PROTEINURIA AND MICROALBUMINURIA: WHAT'S ALL THE FUSS ABOUT?

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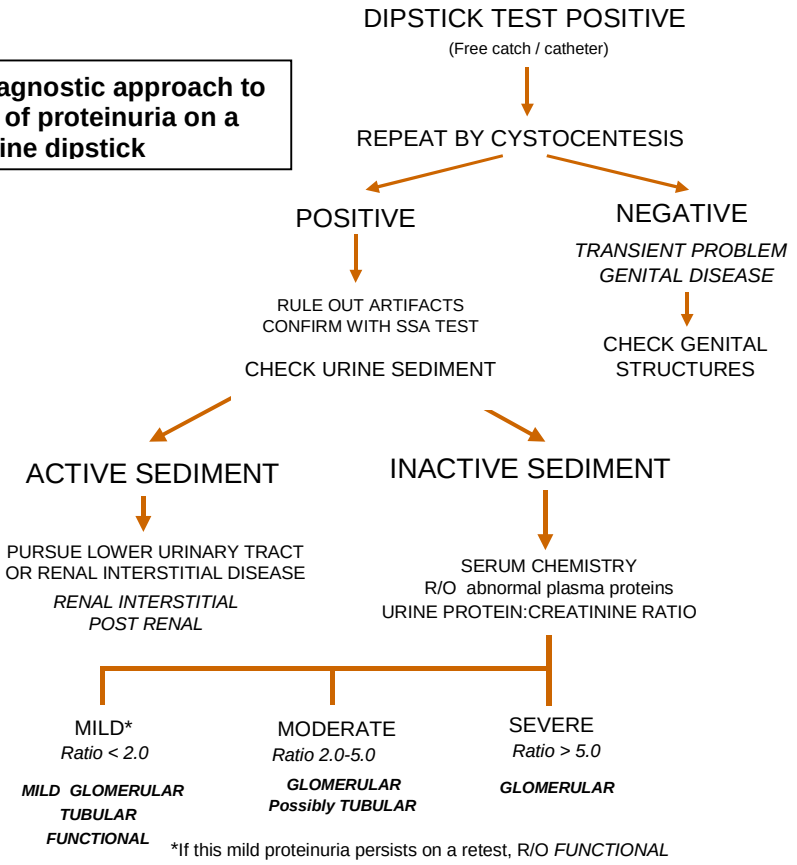
Proteinuria–an excessive amount of protein in urine–has lately come under increased scrutiny because of emerging insights into its role as a marker for, and perhaps direct mediator of, progressive renal disease in dogs and cats. Proteinuria may be detected as an incidental finding during routine laboratory screening of pre-operative, geriatric and ill patients or an astute clinician may suspect its presence and test specifically for it. Proteinuria is often an important clinical finding and should prompt a sequence of diagnostic and sometimes therapeutic steps that have been well described in recent textbooks and articles. In dogs with chronic renal failure (CRF) it has recently been shown that proteinuria at the time of initial CRF diagnosis is associated with a greater risk of progression of renal failure, development of uraemic crises and death. Last year, the American College of Veterinary Internal Medicine published a consensus statement on assessment and management of proteinuria in dogs and cats.

An initial diagnostic approach to detection of proteinuria on a urine dipstick



*If this mild proteinuria persists on a retest, R/O *FUNCTIONAL*

Much recent attention has been focussed upon the potential value of detecting persistent, *mild* proteinuria. This is partly because detection of mild proteinuria may serve as a useful early warning system for detection of renal lesions (and perhaps non-renal diseases) and–more pragmatically– because sensitive and specific in-practice diagnostic test kits for detection of small amounts of canine and feline urine albumin have recently become commercially available to veterinarians in many parts of the world (E.R.D.-HealthScreen® Canine and Feline Urine Tests; Heska).

Like azotaemia, proteinuria can be categorized as prerenal, renal or post renal. Renal proteinuria can be further categorized as functional, glomerular, tubular or interstitial. Glomerular proteinuria is by far the most important category and arises as a consequence of lesions that change the permselectivity of the glomerular filter and allow excessive protein (mostly albumin) to pass through the filter and into the filtrate. These lesions often arise as a consequence of immune complex deposition and may reflect systemic inflammatory, infectious or neoplastic disease. Glomerular proteinuria can vary in magnitude from very mild to extremely severe depending on the extent of glomerular damage and other factors at the time of diagnosis. Severe glomerular proteinuria may lead to hypoalbuminaemia, hypercholesterolaemia and sometimes oedema (the so-called nephrotic syndrome). It has been suggested that proteinuria may, in-and-of-itself, be harmful, partly because renal tubular cells sustain damage in the process of resorbing excessive protein from the tubular lumen. Whether persistent *mild* proteinuria, for example at concentrations well below the limit of detection of conventional urine dipsticks, can be directly harmful to dogs and cats is unknown.

The in-practice diagnostic test kits mentioned above are semi-quantitative immunoassays. Separate kits are available for detection of canine and feline urine albumin, because the target proteins of these two species differ somewhat. To take account of differences in urine concentration, it is recommended that urine samples be diluted to a specific gravity of 1.010 prior to testing. In addition, quantitative immunoassays for canine and feline urine albumin are available through some veterinary clinical laboratories. Results of these quantitative tests are often expressed as urine albumin:creatinine ratios.

The term ***albuminuria*** is used in preference to the more generic ‘proteinuria’ when excessive urinary albumin is detected using one of these quantitative or semi-quantitative immunoassays. The term ***microalbuminuria*** (MA) is used to describe urine albumin content that is abnormally high, but below the limit of detection of conventional urine dipsticks. Conversely, ***overt albuminuria*** describes dipstick-detectable levels of albuminuria.

There is strong evidence that MA can be used effectively to predict onset of *human* diabetic nephropathy and help guide cost-effective management. MA is also a useful indicator of microvascular damage in humans with essential hypertension. Direct application of these findings to canine and feline medicine is difficult because essential hypertension and diabetic nephropathy are rare or poorly-characterized in dogs and cats. MA is prevalent in human patients with a variety of chronic inflammatory and neoplastic disorders, tending to be more severe in patients with active, extensive, or severe disease. Despite this, screening of the human population for MA has not found favour and is not practiced.

MA has been reported to be a reliable, early marker of developing glomerulopathy in male dogs with X-linked familial nephropathy. The advantage of MA detection over conventional urine protein:urine creatinine ratio (UPC) measurement would have been much smaller, or perhaps non-existent, if a lower UPC cut-off value had been chosen to define proteinuria (UPC $\geq$ 2 was used). In September 2005, use of semi-quantitative test kits for detection of MA in Soft-coated Wheaten terriers (SCWT) was being strongly advocated in the UK by the Wheaten Health Initiative (http://www.wheaten-health-initiative.co.uk/erd.html). Whether use of semi-quantitative test kits to monitor SCWTs will offer any advantages over UPC remains to be determined, despite some preliminary research in this area.

It was recently recommended that apparently healthy dogs $\geq$ 6 years and cats $\geq$ 8 years be tested for MA when conventional evaluations for proteinuria are negative and a more sensitive test is, for some reason, desired by veterinarian or owner. This recommendation, which relates to dogs and cats not known to be at particular risk for developing glomerular disease, seems to be ahead of our current understanding of the possible health benefits of MA screening. It may encourage widespread screening for MA, which may, in turn, lead to a great deal of possibly unwarranted, expensive and potential harmful 'secondary' diagnostic testing. Screening apparently healthy pets for MA seems to fulfil very few of the necessary criteria for a good screening test, as described by Grimes and Schulz in 2002.

Not enough has been published in peer-reviewed journals on the amount of albumin to expect to find in the urine of healthy dogs and cats of different ages, breeds and sexes. This is disconcerting, because a strikingly high proportion of apparently healthy *older* cats and dogs have been categorized as microalbuminuric based on limited work that has led to the currently accepted upper limit of normal (72.7% of cats 16-23 years old and 49.1% of dogs > 12 years) . It is argued that older animals positive for MA are very likely to have renal lesions. Yet the significance of these putative lesions to pet and pet owner is presently unclear; lesions may be transient, persistent, or progressive. It seems possible that the currently accepted

upper limit of normal for urine albumin is inappropriate for use in geriatric animals. Controlled, prospective studies that follow 'microalbuminuric' geriatric patients to determine whether or not MA is a useful marker for future morbidity and mortality are needed. After that, randomized studies to determine whether screening for MA actually leads to happier owners and healthier pets will be needed (what good is screening, if interventions do not lead to better quality or quantity of life?). The medical and ethical standards of screening need to be particularly high because every adverse outcome of screening is iatrogenic and preventable.

Evidence that MA is a useful predictor of the presence of serious inflammatory, infectious, metabolic and neoplastic disease in dogs and cats is weak. For example, in one study, 56.3% of 572 microalbuminuric dogs were subsequently found to have infectious, inflammatory, neoplastic, metabolic or other diseases. A serious flaw in this work was that veterinarians were instructed to 'go back' and actively search for something wrong with the microalbuminuric dogs but *not* in a control group of non-albuminuric dogs of similar age, breed and sex. Indeed, it would have been desirable to 'blind' participating veterinarians to the urine albumin test results to prevent them from looking harder for abnormalities in dogs known to be positive. Many of the reported findings in MA pets may have been trivial or readily diagnosed on careful physical examination.

As a profession, we are still near the beginning of our efforts to understand the meaning of MA in dogs and cats. The current dearth of reliable research data will be progressively remedied as full studies pass through peer-review. Some of the studies currently being cited in support of the screening use of MA detection kits are weak and may not undergo or withstand peer-review. Human medicine is littered with examples of well-intended but clumsy and ultimately harmful use of screening tests. The potential health benefits of widespread MA screening of apparently healthy dogs and cats remain to be established. It would be premature to recommend such screening for routine use in practice.

Further Reading

Grimes, DA; Schulz, KF. Uses and abuses of screening tests. Lancet 2002; 359: 881-884.

Jacob, F; Polzin, DJ; et al. Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure. Journal of the American Veterinary Medical Association 2005; 226: 393-400.

Lees, GE; Brown, SA; et al. Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (small animal). Journal of Veterinary Internal Medicine 2005; 19: 377-385.