# Prolonging the life of the feline renal failure patient

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**KEY POINTS**

- Many cases of feline chronic renal failure (CRF) progress to end stage and die of their renal disease.
- Progression can be due to repeated renal insults and/or to maladaptive responses to the uraemic syndrome leading to loss of functioning nephrons.
- Secondary renal hyperparathyroidism resulting from phosphate retention is one such maladaptive response.
- Control of this syndrome by dietary phosphate restriction leads to increased survival in naturally occurring feline CRF.

## Introduction

Feline chronic renal failure (CRF) is a common clinical problem, particularly affecting the ageing cat population. The first goal in the management of clinical CRF is to identify and treat any underlying cause of renal disease. Where this is not possible, as is often the case, other treatment goals are to manage the complications of renal failure to improve the quality of life of the animal (1). In addition, by correcting some of these complications, it has been suggested that the progression of CRF to its end stage may be slowed.

Progression of CRF to end stage is thought to be an inevitable process in some species (2). Experimental evidence seems to suggest that, following surgical reduction in renal mass in the cat, progressive deterioration of renal function is difficult to demonstrate over a 12-month period (3, 4). In clinical patients, however, progressive loss of remaining functioning nephrons does seem to occur (5, 6) albeit in stepwise decrements at highly variable intervals rather than as a gradual linear progression. **Figures 1a** to **c** show sequential data from three cats showing the patterns of progressive deterioration of renal function observed in a recent study (6). Of the 39 cases that died or were euthanised during this study, 21 were documented to have suffered from deteriorating renal function as the cause of their death. Most cases that died of renal failure demonstrated stepwise decrements in renal function as seen in **Figures 1a** and **b**. There were very few examples of cases that showed clear evidence of linear increases in plasma creatinine concentration accompanied by progressive loss of weight such as that shown in **Figure 1c**.

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## Why do cases of CRF tend to show progressive renal dysfunction?

There are two main reasons why renal function tends to deteriorate once CRF has been diagnosed in a clinical patient (7). First, there may be repeated insults that damage the remaining functioning nephrons and lead to the stepwise falls in glomerular filtration rate. Secondly, the adaptive responses the body makes to loss of functional renal tissue, once this has been reduced to a critical level, lead to the death of further nephrons and a vicious cycle ensues culminating in end stage renal failure. These responses can, therefore, be described as 'maladaptation'.

Maladaptation may be contributed to by many of the body's responses to azotaemia that lead to the uraemic syndrome (8). Examples include the following.

### Hypersecretion of parathyroid hormone

Hyperparathyroidism results from accumulation of phosphate in the body (9). In a normal animal, parathyroid hormone (PTH) would cause increased excretion of phosphate ions in the urine and a restoration of phosphate balance. With severe loss of functioning nephrons, however, PTH is unable to rid the body of excess phosphate and the response is maladaptive because it adds to the problem of hyperphosphataemia by releasing more phosphate from stores within bone. Calcium is released with phosphate, soft tissue mineralisation occurs and, some hypothesise, mineralisation of renal tissues will lead to progressive loss of functioning nephrons (10).

### Glomerular capillary hypertension and hyperfiltration

Another maladaptation occurs at the level of the glomerulus itself and leads to glomerular hypertension and hyperfiltration. This has been documented to occur in cats with experimentally induced renal failure by surgical reduction of renal mass (11). The change in glomerular haemodynamics that accompanies reduction in renal mass is postulated, in species such as the rat, ultimately to damage the hyperfiltrating nephrons and lead to their demise.

### Renal adaptation to metabolic acidosis

A final example of a maladaptation in CRF is the response to metabolic acidosis, a common disturbance that accompanies CRF (12) but one that has been poorly studied in the cat. Ammonia generation in the distal tubule aids hydrogen ion secretion by the remaining functioning nephrons but excess ammonia may itself be detrimental and lead to activation of complement and damage to the failing kidney (13). In addition, metabolic acidosis can cause excessive potassium losses (14), which in turn can lead to hypokalaemic nephropathy (15).

## Prognosis for cats presenting with CRF

It would be helpful for practising veterinary surgeons to be able to predict at initial diagnosis, which cats with CRF will progress rapidly to end stage renal failure regardless of the treatment they receive and which, given the right treatment, will remain stable for a long period of time. One might expect the plasma creatinine after rehydration at initial presentation to be a reasonable guide. Many cases where the plasma creatinine concentration remains above 500 $\mu$mol/l when the cat has been adequately rehydrated tend to represent very quickly for further fluid treatment and are often very difficult to manage for the complications of their renal failure. For those cats that present in stable CRF where the plasma creatinine concentration is less than 500 $\mu$mol/l, this biochemical assessment at initial presentation does not predict which cats will progress and which will remain stable. In a retrospective study, the correlation between plasma creatinine and survival in cats that presented with signs of stable CRF was very poor, with only 5% of the variation in survival time being predicted by the initial plasma creatinine concentration (5). This finding perhaps merely confirms what a crude index of renal function plasma creatinine really is and highlights the need for more sensitive indices to be developed that can be used in routine

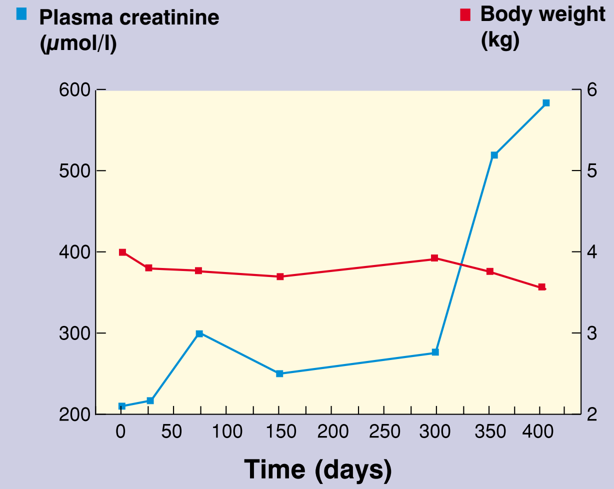


Figure 1a

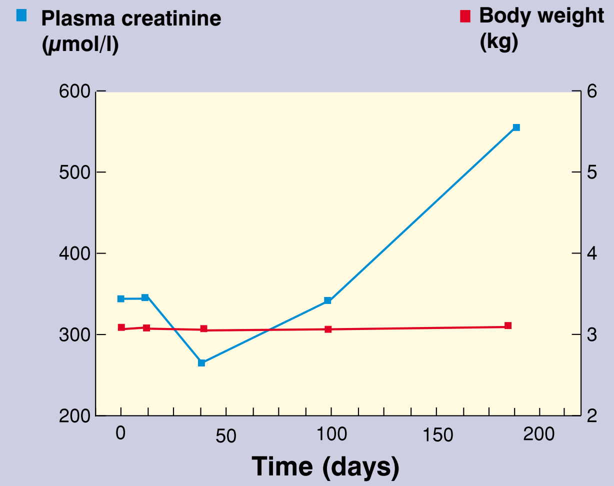


Figure 1b

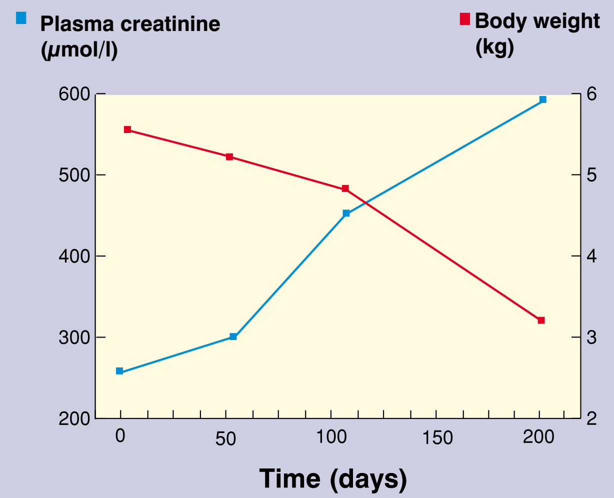


Figure 1c

**Figure 1** *Graphs showing the changes in plasma creatinine and body weight with time in three clinical cases of naturally occurring chronic renal failure.* **(a)** *A 12-year-old female neutered domestic short-haired cat where there were two progressive increases in creatinine, two and 15 months following initial diagnosis. The cat was euthanised 17 months following diagnosis.* **(b)** *A 16-year-old male neutered domestic long-haired cat where stable renal function was demonstrated for the first three months and a rapid deterioration occurred five months following initial diagnosis. This cat was euthanised after six months.* **(c)** *A four-year-old male neutered domestic long-haired cat where a gradual increase in plasma creatinine accompanied by loss of weight was noted at each visit. This cat was euthanised nine months following initial diagnosis.*

Table 1

**Plasma phosphate and parathyroid hormone values from cats with CRF at initial diagnosis and mid-survival time**

| *Value (reference range)** | *Maintenance diet group* | | *Restricted phosphate group* | |
|---|---|---|---|---|
| | *Initial diagnosis (n)* | *Mid-survival (n)* | *Initial diagnosis (n)* | *Mid-survival (n)* |
| Plasma phosphate (0.68 to 1.86 mmol/l) | 1.85 ± 0.12 (21) | 2.18 ± 0.22 (21) | 2.04 ± 0.17 (29) | 1.50 ± 0.08 (29) |
| Plasma PTH (2.5 to 25.5 pg/ml) | 119.7 ± 32.2 (21) | 215.7 ± 50.4 (21) | 162.7 ± 26.2 (29) | 86.3 ± 18.2 (29) |

** Where appropriate, the laboratory or aged-matched reference range is quoted*

*(Data are taken from reference 6)*

clinical practice. Alternatively, it may support the contention that progressive deterioration of renal function is not a linear uniform process but occurs in discrete steps separated by highly variable periods of time during which renal function remains very stable. This would mirror the situation in experimental nephrectomy models of feline renal failure where glomerular filtration rate (GFR) remains stable for at least 12 months after induction of renal failure (3, 4, 16).

One haematological finding that may be of prognostic value is that of anaemia. In a retrospective study, one-third of the stable CRF cases were anaemic at initial diagnosis and these fared much worse in terms of their survival when compared with those whose packed cell volume was above 0.27 l/l on first presentation (5). Further studies are required involving large populations of cats with stable CRF to determine what other factors might be of useful prognostic value in determining their longevity following initial diagnosis.

## Repeated renal insults from exogenous factors

One insult that may repeatedly damage the feline kidney was proposed over thirty years ago to be bacterial infection (17). A proportion of cases of feline CRF presenting for the first time, or those that represent after a period of stability, will have subclinical bacteriuria. In a prospective survey of 36 cats with naturally occurring CRF, 268 urine samples were collected by cystocentesis and submitted for bacteriological culture (18). A positive culture was found in 22 samples obtained from 11 cats giving the prevalence of subclinical bacteriuria as 8.2% and the incidence as 30.5%. A significantly higher incidence was noted in female cats (53%) when compared with male cats (14.3%), suggesting these infections were ascending. Urine collected by cystocentesis and its submission for culture would, therefore, seem to be a necessary part of any routine procedure in the monitoring a cat with CRF. Examining the urine sediment for evidence of bacteriuria (see **Figure 2**) is a fairly simple procedure that, when performed carefully, will detect the majority of cases where positive cultures are obtained. Thus, even if the owner is not prepared to pay for routine cultures, monitoring can be achieved in all clinical cases.

Early detection of a lower urinary tract infection and appropriate treatment with antibiotic therapy may prevent an infection from ascending to the kidney and causing further renal damage. It would be logical to assume that cats with CRF where bacterial urinary tract infections have been identified have some renal involvement and so should receive antibacterial treatment that is appropriate for pyelonephritis (19). The course of treatment should be of 4 to 6 weeks' duration. In addition, the choice of drug should be based on a sensitivity test that uses the plasma concentration of the drug achieved by the proposed dose rate. In the prospective study referred to above (18), all the isolates cultured were *E. coli* and all proved sensitive to fluoroquinolone antibacterial drugs. The only other groups of drugs to which more than 90% of the isolates were sensitive were potentiated sulphonamides and tetracyclines, neither of which was particularly appropriate for these cases. Empirical treatment should be avoided and antibacterial drug selection should, where possible, be based on culture and sensitivity testing. What proportion of feline CRF cases seen in general practice deteriorate because of an ascending bacterial infection remains to be determined but this is one cause of further renal damage that, through careful monitoring and appropriate treatment, can be prevented.

## Effects of phosphate and protein restriction on survival

Experimental studies in the rat and dog have demonstrated the positive value of phosphate restriction in slowing the progressive deterioration of renal function in animals with surgically reduced renal mass (20, 21). As discussed above, hypersecretion of PTH can be considered maladaptive. How much PTH itself contributes directly to this process is controversial and difficult to determine because PTH, phosphate, and calcium are all intrinsically linked and difficult to study individually. At the very least, plasma PTH concentrations probably serve to indicate those animals that are overloaded with phosphate and would therefore benefit from phosphate restriction.

Secondary renal hyperparathyroidism is an extremely common finding in feline CRF, even in those animals that are normophosphataemic (9). In many cases where treatment is possible, dietary phosphate restriction results in a reduction in plasma PTH concentration, which lags behind the fall in plasma phosphate (22). A study of the effects of phosphate restriction and control of PTH on the survival times of cats with naturally occurring CRF has been undertaken in a prospective clinical trial (6). Fifty cats were entered into this trial, 29 were successfully fed phosphate-restricted (diets used provided a phosphate intake of no more than 0.25 g/MJ) and 21 received standard maintenance diets (estimated phosphate intake of about 1.14 g/MJ) owing to limited intake of the renal diets by the cats or the owner being resistant to diet change. The clinical diets fed in this study (WALTHAM Veterinary Diet: Whiskas® Feline Low Phosphorus Low Protein) are also moderately restricted in protein, lower in sodium, higher in energy and supplemented with B vitamins when compared with standard maintenance cat foods. Plasma phosphate and PTH concentrations were assessed at the mid-survival time point in each group. A significant increase in PTH had occurred with time in the group that were not phosphate restricted, whereas PTH concentrations were lower than at the time of entry to the study in 69% of the group receiving phosphate restriction (see **Table 1**).

Kaplan Meier survival curves were constructed for the two groups of cats and are presented in **Figure 3**. The Kaplan Meier analysis gave median

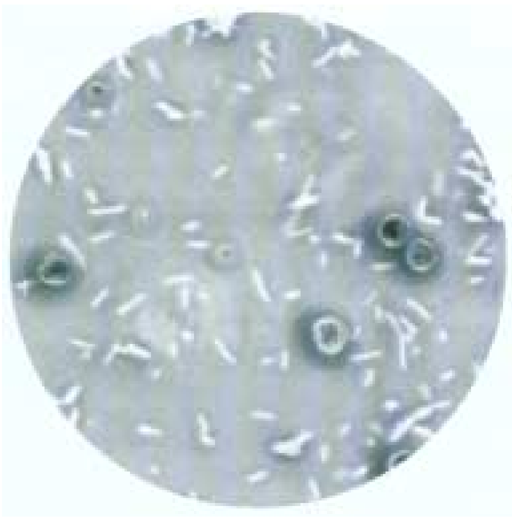

**Figure 2** *A photomicrograph of urine sediment viewed at 400x magnification under a phase contrast microscope. The rod-shaped organisms in focus were found to be* E. coli *on urine culture. White blood cells were also present but are out of focus on this field of view.*

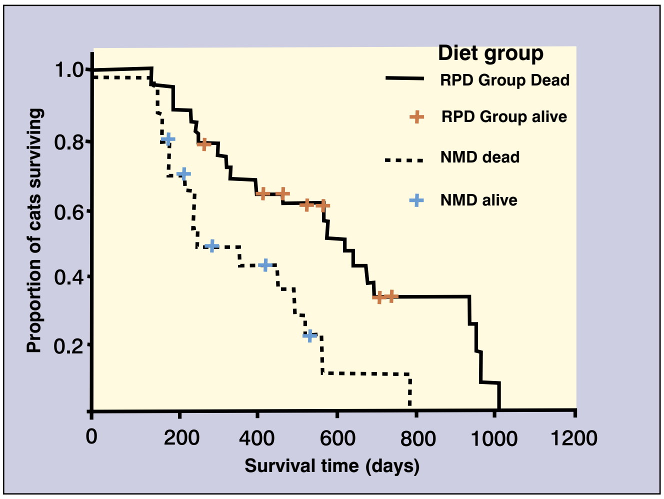


**Figure 3** *Kaplan Meier survival curves. Dotted line represents the data from the normal maintenance diet (NMD) group with the blue symbols representing those animals still alive at the time of analysis. Solid line represents the restricted phosphate diet (RPD) group with the red symbols representing those animals still alive at the time of analysis.*

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survival times of 264 days (interquartile range of 190 to 535 days) and 633 days (interquartile range of 338 to 950 days) for the maintenance diet and phosphate-restricted groups respectively. When the two curves were compared by log rank analysis, a highly significant difference was found ($P = 0.0036$) suggesting that the effect of feeding the phosphate- and protein-restricted diet was to increase survival time.

Although this study was non-randomised and open rather than double blind and placebo controlled, the cats that accepted the phosphate-restricted treatment regimen lived considerably longer than those that were fed standard maintenance diets. It cannot be concluded that phosphate restriction was the only factor responsible for this finding but it seems likely to have played a major part given the evidence from other species, including the dog (21). Based on the results of this study and the evidence from experimental studies, phosphate restriction should be a standard part of any treatment regimen for CRF in cats.

## Hypertension and progression

Systemic hypertension has been recognised to occur in a proportion of cats with naturally occurring CRF (23). In human medicine, prospective clinical studies have shown progressive renal damage can be slowed by lowering arterial blood pressure. Moreover, the target arterial blood pressure required should be based on the degree of proteinuria recorded in each patient (24). One maladaptation to renal failure described above was the increase in glomerular capillary pressure and hyperfiltration that can be detected in experimental models of CRF involving a reduction in renal mass. Hyperfiltration and glomerular hypertension will lead to increased losses of small amounts of albumin across the filtration membrane. Glomerular capillary pressure has been shown to be raised in cats where renal mass has been surgically reduced and that hyperfiltration occurs leading to increased protein loss (25).

From this information derived from experimental animal studies and human clinical studies there seem to be a number of questions that need to be addressed in cats with CRF. Currently, antihypertensive therapy is prescribed for those cats with systolic arterial blood pressures that are persistently elevated above 175 mmHg. This is done primarily to protect these cats from catastrophic events such as brain haemorrhage or retinal detachments. Lowering blood pressure below 170 mmHg seems to achieve this goal and the drug that consistently produces this response is the calcium channel blocker, amlodipine. In a recent study of the prevalence of systemic hypertension in cats with CRF, approximately 30% of the cases had systemic blood pressure of between 130 and 175 mmHg (26). How many of these cats would benefit from antihypertensive therapy? What should the target systemic arterial blood pressure be in order to produce a protective effect on the nephrons of the failing kidney? What drugs should be used to lower glomerular capillary pressure and will this therapy prove beneficial in naturally occurring feline CRF?

Glomerular pressure cannot be measured in clinical practice. The use of drugs to lower glomerular capillary pressure seems a logical therapeutic goal. Angiotensin-converting enzyme inhibitors (ACE-I) would seem to be the obvious choice of drugs for this purpose since angiotensin-II preferentially constricts the efferent arteriole in the glomerulus and hence raises intraglomerular pressure. Avoidance of systemic hypotension would be an important precaution hence the introduction of an ACE-I such as benazepril or enalapril should be accompanied by monitoring of systemic arterial blood pressure and should, ideally, be used only in cats where they would be beneficial. The effect of amlodipine on glomerular haemodynamics remains to be studied although several properties of this drug suggest that it too may be beneficial in counteracting the adaptation that occurs within the glomeruli of failing kidneys.

At the present time there are no published data from cats with naturally occurring CRF to suggest that antihypertensive treatment slows progression or that address the questions raised above. In one study, hypertensive cats that responded to antihypertensive treatment fared no better than those whose blood pressure remained poorly controlled (27). The difficulty of assessing the true arterial blood pressure of individual cats in the clinic is one problem that will hamper any clinical studies in this area. Nevertheless, this is certainly an area where further work may well lead to new drug treatments that could prove to be renoprotective and prolong the survival of cats with CRF.

## Conclusion

Improving the quality of life of our renal failure patients is far more important than increasing their life span. Nevertheless, many do enjoy good quality of life for extended periods such that some die of diseases other than their renal failure. It is important to remember that any treatment needs to be appropriate for the stage of renal failure in each individual patient. Monitoring these patients for the presence of urinary tract infections is an important part of any management regimen as prompt and effective treatment may well prevent further renal damage occurring. Scientific evidence supports a beneficial effect of restricting phosphate intake in many cases and the positive benefit of this measure appears to include extending the survival of feline CRF patients. Many other areas of management remain to be explored in detail. Antihypertensive therapy may well be a promising area for future development but several important questions remain to be answered.

Surgical renal transplantation may be an option for feline CRF cases in the future on a more routine basis. We should remember, however, to compare the quality of life of transplanted patients with that which can currently be achieved medically with current and future developments before adopting renal transplantation as the routine method.

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