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INTRODUCTION

Renal disease leading to renal insufficiency and failure is an extremely common finding in ageing cats. Good epidemiological studies are lacking to determine the true prevalence of chronic kidney disease (CKD) but estimates suggest 1 in 3 cats over the age of 12 have some form of renal insufficiency.

We recently reported on a prospective clinical study where we recruited healthy cats over the age of 9 years that were normal on physical examination and routine clinical biochemistry testing. These cases were followed for 12 months and of the 98 cats with this length of follow-up, 29 (29.6%) had plasma creatinine concentrations outside of our laboratory reference range and met the diagnostic criteria of having CKD (Jepson 2008).

To reach this stage of insufficiency (non-azotaemic but inadequate urinary concentrating ability; IRIS stage I) or mild failure (mildly azotaemic; plasma creatinine concentration 140 to 250 umol/l; IRIS stage II) we would estimate a loss of 66 to 75% of the 400 000 functioning nephrons has occurred.

The intact nephron hypothesis (Brenner et al., 1982) would predict that intra-renal mal-adaptation to the loss of this number of functioning nephrons would lead to glomerular hypertrophy, hyperfiltration, glomerular capillary hypertension, proteinuria and progressive renal injury in the absence of continued insult from the primary disease process(es).

EXPERIMENTAL STUDIES IN THE CAT

The intact nephron hypothesis was based on experimentally nephrectomised rats where progressive renal injury is predictable and rapid. The same does not appear to be true in cats, where the process is slow such that decrements in glomerular filtration rate (GFR) can not be detected in partially nephrectomised cats up to 12 months after reduction in renal mass.

Nevertheless, experimental cats do demonstrate glomerular hyperfiltration, glomerular capillary hypertension and increased urinary protein loss (Brown & Brown 1995). Furthermore, histopathological lesions compatible with progressive renal injury are seen in remnant kidneys from this model.

PROGRESSION OF NATURALLY OCCURRING RENAL DISEASE IN CATS

The clinical presentation of severe ‘end-stage’ CKD in cats is not uncommon in clinical practice suggesting that progressive renal injury does occur. However, the patterns of progression are highly variable. Some cats remain in a mildly azotaemic ‘compensated’ state of CKD for years and die of another disease rather than progressive CKD. Other cats remain in stable compensated CKD for a period and then apparently suddenly deteriorate in a step-wise fashion to develop a uremic crisis, suggestive of recurrence of an extrinsic disease process causing loss of remaining functioning nephrons. Nevertheless, there is a sub-group of cats where gradual progressive loss of functioning nephrons occurs and so-called linear progression of CKD is observed. In a longitudinal study of 55 cats with naturally occurring CKD, 60% showed no evidence of progression, 25% showed stepwise progression and 15% showed linear progression [Elliott et al., 2003]. Part of the inability to detect intrinsic progressive renal injury may result from the reliance on serial measurement of plasma creatinine concentration rather than repeated measurement of GFR to detect functional progression.

ROLE OF PROTEINURIA IN PROGRESSIVE RENAL INJURY

In human patients with naturally occurring CKD, proteinuria is an independent risk factor for progressive loss of renal function. This has been best documented in diabetic patients where interventions to reduce urinary protein loss effectively slow progression of diabetic nephropathy, a leading indication for renal transplantation. Further studies have documented a beneficial effect of controlling mean arterial blood pressure (MABP) to lower levels than the previously recommended targets in CKD patients. The higher the degree of proteinuria, the greater the additional benefit obtained, in slowing the rate of decline in GFR, by reducing MABP to new lower target levels.

It is now appreciated that leakage of protein across the glomerulus can trigger a sequence of events that leads to tubulointerstitial injury [Remuzzi & Bertani 1998]. If the filtered load of protein overwhelms the proximal tubular absorptive mechanisms, activation of inflammatory cascades occurs, resulting in tubular injury and interstitial inflamm-
tion and fibrosis. The cellular and sub-cellular mechanisms involved in these processes are being unraveled. Nevertheless, this response to proteinuria can be reduced by drug treatments that inhibit glomerular protein leakage.

**RISK FACTORS FOR PROTEINURIA IN CATS WITH RENAL DISEASE**

In our clinical practice, many cats with stable CKD, which are IRIS stage II or III (serum creatinine 140 to 440 umol/l), will be non-proteinuric (urine protein to creatinine (UPC) ratio of <0.2) or borderline proteinuric (UPC ratio of 0.2 to 0.4) and the minority are proteinuric (UPC>0.4). Risk factors for proteinuria include serum creatinine concentration (the higher the creatinine the more likely the cat is to be proteinuric) and systolic arterial blood pressure (the higher the blood pressure the more likely the cat is to be proteinuric) [Syme et al 2006]. Furthermore, proteinuria, as assessed by UPC, worsens with decrements in renal function over time although no evidence has been found for a worsening of proteinuria preceding the deterioration in renal function. However, the interpretation of changes in UPC in the face of loss of functioning nephrons is complex as the tendency for protein loss to increase will be offset by the reduced number of nephrons. Finally, proteinuria is also predictive of development of azotaemia in apparently healthy aged cats (Jepson 2008).

**INFLUENCE OF PROTEINURIA ON SURVIVAL OF CATS WITH RENAL DISEASE**

Two studies of naturally occurring CKD in cats have demonstrated that proteinuria is a predictive indicator of long-term survival [Syme et al., 2006; King et al., 2006]. In the first study involving 117 cats, UPC proved to be an independent predictor of survival when assessed by multivariate logistic regression analysis in combination with age and serum creatinine concentration [Syme et al., 2006]. This study used all-cause mortality as the end point and 47% of the cats included in the study reached this end point. The second study was a randomised controlled clinical trial involving 193 cats designed to examine the effect of benazepril on progression of CKD (King et al., 2006). This study showed an inverse correlation between initial UPC ratio and survival time in the placebo group.

**TREATMENT OF CATS WITH ANTI-PROTEINURIC DRUGS – EFFECT ON SURVIVAL**

From the above discussion there appears to be reasonable evidence that mild proteinuria is predictive of reduced survival time in cats with CKD. It would seem logical that a reduction in proteinuria might be protective of progressive renal injury, even when proteinuria is very mild. At the present time definitive data to support this assumption have not been produced.

Angiotensin converting enzyme inhibitors have been shown to reduce glomerular capillary pressure in cats with surgically reduced renal mass [Brown et al., 2001]. The BENRIC study showed that benazepril at a dose rate of 0.5 to 1.0 mg/kg reduced UPC ratio in all cats receiving the active drug regardless of their initial UPC ratio at entry to the study. Nevertheless, no overall significant beneficial effect of benazepril treatment on survival was observed in this study [King et al., 2006]. Thus, the possibility that proteinuria is a marker of progressive CKD, rather than the cause, needs to be considered.

**REFERENCES**


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