

Renal Fibrosis in Cats

Scott Brown, Athens, GA, USA

Chronic kidney disease (CKD) is common in cats.^{1,2} The majority of affected cats exhibit renal lesions that are mostly confined to the tubulointerstitial compartment. Primary glomerular diseases have been described in cats,^{3,4} however in most cases, glomerular involvement is only mild, and presumably secondary.^{5,6} Renal lesions of feline CKD are characterized as interstitial fibrosis, interstitial inflammation, and tubular degeneration.^{5,6}

It was presumed previously that these tubulointerstitial changes were secondary and reflective of the final common pathway of end-stage CKD. With the exception of acute kidney injury (AKI), primary renal diseases affect a very small number of cats, occur in only specific breeds, or produce histologic changes that are not consistent with the pathological changes observed in most cats with spontaneous CKD. ranges (i.e., 1.4 and 1.6 mg/dl in dogs and cats, respectively).⁸

Tubulointerstitial lesions are already present in cats with IRIS CKD Stage 2 and the severity of these changes are positively correlated to the IRIS CKD stage.^{5,6} Even in IRIS Stage 2 and 3 CKD, the lesions are distributed segmentally,^{5,6} affect only a portion of the kidney, and suggest a localized, rather than generalized, insult. These observations are consistent with the hypotheses that i) tubulointerstitial changes are reflective of a common primary insult in cats or ii) multiple types of insults activate a common response to injury in cats.

Much of the research in feline CKD to date has focused on progression of the disease in cats with preexisting CKD, rather than identifying the primary or initiating renal insult. Many of the factors implicated in progression of CKD in cats, including proteinuria, hyperphosphatemia, systemic hypertension, anemia, hypoxia, chronic inflammation, and aging, are viewed as promoters of interstitial fibrosis.^{7,8} While existing evidence suggests these factors may contribute to the progression of renal injury and fibrosis in established CKD in cats, it is also plausible that one or more of them could play a role in the initiation of renal injury in this species.

For example, a longitudinal study demonstrated that blood pressure increases with age in both healthy and CKD cats⁹ and another study demonstrated a correlation between age and blood pressure in cats.¹⁰ These findings could be interpreted as evidence that hypertension precedes, and perhaps causes, CKD in some cats.

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In people, CKD is accompanied by increased blood concentrations of a phosphaturic hormone (fibroblast growth factor-23 or FGF-23) and a deficiency of Klotho, its co-receptor.^{11,12} These changes could be important promoters or initiators of renal fibrosis.¹³ In cats, increased FGF-23 concentrations predict the development of azotemia in geriatric individuals,¹⁴ suggesting this might play a role in the initiation of renal fibrogenesis in cats.

In experimental studies, a single episode of renal ischemia induced chronic renal structural changes in cats that paralleled findings in spontaneous feline CKD.¹⁵ It is plausible that ischemia, or multiple bouts of ischemic AKI, could initiate CKD in cats.¹⁵ A variety of host factors and conditions could contribute to acute or chronic bouts of renal hypoxia in cats, for example, anemia, transient insults to renal hemodynamics (such as episodes of dehydration, hypotension or stress-induced renal vasoconstriction), increases in tubular metabolic activity associated with fluctuations in dietary intake, exposure to agents with vasoactive properties such as NSAIDs, or intrarenal inflammation associated with immunizations.⁸ Furthermore, systemic and renal changes associated with aging could predispose the geriatric nephron to hypoxic injury.

Whether these or other factors serve as initiating events in feline CKD remains speculative. However, recent studies of the histologic appearance of kidneys from cats with CKD^{5,6} have refocused our attention on the importance of tubulointerstitial changes as a primary event and review articles have discussed mechanisms that could contribute to the interstitial fibrosis.^{7,8} If renal fibrosis is a primary renal event or a consequence of pro-fibrotic primary tubular injuries,¹⁶ then the impact of existing therapies, such as inhibitors of the renin-angiotensin-aldosterone system, on feline renal fibrosis should be elucidated.

Future studies that define the cellular and molecular events that contribute to interstitial fibrosis, inflammation and tubular cell death in cats could focus our attention on the potential benefits of therapies designed to interfere with the development of renal fibrosis and interstitial inflammation. Various novel anti-fibrotic therapies that interfere with fibrogenesis (for example, antagonists of transforming growth factor- β ; bone morphogenetic proteins; the connective tissue growth factor CCN2^{17,18}, inhibitors of trans-differentiation of tubular cells or inflammatory cells into myofibroblasts^{19,20}) could play a crucial role in future treatments of this common disease.

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