



Chronic Kidney Disease: Pathophysiology, Progression and Interventions

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Until recently, diagnosis of chronic kidney disease (CKD) in dogs and cats occurred late in the course of disease, usually after kidney function loss of 75% or more. Late recognition of CKD is largely due to insensitivity of serum creatinine concentration as a measure of kidney function. A new kidney function test, symmetric dimethylarginine (SDMA), has been reported to diagnose CKD in dogs and cats with a decline in kidney function as little as 25% to 40%. It has been hoped that earlier diagnosis of CKD may lead to recognition of primary kidney diseases that cause CKD and thereafter specific therapy directed at these diseases. However, despite earlier recognition of CKD, diagnosis of a treatable primary kidney disease remains rare. Failure to diagnose kidney diseases that initiate CKD in dogs and cats may result from insufficiently aggressive diagnostic evaluations and/or limited or inadequate diagnostic testing options for dogs and cats with early International Renal Interest Society (IRIS) CKD Stage 1. It is also possible

that dogs and cats with CKD do not develop kidney disease subsequent to a single identifiable primary kidney disease (e.g., pyelonephritis, immune-mediated glomerular disease, amyloidosis, etc.). An alternative scenario is that CKD may result from a series of smaller individual renal insults of diverse origin leading to sufficient loss of kidney function to prompt compensative processes that help sustain renal function but ultimately lead to self-perpetuating loss of nephrons and progressive CKD. Regardless of which of these possibilities are in fact the causes of CKD as we recognize it clinically, they ultimately are all characterized by processes in the injured kidney that promote progressive CKD. It is useful to recognize these processes, their impact on the kidneys and what therapies that may be useful in managing CKD, with the ultimate goal of maximizing length and quality of life.

While a primary or initiating cause for CKD is rarely identified, lesions typical

of CKD in dogs and cats include loss of nephrons, inflammation and fibrosis. These lesions serve as a framework from which CKD can progress over time.

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The key to successful management of CKD is to slow the spontaneous progression of CKD. A recent study of renal histopathologic lesions in cats from all 4 IRIS CKD stages found that potentially reversible lesions were found among all 4 IRIS stages of CKD; however, irreversible lesions were more prevalent in later IRIS stages of CKD.¹ This observation provides hope that diagnosis of dogs and cats in early IRIS CKD Stages may provide an opportunity to alter or even reverse the course of CKD.

There are 7 mechanisms thought to promote progression of CKD (Table 1). Recognition of these mechanisms provides an opportunity to attempt to alter the course of CKD such that a clinically important slowing or terminating of a patient's progressive clinical course can be achieved.

TABLE 1

MECHANISMS THOUGHT TO PROMOTE PROGRESSION OF CHRONIC KIDNEY DISEASE

- ▶ Activation of the Renin-Angiotensin-Aldosterone System and Angiotensin II
- ▶ Hemodynamic Adaptations (Glomerular hypertrophy, hyperfiltration, and hypertension)
- ▶ Proteinuria
- ▶ Systemic Hypertension
- ▶ Phosphorus Retention (Hyperphosphatemia)
- ▶ Hypoxia
- ▶ Oxidative Stress

Pathophysiology of Progression of CKD

Activation of the Renin-Angiotensin-Aldosterone System (RAAS).

The RAAS modulates blood pressure and body fluid balance by managing sodium and water homeostasis in the kidneys. However, there are two RAASs in the kidneys: the systemic RAAS and the local renal active tissue-specific RAAS. Measures of plasma angiotensin II levels reflect activity of the systemic RAAS but do not provide information about activity of the renal tissue-specific RAAS. The local renal tissue-specific system is the predominant system in the kidneys managing intrarenal hemodynamics and glomerular filtration.

Kidney injury and/or loss of renal mass are typically associated with increased activity in the renal tissue-specific RAAS and specifically angiotensin II (Ang II). Increased activity of Ang II locally appears to have a significant role in progression of CKD. As a potent renal vasoconstrictor, Ang II in increased levels promotes glomerular hypertension and hyperfiltration. In addition, Ang II modulates glomerular barrier permselectivity by promoting glomerular capillary hypertension and altering podocyte structural interactions. These effects cause renal injury by altering glomerular hemodynamics and promoting development of proteinuria and glomerulosclerosis. Proteinuria has direct fibroproliferate and inflammatory effects via increased transcription and production of inflammatory and profibrogenic molecules, including FGF- β .² Aldosterone also has independent profibrotic effects.

Hemodynamic Adaptations (Glomerular hypertrophy, hyperfiltration, and hypertension).

Loss of functional nephrons has been shown to promote glomerular hypertrophy, hypertension and hyperfiltration in the remaining functional nephrons in rodents, dogs and cats.³ At least in the short term, this renal adaptation appears to be beneficial in that it minimizes the loss in renal function. However, in the longer term, these adaptations become detrimental in that they appear to initiate a self-perpetuating loss of surviving nephrons, resulting in progression of CKD. These adaptations have been demonstrated in rodents, dogs and cats using a combination

of nephrectomy and partial renal ablation of the surviving kidney (remnant kidney model). Examination of surviving tissue from the remnant kidneys revealed evidence of fibrosis and inflammation. However, in cats and dogs, CKD induced by this model fails to duplicate progressive CKD in that kidney function typically remains stable for extended periods. Only after loss of 15/16 of the kidney mass will dogs develop self-perpetuating decline in kidney function. Proteinuria consistently develops in this model of CKD in dogs and cats when they are fed maintenance diets. Proteinuria is significantly lower when they are fed "renal diets."

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These remnant kidney studies were performed in young dogs and cats (not the typical demographic of dogs and cats developing CKD), and one could speculate that performing these same studies in old dogs and cats might yield a different outcome. The significance of hemodynamic adaptations in progressive CKD in dogs and cats remains unclear in terms of their role in progression of CKD.

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Proteinuria in Chronic Kidney Disease.

Proteinuria has been shown to be associated with progression of spontaneous CKD in dogs and cats. It has been proposed that proteinuria in CKD occurs, at least in part, as a consequence of glomerular hypertension, hyperfiltration and altered permselectivity of the glomerular filtration barrier. Delivery of large amounts of albumin (the major constituent of proteinuria in CKD) to the renal tubules promotes an apoptotic response in tubular cells, altered phenotype of tubular cells and development of tubulointerstitial inflammation and fibrosis.² Delivery of high concentrations of albumin to the proximal tubular cells is reported to promote activation of the renal RAAS. The inflammatory and fibrotic response to proteinuria may be abrogated by therapy reducing proteinuria.² Studies in humans have shown that proteinuria accelerates the decline in GFR and promotes progression to end-stage CKD; however, reducing proteinuria with angiotensin converting enzyme inhibitors (ACEi) or angiotensin

receptor blockers (ARB) can slow the decline in kidney function.² Similar studies have not been reported in dogs and cats.

Systemic Hypertension.

In one study, systemic hypertension was reported to be associated with adverse outcome in dogs with CKD; however, this study failed to exclude interaction with proteinuria.³ In contrast, systemic hypertension has not been confirmed to be an independent factor in progression of CKD or increased mortality in cats with CKD.

Importantly, hypertensive CKD cats have been shown to be more proteinuric than CKD cats that were normotensive, thus confounding the individual impact of hypertension versus proteinuria.² An important factor limiting the ability to define a role for hypertension in progression of CKD in dogs and cats is that hypertension is treated when recognized. Although unproven, it seems likely an interaction between systemic hypertension and proteinuria may influence progression of CKD.

Phosphorus Retention (Hyperphosphatemia).

Excessive phosphorus ingestion and hyperphosphatemia have been implicated in promoting progression of CKD in dogs and cats. The harmful effect of phosphorus has been supported by experimental and clinical studies in dogs and cats where dietary phosphorus restriction has reduced renal injury and reduced mortality. Further, the phosphaturic hormone, fibroblast growth factor-23 (FGF-23), an early marker of phosphorus retention

in CKD, has been shown to predict future progression of CKD.⁴ Similarly, FGF-23 levels predict outcome in cats with CKD.²

The pathogenesis of excess phosphorus intake and hyperphosphatemia leading to increased mortality in CKD is incompletely understood. It has often been proposed that hyperphosphatemia leads to renal mineralization with subsequent renal inflammation and fibrosis. It has also been proposed that phosphate imbalance and altered homeostasis can result in deposition of calcium phosphate in blood vessels, leading to stiffening of arteries and effects on endothelial cell function. These alterations in the renal microvascular system may lead to areas of ischemia and hypoxia, which then promote renal fibrosis. Other proposed effects of hyperphosphatemia that may be associated with progression of CKD include increased production of profibrotic mediators, activation of the RAAS, cellular apoptosis, cellular senescence and oxidative stress.²

Renal Hypoxia.

Deranged oxygen metabolism has been recognized to occur in CKD, and the consequent oxidative stress may be a contributor to progression of CKD as a result of and cause for tubulointerstitial fibrosis.⁵ Studies in cats have indicated that anemia is a marker for reduced survival and predictor of progression of CKD.²

While approximately 20% of the cardiac output flows through the kidneys, blood perfusion is not equally distributed throughout the entire kidneys. As a consequence,

there are anatomic areas, such as the renal medulla, that receive marginal oxygen delivery despite considerable metabolic demands. In CKD, hemodynamic modifications support renal function by activation of the RAAS and Ang II, increasing intraglomerular pressure; however, the trade-off is a decrease in blood flow through later segments of the nephron, thus exposing post-glomerular tubular segments to hypoxia.² As described above, hemodynamic and structural lesions that develop with CKD promote hypoxia. In turn, hypoxia itself has been shown to stimulate fibrogenic modifications in tubular epithelial cells,

Interstitial disruption in CKD leads to impaired erythropoietin production, thus leading to anemia, which further impairs renal oxygenation.

fibrocytes and endothelial cells. Thus, these processes have the potential to lead to a self-promoting loss of renal oxygenation. Further, uremic toxins have been proposed to be an important contributor to progressive renal fibrosis.⁴ Some of the uremic toxins implicated include indoxyl sulfate, p-Cresol, and p-Cresyl sulfate.

In addition, interstitial disruption in CKD leads to impaired erythropoietin production, thus leading to anemia, which further impairs renal oxygenation. Tubulointerstitial inflammation and fibrosis and interstitial microvascular and capillary loss consequent to hypoxia can further

challenge adequate delivery of oxygen to metabolically active tubular cells.

Oxidative Stress.

Renal oxidative stress is defined as an imbalance between reactive oxygen species (ROS) and antioxidant defense mechanisms. ROS can cause damage to DNA, lipid, protein, and carbohydrates that results in structural and functional cellular damage, leading to apoptosis and necrosis and thus stimulating inflammation and fibrosis.² Oxidative stress may develop in CKD when glomerular hyperfiltration demands hyperfunction in the remainder of the nephron, where at least large portions have high metabolic activity and are likely to produce increased ROS. Other factors that can also contribute to generation of ROS include proteinuria, RAAS activation and Ang II, hyperphosphatemia, inflammation, ischemic and hypoxic areas, and uremic toxins.

Treatments for Slowing Progression of Chronic Kidney Disease

ACEi and (ARB).

Because RAAS activity is typically increased in CKD and implicated in renal injury and proteinuria in CKD, ACEi and ARB are logical therapy to reduce renal injuries consequent to activation of the RAAS and proteinuria in dogs and cats. They are primarily prescribed for dogs and cats with CKD that have proteinuria (urine protein:creatinine ratios >0.5 in dogs and 0.4 in cats). There are several different approaches to this therapy. It is logical to use these drugs with the goal of reducing the patient's proteinuria, essentially using proteinuria as evidence of drug

effectiveness. This approach involves gradually increasing the dose of the ACEi or ARB while monitoring the effect of the drug on serum creatinine and potassium concentrations, blood pressure and proteinuria. ACEi and ARB can be used together to achieve the desired reduction in proteinuria; however, the combination may be associated with a greater risk of complications, including hyperkalemia, reduced renal function and decline in blood pressure. Despite the logic underlying the application of these drugs in proteinuria, convincing evidence supporting that they slow progression or improve survival of dogs and cats with CKD are lacking. Further, the optimum scheme for suppressing the RAAS and improving survival outcome in dogs and cats with CKD has yet to be established.

Minimizing Hemodynamic Adaptations and Proteinuria.

Reduced protein intake has been shown to reduce glomerular hypertrophy, hypertension, and hyperfiltration as well as proteinuria. In rodent models, these modifications have also been associated with improved survival. High protein intake was shown to be associated with increased glomerular hypertrophy, hypertension and hyperfiltration as well as proteinuria.

ACEi and/or ARB also reduce glomerular hypertension, hyperfiltration and proteinuria by reducing resistance in the efferent glomerular arteriole, which lowers pressure within glomerular capillaries. In addition, ACEi and/or ARB will reduce proteinuria by restoring slit diaphragm integrity and increase negative charge on glomerular membrane.

Minimizing Systemic Hypertension.

The preferred anti-hypertensive drug for dogs and cats is amlodipine, a calcium channel blocker. Treatment of hypertension usually begins with this drug. It is effective in most instances of hypertension and severe hypertension associated with CKD, but dosage must be titrated to effect for optimum response. Since amlodipine is a vasoactive drug, it may increase proteinuria unless hypertension is well managed. It can be used with ACEi when proteinuria is a concurrent problem.

Telmisartan is an ARB with considerable anti-hypertensive effect. As with amlodipine, dose must be titrated to manage hypertension. It has the advantage of reducing proteinuria concurrent with the hypertension in cases in which a single drug may be the first choice to manage both conditions.

ACEi drugs such as benazepril and enalapril are relatively weak anti-hypertensive drugs that usually fail to produce reductions greater than 10 to 15 mmHg in blood pressure. For dogs and cats that have mild hypertension and proteinuria, these drugs may be a good choice.

Minimizing Hyperphosphatemia.

The IRIS CKD guidelines (www.iris-kidney.com) provide targets for serum phosphorus concentration that increase as patients increase in IRIS CKD Stage. The serum phosphorus concentration targets for dogs and cats in IRIS CKD Stages 2, 3 and 4 are <4.5 mg/dl, <5.0 mg/dl and <6.0 mg/dl, respectively. The first step in lowering serum phosphorus concentration is to provide a renal disease diet, due to the limited phosphorus content in such diets.

If the serum phosphorus concentration remains above the target after 4 to 6 weeks of consuming the reduced-phosphorus diet, intestinal phosphorus binders should be considered.

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Minimizing Hypoxia.

Hypoxia is largely the result of altered anatomy due to fibrosis and inflammation. As such, many of the therapies noted above such as suppressing the RAAS and Ang II and minimizing hemodynamic adaptations and uremic toxins are directed toward minimizing renal tissue hypoxia. Additionally, treating anemia of renal failure with darbepoetin has the potential to improve renal hypoxia.

Oxidative Stress.

Antioxidants as well as renal diets, which incorporate antioxidants, are provided to mitigate oxidative stress. In addition, the strategies described above directed toward limiting activation of the RAAS and Ang II, hyperphosphatemia, inflammation, ischemia and hypoxic areas, and uremic toxins are all potentially beneficial in reducing oxidative stress by lowering ROS production.

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