FELINE CHRONIC KIDNEY DISEASE AND THE PROTEINURIA CONUNDRUM

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Chronic kidney disease (CKD) is a common and important cause of morbidity and mortality in cats. The hallmark of CKD is a chronic decline in the population of functional nephrons to a point where the glomerular filtration rate (GFR) is no longer adequate to maintain normal excretory function. This leads to azotaemia (elevation in plasma urea and/or creatinine concentrations) and the retention of other plasma solutes and protein catabolic products normally eliminated via the kidneys. Ultimately, renal dysfunction and the retention of these products results in a spectrum of clinical signs associated with CKD, commonly referred to as the 'uraemic syndrome'.

In the early stages of CKD, the declining number of nephrons is compensated for by increased individual (single) nephron GFR (SNGFR), mediated through both glomerular hypertrophy and hypertension so that the overall decline in GFR is not proportional to the number functioning nephrons lost. By the time clinically evident renal failure is present, there is generally loss of at least 70% of functioning nephrons. CKD is most commonly seen in middle to old-age cats with the risk rising progressively and dramatically from around 7 years of age.

Aetiology of feline CKD

The underlying aetiology of feline CKD is often obscure although a variety of causes have been documented. Histological evaluation of kidneys from affected cats most commonly reveals the presence of chronic interstitial nephritis (CIN) characterised by the presence of progressive fibrosis, loss of nephrons and the presence of sterile inflammation, but the cause of this uncertain. It has been speculated that chronic pyelonephritis or glomerulonephritis may account for at least some of these 'end stage' cases of CKD, and more recently it has been suggested that there may be a link with a newly identified feline morbillivirus. Other recognised causes of CKD in cats include toxic damage to the kidneys, amyloidosis, polycystic kidney disease, neoplasia, obstructive uropathy and chronic hypercalcaemia. Whatever the underlying cause, unlike many cases of human renal failure, this is not predominantly a glomerular disease in cats, but rather a tubulointerstitial disease (with glomerular involvement) that results in nephron loss.

Clinical signs and diagnosis of feline chronic kidney disease

The clinical manifestations of feline chronic kidney disease are often non-specific, with dehydration, anorexia, lethargy and weight loss being most commonly reported. Polyuria and polydipsia (PU/PD), which are major signs in canine CKD, are reported less frequently in cats. This is likely to be due to both reduced awareness of these signs in cats (their lifestyle may mean some owners are unaware of PU/PD), and to the fact that at least some cats may retain better urine concentrating ability in the face of CKD than dogs.

Abdominal palpation in cats with CKD may reveal small, normal or enlarged kidneys, depending on the underlying disease process, and the kidneys may or may not be palpably irregular and misshapen. Other common manifestations of CKD include poor hair coat, vomiting (due to central effects of uraemic toxins, hypergastrinaemia and uraemic gastric ulceration), pale mucous membranes (due to anaemia), and hypertensive retinopathy (including retinal detachments).
The diagnosis of CKD is usually based on the presence of appropriate clinical signs together with the demonstration of azotaemia and inappropriately concentrated urine. Isosthenuria is generally not observed unless CKD is advanced and up to 50% of cats with CKD may have some degree of hypersthenuria. However, few cats with well-established CKD can concentrate urine above 1.035 so a combination of appropriate signs, azotaemia and a USG ≥1.035 -1.040 is often taken as evidence of probable CKD. Nevertheless, the ability to concentrate urine above 1.040 cannot exclude the existence of CKD.

In addition to azotaemia, a number of other clinicopathological changes are commonly observed including hyperphosphataemia, renal secondary hyperparathyroidism, acidosis, hypokalaemia, and anaemia. Some other commonly observed changes (eg. leucocytosis, lymphopenia, hyperglycaemia and hyperproteinaemia) may simply reflect the effects of stress and/or dehydration. Hypokalaemia may be seen in up to 20% of feline CKD patients and appears to be mainly a result of inappropriate kaliuresis.

Assessment of renal function/GFR

Evaluation of serum urea and creatinine levels is usually used as an indirect indicator of renal function. If non-renal factors are eliminated, azotaemia implies functional loss of around 75% or more nephrons. Care needs to be exercised in interpreting urea and creatinine levels though, particularly in the high-normal to mildly elevated range, as even a

quite substantial deterioration in renal function here will only result in relatively small elevations of urea/creatinine. Conversely, late in renal disease a relatively small deterioration in renal function can cause a marked increase in urea/creatinine concentrations. In general, serum creatinine concentrations reflect renal function more accurately than urea concentrations.

In some situations it may be difficult to be sure whether early renal failure is present and/or it may be desirable to more accurately quantify and monitor renal function. Direct measurement of GFR in such cases is feasible by evaluating the plasma clearance of substances purely excreted through glomerular filtration and neither influenced by tubular absorption nor tubular secretion. The three substances that are in common use for this are inulin, creatinine and iohexol, although others are also available.

Stages of feline CKD

The IRIS (International Renal Interest Society) group has defined four stages of renal failure in cats and these may help in establishing prognosis and to some extent targeting therapy for CKD:

Stages of feline chronic kidney disease (IRIS)					
	Creatinine µmol/l	Signs	Specific therapy	Renoprotective therapy	Symptomatic therapy
Non-azotaemic	<140	None	+++	+	+
Mild azotaemia	140-250	Mild	+++	+++	+
Moderate azotaemia	251-440	Transitional	++	+++	+++
Severe azotaemia	>440	Uraemic	+	+	+++

Although CKD is often diagnosed after cats have developed azotaemia, many cats may present with diseases where there is renal damage even though they have not progressed to overt azotaemia (eg, pyelonephritis, glomerulonephritis, renal lymphoma, nephrotoxins etc.) – such cats may fall into the early 'non-azotaemic' category of CKD cases.
In earlier cases of CKD, the priority is likely to be specific therapy for the underlying disease and preventing further renal damage, through adequate diagnosis and management. By the time azotaemia has developed, it can be assumed that around 75% of functioning nephrons have been lost, but even at this stage, clinical signs will be relatively mild or even non-existent early on. If an underlying disease can be diagnosed and specific treatment instituted this will again provide significant benefits in preventing further progression of disease.

As cats progress though the period of moderate azotaemia, there is an increasing likelihood of clinical signs developing relating to the CKD (development of uraemic signs), and an increasing need to provide symptomatic and supportive therapy to address the manifestations of CKD and, to some extent, a lesser emphasis on therapies to slow progression as this may become more difficult in advanced renal failure.

The IRIS staging system also incorporates target serum phosphate concentrations in different stages of CKD and sub-staging based on blood pressure, and proteinuria, all of which are considered important in the prognosis and management of feline CKD:

Staging of feline chronic kidney disease (IRIS) – target serum phosphate				
Stage	1	2	3	4
Serum Creatinine µmol/l	<140	140-250	251-440	>440
Signs	None	Mild	Moderate	Severe
Target serum phosphate mmol/l	0.9-1.45	0.9-1.45	0.9-1.6	0.9-1.9

Sub-staging of feline CKD based on proteinuria			
Sub-stage	Non-proteinuric	Borderline proteinuric	Proteinuric
Urine protein:creatinine ratio	<0.2	0.2-0.4	>0.4

Sub-staging of feline CKD based on systolic blood pressure				
Sub-stage	Minimal risk	Low risk	Moderate risk	High risk
Systolic BP (mmHg)	<150	150-159	160-179	≥180

Wherever possible, cats with CKD should be fully staged and have a full blood and urine profile performed (including a quantitative assessment of proteinuria) so that complications of CKD can be accurately identified, the stage of CKD can be identified, therapeutic targets can be appropriately identified, and the prognosis can be more clearly assessed.

Practical management of feline CKD

Following initial diagnosis of CKD it is important to identify and treat reversible causes or contributory factors. Identifying conditions such as pyelonephritis, glomerulonephritis and nephrotoxins may allow intervention to arrest further renal damage. In addition, many cats when first presented may have decompensated CKD and may be dehydrated so supportive intravenous fluid therapy may also be a priority.

Inadequate water intake in CKD is associated with dehydration, reduced renal perfusion and further impairment of renal function. Maintaining adequate fluid intake is therefore of prime importance and can be achieved by feeding moist or wet rather than dry foods, supplementing the diet with water or broths, providing running water (pet fountains) and flavoured water, and by intermittent use of intravenous or subcutaneous fluid therapy. Fluids can be supplemented with potassium if needed.

Dietary protein and phosphate restriction

It is generally accepted that moderate dietary protein restriction is beneficial in improving quality of life in feline CKD patients (by reducing the accumulation of uraemic toxins), but this must not be too severe (protein malnutrition must be avoided), and it probably has minimal (if any) effects on progression of CKD. Conversely there is excellent evidence now that restriction of dietary phosphate (and the additional use of phosphate binders where necessary) is of real benefit in reducing the histological severity of renal lesions and in slowing the progression of feline CKD and this forms an integral part of clinical management.

Managing phosphate levels is similarly regarded as extremely important in advanced human CKD to slow progression of disease. However, whilst vitamin D deficiency is well recognised in human CKD and supplementation with vitamin D is a mainstay of the management of phosphate, calcium, and parathyroid hormone concentrations in humans, calcitriol supplementation has not so far been proven to be beneficial in cats with CKD. Further studies are needed in this area to explore the role of vitamin D in feline CKD. Current recommendations are to meet IRIS target levels for serum phosphate (see Table) in cats using therapeutic renal diets and with phosphate binders such as calcium acetate and lanthanum carbonate.

Control of hypertension

Unlike human medicine, it is not yet certain whether systemic hypertension actually contributes to on-going damage in feline CKD. However, even in the absence of this, there are substantial risks to other ‘target organs’ with feline hypertension, so measurement of systolic blood pressure should be routine in CKD patients, with management in line with the IRIS guidelines. Angiotensin converting enzyme inhibitors (ACEIs) may have some anti-hypertensive effect, but in most cases the calcium channel blocker amlodipine will be more effective in cats. Angiotensin receptor blockers (ARBs) are a new class of drugs available in veterinary medicine and it is yet to be determined how effective they may be in helping to control hypertension. However, to prevent target organ damage and potentially to help slow progression of CKD, it is essential that blood pressure is adequately controlled whatever drug or combination of drugs is used.

Proteinuria and renin-angiotension-aldosterone system (RAAS) blockade

In both humans and cats, the magnitude of proteinuria at the time CKD is diagnosed is important for prognosis. The greater the level of proteinuria the more rapid the progression of CKD is likely to be. It is thought, in humans at least, that proteins in the tubular fluid (passing through a damaged glomerulus) provoke an inflammatory response that produces further renal damage. In humans, where proteinuria is present treatment by blocking RAAS activation with ACEI (such as benazepril) or angiotensin receptor blockers (ARBs - such as telmisartan) are considered standard of care. The two types of drugs may be used interchangeably but ARBs are useful if ACEIs are not tolerated and have at least the theoretical advantage of avoiding escape from inhibition by ACEIs. In humans, reduction of proteinuria with ACEIs or ARBs can dramatically delay progression of CKD, and some studies have looked at the combination of both ACEIs and ARBs in an effort to get even better control of proteinuria. The greatest benefit appears to be in humans with CKD associated with diabetic nephropathy, where glomerular damage and proteinuria are common. However, studies suggest that other forms of proteinuric CKD in humans may also benefit from ACEi or ARB therapy resulting in delayed progression of disease and improved prognosis.

Although proteinuria in cats with CKD (a UPC >0.2) has been shown to be a negative prognostic indicator (just as in humans), interventional treatment with ACEIs, while reducing the degree of proteinuria has not yet been shown to have a survival benefit. The reasons for this are currently unclear and several explanations are possible. It may be that CKD in cats has a different pathophysiology to CKD in humans and anti-proteinuric therapy simply does not have the same therapeutic benefit. While this could be a partial explanation this would not explain the relationship between proteinuria and progression of CKD, which is broadly the same in both species. It may be that certain types of CKD in cats may benefit form anti-proteinuric therapy, but perhaps not all cases, and that our current ability to identify and target those cats at most benefit is lacking – certainly there is some evidence that those cats with more severe proteinuria may benefit from therapy. It should be noted too that current studies have been performed with relatively small numbers of cats and over relatively short time periods – a trend for improved survival has been seen with anti-proteinuric therapy and it may simply be that if larger studies were performed over a longer period that this might reveal a significant survival benefit from these drugs. Again, the introduction of a veterinary licensed ARB (telmisartan) offers a new class of drug in the attempt to manage proteinuria in CKD and it will be important that further large-scale studies are conducted to evaluate the efficacy of this drug in managing feline CKD and in identifying which cats are likely to benefit most from therapy. Current IRIS recommendations are to institute therapy for proteinuria in azotaemic cats with a UPC >0.4, but whether this is an appropriate cut-off remains to be determined as while the prognosis for these cats appears poorer, there is also a significantly increased risk of death in CKD cats with a UPC of 0.2-0.4 (compared with those having a UPC <0.2).

Other therapies

Many other therapeutic interventions may be beneficial in feline CKD and these should not be ignored. A renal therapeutic diet may help to manage acidaemia and oxidative stress, and may also help reduce the risk of hypokalaemia. Potassium monitoring is important though and potassium gluconate supplementation used if hypokalaemia develops. The haematocrit should also be monitored and appropriate interventions used where necessary such as iron supplementation or use of darbepoetin. Nausea, vomiting and inappetence are also prevalent in feline CKD and may need management with antacids, gastric protectants, antiemetics and possible nutritional support.
In such a complex disease it is not surprising that management too can be complex. It is important to address each cat with CKD as an individual and tailor treatment appropriately to the needs of the cat. This may often mean prioritising therapy, as it may not always be possible to use the full array of interventions that might ideally be indicated. For the future, there remain some extremely important areas of research so that we can better understand both the pathogenesis and which treatments are most effective for feline patients.

Further reading

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