

CHRONIC RENAL FAILURE: IS PROGRESSION INEVITABLE?

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Chronic renal failure (CRF) is the most common kidney disease of dogs and cats, with 53% of cats over 7 years and 45% dogs over 10 years being affected. Unfortunately, CRF is often an irreversible and progressive disease that eventually results in death of the patient. There are many different causes of chronic renal failure including congenital (polycystic kidney disease, renal dysplasia) and acquired (leptospirosis, glomerulonephritis, amyloidosis, pyelonephritis) disorders.

The kidney responds to injury in three defined ways; hypertrophy, hyperplasia and eventually fibrosis. When part of the kidney is damaged, the remaining nephrons will increase their individual glomerular filtration rate (GFR) in an attempt to maintain the overall GFR. The remaining nephrons will become hypertrophied in response to the increased load, and eventually hyperplastic and then fibrotic as the disease progresses. It is important to remember that any disease process within part of the nephron, will result in eventual damage to the rest of the kidney (e.g. glomerular disease will eventually result in tubular damage and azotemia).

It is important when treating dogs and cats with CRF to identify factors that affect the progression of disease. Although we cannot stop the progress of disease, we can potentially slow down the process. There are two broad categories of factors that affect progression; 1) factors that **hasten** progression, and 2) treatments that **slow** progression.

Factors that hasten progression

Since diseases such as pyelonephritis, nephrolithiasis, hypercalcemia, glomerulonephritis can result in decompensation of a stable patient and potentially incite an acute uremic episode or systemic disease, it is essential to identify, characterize and treat comorbid disease conditions. This diagnostic process includes performing serum biochemical analysis, complete blood count, urinalysis, urine culture and a urine protein:creatinine ratio (if inactive sediment). In addition, diagnostic imaging such as abdominal radiographs and ultrasound are also important for assessing kidney size, structure, and other underlying disease processes. These diseases need to be treated as deemed appropriate.

Any factor that results in decreased perfusion to the kidney can result in damage to renal tissues. Conditions that result in intravascular volume depletion (i.e. dehydration, hemorrhage) and decreased effective blood volume (hypoalbuminemia, congestive heart failure) need to be identified and managed. In addition, any drug that can injure the tubular epithelium or alter renal hemodynamics should be avoided (e.g. non-steroidal anti-inflammatory drugs).

Proteinuria and hypertension are two well known risk factors that contribute to disease progression in human medicine. Similar studies in dogs and cats have also proven that these entities can also hasten the progression of disease, and hence early identification of them is recommended. Proteinuria is toxic to the kidneys by inciting inflammatory reactions within the tubules that can result in damage to the tubular cells and also result in physical blockage of the tubules. Studies in dogs and cats have established that proteinuria is a risk factor for increased numbers of uremic episodes and earlier death. In dogs, a urine protein creatinine ratio (UPC) of >1 and UPC of >0.25 in cats are associated with increased morbidity and mortality. The normal reference ranges are generally UPC <1 . Angiotensin converting enzyme inhibitors (ACE-I) have been used to manage proteinuria in dogs and cats. This class of drugs are believed to reduce proteinuria by decreasing the efferent glomerular arteriolar resistance (and lowering intraglomerular pressure), decreasing glomerular size and limiting glomerular hypertrophy, inducing efferent arteriole dilation and inhibiting the degradation of bradykinin.

Similarly, hypertension whether caused by renal disease or other mechanisms, has been shown in rats, dogs and human studies to promote renal damage and contribute to the progression of CRF. Although CRF is the most common cause of hypertension in dogs and cats, other causes, such as hyperthyroidism in cats and Cushing's disease in dogs, may also be involved. Hypertension has been associated with an increased number of uremic episodes in dogs, but the relationship has not been as well defined in cats. In many cases, especially in cats, hypertension coexists with proteinuria, and hence this may also contribute to the decline of renal function. The calcium channel blocker, amlodipine, is the most effective antihypertensive agent for use in cats, whereas ACE-I and calcium channel blockers have been used with similar effects in dogs. Combination therapy is often used in human medicine, including the use of calcium channel blockers and ACE-I. Other drugs that are used in humans include angiotensin receptor blockers and aldosterone receptor blockers. The clinical benefits of these medications in veterinary medicine is yet to be evaluated.

Factors that slow progression

Many studies have been performed that evaluate the effect of diet on the progression of CRF. These studies have mainly evaluated diet as a single entity, and have determined that there is a 'diet effect' that can increase survival time. These renal diets are phosphate, protein, sodium restricted, alkalinizing, and contain added omega 3 polyunsaturated fatty acids (PUFAs). Most of these diet modifications have been shown to be of benefit in later stages of CRF, mainly the IRIS (international renal interest society) stages 3-4 (table 1). There is no proven benefit of starting a dog or cat with early renal insufficiency on a renal diet (i.e. stage 1-2). There are many commercial renal diets available for veterinarians to choose from.

Omega 3 fatty acids have been well documented to slow the progression of renal failure in experimental studies in dogs. Dogs fed omega 3 PUFA supplemented diets lived significantly longer than the control group (saturated fatty acid) and dogs fed omega 6 PUFA. The results of these studies suggested that omega 3 fatty acids are renoprotective. The exact mechanism for this is not clear, but theories extrapolated from human and rat studies include omega 3 PUFA induced suppression of inflammation and coagulation cascades, antioxidant effects and an antihypertensive effect. The additional of omega 3 PUFAs may be an important reason why renal diets are so effective in the later stages of renal failure.

Summary

Ultimately, CRF is an irreversibly progressive disease. However, the rate of progression can be modified. Since factors such as hypertension, proteinuria and comorbid diseases may contribute to a more rapid rate of decline, these factors need to be identified and treated appropriately. Renal diets and the use of omega 3 fatty acids have been proven to be beneficial in reducing the rate of progression in patients with more advanced stages of CRF.

Stage	Plasma creatinine mg/dl		Comments
	Dogs	Cats	
1	<1.4	<1.6	Non-azotemic: Some other renal abnormality present e.g. inadequate concentrating ability; abnormal renal palpation and/or abnormal renal imaging findings; proteinuria of renal origin; abnormal renal biopsy
2	1.4 – 2.0	1.6 – 2.8	Mild renal azotemia Clinical signs usually mild or absent
3	2.1 – 5.0	2.9 – 5.0	Moderate renal azotemia Many systemic clinical signs may be present
4	>5.0	>5.0	Severe renal azotemia Many extra-renal clinical signs present

Table 1 Adapted IRIS staging scheme

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