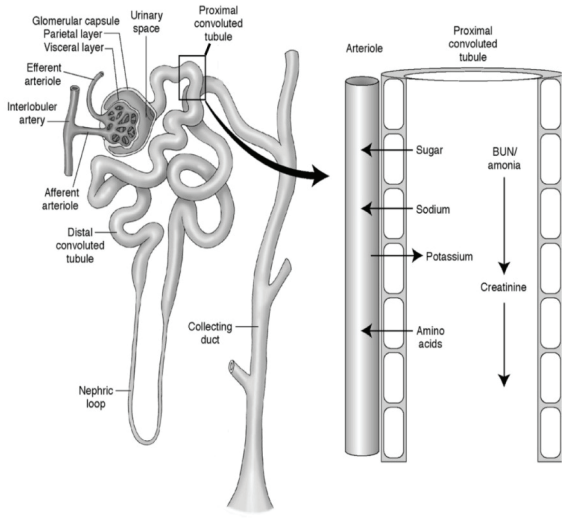
The glomerulus performs the first step in renal function, which is to filter the blood. In healthy animals, very little protein can filter through the glomerulus, preventing protein loss into the urine.

Most plasma proteins are relatively large and contain electrical charges that inhibit filtration across the glomerulus. In healthy pets, a very small amount of albumin is filtered across the glomerulus, but nearly all of the albumin is reabsorbed by the proximal tubule, so that next to no albumin is excreted. The integrity of the glomerular barrier ensures that very little albumin is lost into the eventual urine.



When excess protein is detected with a urine reagent strip, urinary protein-to-creatinine ratio (UPC), or microalbuminuria (MA) testing, the clinician must decide if it is originating from the kidney. The causes for proteinuria can be classified into pre-renal, primary renal, and post- renal categories (See Table I).

An example of pre-renal proteinuria includes entry of hemoglobin (systemic hemolysis) and myoglobin (muscle trauma) into the urine since these are small molecular weight proteins that readily filter through the glomerulus. Hypertension is another cause of pre-renal proteinuria. High systemic blood pressure can increase glomerular capillary pressure and transglomerular forces that favor proteinuria/albuminuria. Amelioration of systemic hypertension often decreases the amount of proteinuria detected. Occasionally, fever/inflammatory disease can lead to pre-renal proteinuria.

The cause for post-renal proteinuria may be obvious after detailed review of the history, physical examination, urinalysis, and abdominal imaging (radiograph and/or ultrasound). The most common causes for post-renal proteinuria include: trauma, infection, inflammation, neoplasia, or stones in the lower urinary tract.

Table I: Cause of Microalbuminuria: Conditions or diseases that may contribute to proteinuria: A variety of systemic and renal disease processes can decrease glomerular barrier integrity so that there is less resistance to passage of plasma proteins (mostly albumin) into Bowman's space.

	Cat[1]	Dog
Pre- renal	Multiple myeloma Systemic hypertension Drug reactions Acute pancreatitis Hyperthyroidism (seizures, heat stroke, fever, extreme exercise, congestive heart failure)	Multiple myeloma Systemic hypertension Drug reactions Acute pancreatitis Hyperadrenocorticism (seizures, heat stroke, fever, extreme exercise, congestive heart failure)
Renal	Acute renal failure Chronic renal failure **Glomerulopathy** Acute pancreatitis Viral disease Drug reactions Systemic hypertension Diabetes mellitus Hyperthyroidism Endocarditis Exogenous steroid use Any severe inflammatory disease, neoplasia, infectious or immune-mediated disease	Acute renal failure Chronic renal failure Glomerulopathy Acute pancreatitis Viral disease Drug reactions Systemic hypertension Diabetes mellitus Hyperadrenocorticism Immune-mediated disease (systemic lupus erythema-tosus, immune-mediated hemolytic anemia, polyarthri-tis, hepatitis) Tick-borne disease Leptospirosis Endocarditis Heartworm disease Exogenous steroid use severe inflammatory disease
Post-Renal	Lower urinary tract disease Reproductive tract disease	Lower urinary tract disease Reproductive tract disease

Once pre-renal and post-renal sources of proteinuria have been ruled out, it is important to decide if proteinuria is due to primary kidney disease or a secondary process. The hallmark of renal-origin proteinuria (regardless of specific disease) is the documentation of excess protein with a non-inflammatory urinary sediment (< 10 RBC/HPF, < 5 WBC/HPF). Glomerular proteinuria can be associated with increased excretion of casts, especially hyaline casts.

Albumin is the protein measured semi-quantitatively on urinary reagent strips. In order to have a positive reaction, as much as 30 mg/dL is required. The reagent strip reactions should be confirmed by some combination of SSA precipitation, UPC, and MA. The degree of urine concentration (specific gravity) influences the protein concentration and the intensity of the colorimetric reaction on the pad.

The documentation of renal proteinuria (urine reagent strip, UPC, or MA) raises concern about ongoing glomerular damage that could result in a progressive loss of renal function. **Renal proteinuria can be detected before increased blood concentration of surrogates for declining glomerular filtration rate (GFR), such as increasing concentrations of creatinine, SDMA, or decreases in urinary specific gravity (USG), occur.** Renal proteinuria can exist in the face of normal or reduced GFR. As kidney disease

advances, severe reductions in GFR can result in decreased renal proteinuria. The magnitude of proteinuria and trends for increasing or decreasing proteinuria over time are important considerations in determining how aggressive the diagnostic approach and/or treatment should be.

Albuminuria is a diagnostic marker that can support the presence of a renal disease in which glomerular permeability has been altered. Additionally, persistent albuminuria appears to promote progressive chronic kidney disease (CKD) through a variety of mechanisms beyond the scope of this white paper. Microalbuminuria (MA) is defined as the finding of 1 to 29 mg/dL of albumin. Normal dog and cat urine contains < 2.0 mg/dL or < 2.5 mg/dL of albumin, respectively, when measured by species specific ELISA methods. Urine is diluted to a standard USG prior to the measurement of MA, in order to remove the effect of highly concentrated urine on results. MA test results for dogs and cats are reported as negative (< 2.5 mg/dL) or with varying degree of positive reactions (mild, moderate, severe) based on the degree of color reaction on the reagent strip. (Test kits designed to detect human MA are not accurate in the measurement of dog or cat MA)

MA develops before overt proteinuria is detected on reagent strips and before UPC exceeds 0.5, and therefore is an extremely sensitive test for the evaluation of glomerular function. When pre-renal and post renal causes of proteinuria have been excluded, a positive MA test result means that the permeability of the glomerulus is altered due to either primary kidney disease or a systemic process. It is recommended to repeat MA testing two weeks following the finding of an initial MA positive result to determine if the abnormality is persistent.

Persistent MA in the dog or cat does not imply that there will be progression to advancing stages of CKD, although that does happen in some patients. Early reports suggested that persistent MA status was mostly associated with kidney dysfunction in animals, but subsequent studies found that many of these patients had systemic diseases responsible for MA, rather than primary renal disease. Higher morbidity and all-cause mortality rates can be found in patients with persistent MA. Greater than 50% of critically ill dogs have been reported with MA.[2]

About 50% of dogs with persistent MA have been associated with underlying infectious, inflammatory, neoplastic, or metabolic diseases (hyperadrenocorticism, diabetes mellitus, hyperthyroidism) that could be associated with alterations in glomerular permeability or secondary glomerular injury, such as with immune complex or amyloid deposition. About 30% of dogs with persistent MA will be diagnosed with primary renal disease (progressive and non-progressive), and the remaining 20% will not have an association or cause that can be identified.

The repeatable finding of MA in a patient with no identifiable pre-renal or post-renal conditions is a tipping point for further investigation. UPC should be measured to see if borderline (0.2 to 0.4) or abnormal (> 0.4 cat and >0.5 dog) proteinuria is documented. If MA is positive and UPC is positive, UPC is followed in the future. If MA is positive and UPC is normal, MA should be followed to see if the magnitude of MA is increasing over time. A low-level of MA that is not increasing may reflect previous damage or a disease process that is no longer active. A low-level of MA that increases over time is a cause for concern that a primary or secondary disease process may be progressively damaging the kidney.

MA positive status, after excluding pre-renal and post-renal causes, can be an entry point for classification into International Renal Interest Society (IRIS) CKD Stage 1. The presence of MA and some combination of further escalation in magnitude of MA, sub-maximally concentrated urine, escalating serum creatinine (even if within the reference range), increased SDMA, and/or renal imaging abnormalities provide compelling data supporting categorization to IRIS Stage 1 CKD. In general, cats with advancing CKD have less proteinuria than dogs.

The finding of MA during routine clinical visits offers the clinician a chance to investigate and diagnose systemic and primary renal disease processes before the patient is clinically ill, and before UPC is increased. Once MA exceeds 29 mg/dL, there is no longer value in future measurement of MA. At that point, continued follow-up should be measured with UPC. IRIS recommends UPC as part of their staging system, and includes MA as a possible entry point into IRIS stage 1.

It has not yet been determined if treatments for IRIS CKD Stage 1 that are designed to lower MA with diets or drugs should be prescribed. In human medicine, controlling MA is a goal in patients with diabetes mellitus and systemic hypertension. Variability in MA over the same day or between days in the same patient has not been studied, as it has with UPC in dogs.

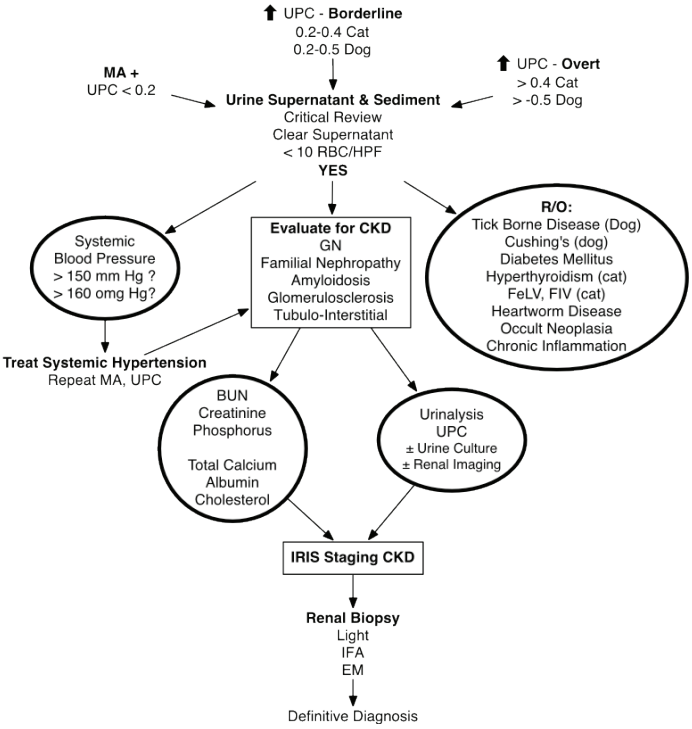
Urine testing for the presence of microalbuminuria should be considered for the following circumstances:

- Screening apparently healthy dogs that are ≥ 6 years old and cats that are ≥ 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.
- Animals with chronic illnesses that may be complicated by proteinuric nephropathies (e.g., systemic lupus).[3]

As a general rule, a urinalysis that includes an initial, semi-quantitative evaluation of proteinuria should be performed on every dog or cat presented for clinical evaluation, in which routine blood work is indicated. Detection of proteinuria should first prompt a diligent search for any underlying disease. If proteinuria is persistent and/or does not resolve after treatment of the underlying disease, then further steps to monitor, treat, or pursue additional diagnostics are indicated.[4]

Summary

Microalbuminuria testing may allow earlier detection of reduced GFR and localization of damage to a particular nephron segment, and is required for diagnosis or exclusion of some causes of kidney injury.[5] Overall documentation of MA is an important screening and diagnostic tool to evaluate the geriatric and ill patient for underlying renal disease, or other disease concerns since the presence of low levels of protein in the urine may be the first indication of serious underlying systemic disease.



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[3] Brown, Scott, Surdyk, Katie, Brown, Cathy, THE IMPORTANCE OF PROTEINURIA AND MICROALBUMINURIA, IRIS Website.
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[5] Pressler, Barrak, M. Clinical Approach to Advanced Renal Function Testing in Dogs and Cats, Veterinary Clinics of North America: Small Animal Practice, Volume 43, Issue 6, November 2013.