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Dietary management of feline chronic renal failure: where are we now? In what direction are we headed?

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Dietary modification is of primary importance in managing cats with chronic renal failure. Diets designed for cats with chronic renal failure are typically formulated to be pH neutral and contain reduced quantities of protein, phosphorus and sodium and an increased quantity of potassium. These changes in diet formulation are designed to ameliorate clinical signs of renal failure by adapting dietary intakes to meet the limited ability of failing kidneys to adapt to the normal range of dietary intakes. Important recent clinical trials support the therapeutic value of dietary therapy in cats with chronic renal failure.

Chronic renal failure (CRF) is characterised by impaired renal excretory, regulatory and biosynthetic functions (Polzin et al 2000). Dietary modification can mitigate the impact of many of these functional impairments, thereby improving patient quality of life and potentially extending survival. The goals of dietary therapy are to ameliorate clinical signs of uraemia, minimise electrolyte and mineral imbalances, optimise nutrition, and limit progressive renal injury.

Contemporary feline renal diets are designed to minimise the effects of impaired excretory, regulatory and biosynthetic functions recognised in cats with renal failure. In addition to restricting dietary protein with the goal of minimising retention of nitrogenous waste products of protein catabolism which are associated with clinical signs of uraemia, renal failure diets have been modified to reduce the consequences of impaired renal regulatory function associated with retention of phosphorus, sodium and protons, and excessive loss of potassium.

Use of renal failure diets as the primary means of managing patients with chronic renal failure has become standard practice in the veterinary profession. While the rationale underlying many dietary modifications is conceptually logical and is supported by results of studies in cats with induced renal failure, the clinical efficacy of renal failure diets in management of patients with naturally occurring renal failure is dependent on results of properly designed and implemented randomised controlled clinical trials (Polzin 1996).

Dietary protein intake

Modification of the quantity and quality of protein has been the cornerstone of diet therapy for renal failure for decades. The premise for recommending dietary protein restriction to treat CRF was originally based on the observation that consumption of excessive quantities of protein by patients in renal failure resulted in clinical signs of uraemia. Retention of protein catabolites normally excreted by the kidneys is associated with increased concentrations of a large number of 'uraemic retention solutes' in extracellular and intracellular fluid. It is generally accepted that retention of catabolites of proteinaceous foods contributes significantly to genesis of the uraemic syndrome.

Nearly 20 years ago, Brenner and colleagues proposed that excessive consumption of dietary protein might promote progression of renal failure by promoting glomerular capillary hypertension and hyperfiltration (Brenner et al 1982). Subsequent to publication of this work, the bulk of research on dietary protein and CRF has focused on the role of protein restriction in limiting spontaneous progression of CRF.

Despite numerous studies on this subject, there is no consensus of opinion as to the impact of

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dietary protein intake on progression of CRF in humans, dogs and cats. Available data has been interpreted to indicate that dietary protein restriction alone does not profoundly alter the course of CRF, nor does excessive dietary protein intake induce renal failure in otherwise healthy humans, dogs or cats. Nonetheless, there is some evidence that protein restriction may be beneficial in slowing progression to uraemia in both humans and dogs (Levey et al 1999, Finco et al 1992).

In humans, a large multicentre clinical trial, entitled the 'Modification of Diet in Renal Disease' (MDRD) study, was designed to test the hypothesis that dietary protein restriction and strict blood pressure control would delay progression of CRF. Despite the magnitude of this study, preliminary results were not conclusive regarding the efficacy of the low protein diets in limiting progression of renal failure. The results were initially interpreted by many as evidence that protein restriction was ineffective in limiting progression of CRF. Recent re-evaluation of these studies, however, has led some investigators to conclude that the results are consistent with the hypothesis that protein restriction was beneficial (Levey et al 1999).

Most studies of the role of dietary protein restriction in limiting progression of CRF in dogs have been performed in dogs with stable renal function. Results of these studies support the contention that moderate to high protein intake does not induce renal failure in dogs. However, studies of dogs with stable renal dysfunction cannot directly address the question as to whether dietary protein restriction slows progressive CRF. Finco and colleagues examined the role of protein intake in dogs with progressive renal failure that were fed two different levels of dietary phosphorus (Finco et al 1992). While these researchers concluded that protein intake did not limit progression of renal failure, mortality rate was lowest among dogs fed the low protein, low phosphorus diet. Due to the design of this study, it is our opinion that a beneficial role for protein restriction in limiting progression of CRF cannot be excluded.

There are two reports of studies examining the role of dietary protein intake on progressive CRF in cats (Adams et al 1994, Finco et al 1998). In one study, proteinuria and significant renal lesions were observed in cats fed a higher protein diet (Adams et al 1994), however, these lesions could have been the result of either increased protein or calorie intake in this group of cats. In the other study, high protein intake did not induce renal lesions similar to those observed in the first study. In both studies, the magnitude of renal dysfunction remained stable over 12 months. While results of both do not provide conclusive evidence that moderate to high protein consumption promotes renal injury in cats, the stable nature of the renal dysfunction does not permit assessment of the role dietary protein restriction plays in limiting progressive CRF in cats.

Two preliminary studies of the efficacy of protein-restricted diets in managing cats with naturally occurring CRF have been reported. Harte and colleagues reported findings obtained from a randomised controlled clinical trial that supports efficacy of dietary protein restriction in ameliorating signs of CRF in cats with naturally occurring renal failure (Harte et al 1994). In this study, cats with CRF were randomly assigned to be fed either a diet containing 15.1 g protein and 0.23 g phosphorus/megajoule metabolisable energy (25 cats) or a diet containing 23.6 g protein and 0.48 g phosphorus/megajoule metabolisable energy (10 cats). The cats were evaluated for 24 weeks following diet assignment. Bodyweight, packed cell volume, serum albumin and total protein values declined in cats fed the higher protein diet. In contrast, these values increased in cats fed the lower protein diet. Over the 24-week period of study, clinical deterioration was reported for cats in both groups with respect to halitosis, gingivitis, appetite and body condition, however, deterioration was subjectively judged to be less apparent in cats fed the lower protein diet. Unfortunately, the method for assessing these clinical observations was not reported.

Mean serum urea nitrogen and creatinine concentrations progressively declined during the study in cats fed the 15.1% protein diet, but progressively increased in cats fed the 23.6 g protein diet. Likewise, serum phosphorus concentrations increased in the 23.6 g protein group and declined in the 15.1 g protein group. The authors concluded that the protein and phosphorus restricted diet was beneficial in slowing the rate of clinical deterioration in cats with CRF as assessed by both owners and clinicians. As both protein and phosphorus levels varied in these diets, it is difficult to ascribe the observed effects to either individual dietary component.

In the second study of naturally occurring renal failure reported in abstract form, Elliott et al compared the efficacy of a protein and phosphorus restricted diet to no dietary intervention (Elliot et al 1999). The study was not

randomised in as much as patients assigned to the protein restricted diet group comprised only cats willing to accept the modified diet. At the time of report, 13 of 22 cats fed the protein and phosphorus restricted diet had died or been euthanised with a median survival time of 581 days. In contrast, 11 of 15 cats fed the unrestricted diets had died or been euthanised with a median survival time of 252 days. Progressive renal failure was judged to be the cause of death or euthanasia in 31% of the cats in the restricted diet group and 73% of the cats in the unrestricted group.

It is not possible to ascribe the beneficial effects observed to either component alone because diets used in these clinical trials varied in both protein and phosphorus. The beneficial effects observed may have resulted from protein restriction, phosphorus restriction, or an interaction between these two dietary components.

Some have questioned whether dietary protein restriction is appropriate in cats because they have a higher dietary protein requirement than dogs or humans. The effect, if any, of renal failure on daily dietary protein requirements in cats is not known, but protein requirements are assumed to be at least as high as that required by normal cats. Thus, the higher protein requirement of cats appears to limit the degree to which protein can be restricted in animals with renal failure. It is not clear what impact, however, this limitation has on the clinical effectiveness of protein restriction in ameliorating clinical signs of renal failure.

While preliminary results provide support for the rationale of recommending dietary protein restriction for cats with CRF, results of reproducibly designed randomised controlled clinical trials directed solely at the role of protein restriction in minimising signs of uraemia and progression of CRF are needed to confirm this recommendation.

Results of a survey of current opinion on management of cats with CRF are available online at: http://www.uga.edu/kidney/renals.htm. It is apparent from examining this survey that a general consensus of opinion as to when dietary intervention is warranted in cats with CRF does not yet exist. This emphasises the importance of clinical studies designed to answer this question.

Dietary phosphorus restriction

Phosphorus is retained in CRF, eventually resulting in hyperphosphataemia, which in turn promotes renal secondary hyperparathyroidism. Hyperphosphataemia has been reported to be a reliable clinical index of hyperparathyroidism in cats with CRF (Barber & Elliott 1998). Hyperphosphataemia has been detected in approximately 60% of cats with CRF with the prevalence increasing as renal function declines (DiBartola et al 1987, Barber & Elliott 1998). In one study, the prevalence of renal secondary hyperparathyroidism in cats with CRF has been reported to be 84% (Barber & Elliott 1998). In this study, all cats with end-stage CRF, 87% of cats with some clinical signs of CRF and 47% of clinically normal cats with only biochemical evidence of CRF had hyperparathyroidism. Hyperparathyroidism was even detected in nine cats with CRF having normal serum calcium and phosphorus concentrations.

Dietary protein/phosphorus restriction has been shown to be effective in significantly reducing plasma phosphorus concentrations and parathyroid activities in cats with naturally occurring CRF (Barber et al 1999). Diet therapy alone was effective in achieving euparathyroidism in eight of 15 cats, and only two of 15 cats in this study required the addition of intestinal phosphorus binding agents to normalise serum phosphorus concentrations. As protein is a major source of dietary phosphorus, most renal diets are restricted in both protein and phosphorus content.

Limiting phosphorus consumption appears to slow progression of CRF. Phosphorus retention and hyperphosphataemia have been linked to increased mortality in humans and dogs with CRF (Brown et al 1991, Finco et al 1992, Block et al 1998). In humans with CRF treated by haemodialysis, the adjusted relative risk of mortality remained stable in patients with serum phosphorus concentrations below 6.5 mg/dl (2.1 mmol/l), but increased significantly when serum phosphorus concentrations were above this level. Patients with serum phosphorus concentrations between 6.6 to 7.8 mg/dl (2.13–2.52 mmol/l) had 13% higher mortality than patients in the reference range (4.6–5.5 mg/dl; 1.5–1.8 mmol/l), and the relative mortality risk was 34% higher when serum phosphate concentrations increased to between 7.9 to 16.9 mg/dl (2.55–5.46 mmol/l). Mild hyperphosphataemia (5.0–6.5 mg/dl; 1.61–2.10 mmol/l) was not associated with an elevated mortality risk. The product of serum calcium concentration multiplied by serum phosphorus concentration showed a mortality risk trend similar to that seen

for patients with hyperphosphataemia. Patients with $Ca \times PO_4$ products greater than 72 mg^2/dl^2 (5.8 $mmol^2/l^2$) had a relative mortality risk of 1.34 relative to products between 42 and 52 mg^2/dl^2 (3.38–4.19 $mmol^2/l^2$) (Block et al 1998). The mechanisms responsible for the adverse effects of hyperphosphataemia on mortality remain unresolved, but may in part be related to mineralisation of the renal parenchyma.

There is evidence that dietary phosphorus restriction also limits renal injury in cats with CRF. In one study of cats with induced renal failure, dietary phosphorus restriction reduced the severity of renal mineralisation (Ross et al 1982) Further, the apparent beneficial effects of dietary protein and phosphorus restriction on longevity observed in clinical trials of cats with naturally occurring renal failure are likely to be associated, at least partially, to dietary phosphorus restriction (Harte et al 1994, Elliot et al 1999). However, direct experimental or epidemiological evidence linking phosphorus restriction alone to a reduction in the rate of progression of CRF in cats has apparently not yet been reported.

Currently, dietary phosphorus restriction is usually initiated when hyperphosphataemia is recognised, however, because hyperparathyroidism occurs before serum phosphorus concentrations exceed the normal range, and because fasting serum phosphorus concentration may not accurately reflect overall phosphorus metabolism, phosphorus restriction may be of benefit when initiated before the onset of overt hyperphosphataemia (Martinez et al 1997, Barber et al 1999). When dietary phosphorus restriction alone fails to normalise serum phosphorus concentrations, addition of intestinal phosphorus binding agents such as aluminum hydroxide or carbonate or calcium acetate is commonly recommended.

Relationship of diet to metabolic acidosis

Metabolic acidosis is a common complication of CRF in cats, reportedly affecting 60 to 80% of patients (Lulich et al 1992, DiBartola et al 1987). Consumption of acidifying diets may in part explain the great frequency of metabolic acidosis in cats with CRF, however, available evidence suggests that, compared with other mammalian species, feline kidneys respond differently to metabolic acidosis.

The kidneys maintain normal acid-base balance through a combination of renal tubular reabsorption of filtered bicarbonate and excretion of protons with ammonia and other buffers. Renal excretion of protons effectively regenerates bicarbonate lost via the gastrointestinal or urinary tracts or through respiratory buffering of metabolic acids. As the quantity of functioning nephrons declines as a result of progressive CRF, urinary excretion of hydrogen ions is maintained largely by increasing the quantity of ammonium excreted by surviving nephrons (increased ammoniagenesis). As CRF becomes more severe, however, further loss of nephrons impairs renal ammoniagenesis and metabolic acidosis ensues.

Results of some studies suggest that the aforementioned compensations to metabolic acidosis may not occur in cats. For example, in one study, acidosis failed to increase the rate of production of ammonia in cultured feline proximal tubular cells (Lemieux et al 1990). Whether cats are at increased risk of developing metabolic acidosis because of this limitation is unknown, but the unexpectedly high incidence of acidosis in cats with CRF would be consistent with this suggestion.

Metabolic acidosis is clinically important because it may promote a variety of adverse effects including anorexia, nausea, vomiting, lethargy, weakness, muscle wasting and weight loss. In addition, studies on the effects of dietary acidification in cats have revealed that chronic metabolic acidosis may promote negative potassium balance (Fettman et al 1992).

Acidosis observed in most cats with CRF is typically mild to moderate and relatively stable, however, a combination of consumption of an acidifying diet by a patient with moderate to severe CRF may result in severe acidosis. Severe acidaemia (blood pH values below 7.20) may result in a reduction in cardiac output, arterial pressure, and hepatic and renal blood flows and centralisation of blood volume (Adrogué et al 1998). Centralisation of blood volume results from peripheral arterial vasodilatation and central venoconstriction. In addition, reduction in central and pulmonary vascular compliance may predispose patients to pulmonary oedema during fluid administration, an effect that may be particularly important in patients with acute uraemic crises requiring intensive fluid therapy.

Metabolic acidosis has also been hypothesised to promote progression of renal failure in some species. Studies in rats suggest that elevated

renal parenchymal ammonia concentrations may be one pathway whereby diverse renal insults result in similar pathologic manifestations of renal injury (Nath et al 1985). Renal ammoniagenesis may be augmented by several means including chronic metabolic acidosis, hypokalaemia and feeding high-protein diets. High tissue ammonium concentrations may activate the third component of complement by the alternate pathway. Complement-mediated renal inflammation is hypothesised to result in tubulointerstitial damage, which may in turn promote progression of renal disease. Prophylaxis of metabolic acidosis has been shown to prevent development of tubulointerstitial lesions in rats with induced CRF.

Based on results of recent studies in rats, however, the role of acidaemia-induced renal ammoniagenesis has been questioned (Throssel et al 1995). Results of long-term studies suggest that the effects reported by Nath and colleagues may have been a transient or short-term effect, possibly related to the timing of therapeutic intervention. Throssell and colleagues concluded that metabolic acidosis neither caused nor exacerbated chronic renal injury. In addition, in their opinion, treatment of uraemic acidosis was unlikely to influence disease progression in patients with chronic renal failure.

Results of studies from our centre indicate that mild to moderate acidosis does not promote renal injury in cats with induced CRF (James et al, unpublished data, 1998). These data suggest that acidifying feline diets similar to those used for prophylaxis of struvite-related urinary tract disorders are an unlikely cause for spontaneous CRF in cats.

Acidosis also appears to promote protein malnutrition in patients with CRF. Protein catabolism is increased in patients with acidosis to provide a source of nitrogen for hepatic glutamine synthesis, glutamine being the substrate for renal ammoniagenesis (Mitch et al 1993). Evidence derived from studies of rat muscle suggests that uraemia directly impairs insulin-stimulated protein synthesis independent of metabolic acidosis. On the other hand, protein degradation is stimulated by metabolic acidosis, even in non-uraemic states. The combined effects of reduced protein synthesis due to uraemia and accelerated proteolysis due to acidosis promote elevations in blood urea nitrogen, increased nitrogen excretion, and negative nitrogen balance typical of uraemic acidosis. Altered branched chain amino acid metabolism appears to be involved. Chronic metabolic acidosis increases the activity of muscle branched chain keto acid dehydrogenase, the rate-limiting enzyme in branched chain amino acid catabolism. This is important in that branched chain amino acids are rate limiting in protein synthesis and play a role in regulation of protein turnover. Alkalisation effectively reverses acidosis-associated protein catabolism. There is speculation that changes in intracellular pH accompanying acidosis lead to alterations in gene transcription which increase the activity the cytosolic, ATP- and ubiquitin-dependent protein degradation pathway. Severe chronic metabolic acidosis has the potential to induce a cycle of progressive protein malnutrition and metabolic acidosis. Excessive protein catabolism may lead to protein malnutrition despite adequate dietary intake. This process may promote further acidosis by accelerating breakdown of endogenous cationic and sulphur-containing amino acids.

Acidosis poses a particularly vexing problem for CRF patients consuming protein-restricted diets. Dietary protein requirements appear to be similar for normal humans and humans with CRF unless uraemic acidosis is present. When acid-base status is normal, adaptive reductions in skeletal muscle protein degradation protect patients consuming low-protein diets from losses in lean body mass. In rats and humans, even mild acidosis my override these adaptive responses. Thus, acidosis may limit the ability of patients to adapt to dietary protein restriction. These findings have not yet been confirmed in cats, however, if valid, minimising acidosis may be an essential component in successful dietary therapy of cats with CRF.

Results of recent studies of uraemic humans treated by chronic ambulatory peritoneal dialysis suggest that correcting mild acidosis of may lead to improved nutrition and notably reduced morbidity (Stein et al 1997). In turn, reduced morbidity means fewer admissions of these patients to hospitals and shorter periods of hospitalisation.

Acidosis appears to be a common and potentially important clinical complication of CRF in cats. While acidifying diets do not appear to cause CRF or promote its progression in cats, the potential adverse clinical and nutritional effects of acidosis justify feeding non-acidifying or neutral diets. The need to provide therapy in effort to maintain normal acid-base balance may increase when cats are fed reduced protein diets.

Dietary potassium and the kidneys

An association between polyuric renal failure and hypokalaemia has been recognised in cats by several investigators (Lulich et al 1992, Dow et al 1992, DiBartola et al 1993). It is unclear whether hypokalaemia is a cause of CRF in cats, a consequence of CRF, or both. In one study, renal dysfunction was observed in three of nine cats and lymphoplasmacytic interstitial nephritis and interstitial fibrosis were observed in five of the nine cats fed a potassium restricted and acidifying diet (DiBartola et al 1993). However, it was not possible to attribute the renal lesions to dietary potassium deficiency conclusively because a control group was not available for comparison.

There is additional evidence to support the concept that CRF predisposes to hypokalemia. For example, in a study performed in our centre, four of seven cats with induced CRF fed a diet containing 0.3% potassium developed hypokalaemia, while four cats with normal renal function fed the same diet did not develop hypokalaemia (Adams et al 1993). In another study, the observation that muscle potassium content was reduced in normokalaemic cats with spontaneous CRF indicates a total-body deficit of potassium may develop before the onset of hypokalaemia (Theisen et al 1997).

Potassium depletion and hypokalaemia in cats with CRF may result from inadequate consumption of potassium, dietary factors, enhanced renal losses, or combinations of these factors. Inadequate consumption of potassium could reflect decreased appetite or insufficient dietary potassium content. In addition diets that are acidifying, magnesium restricted, and/or high in protein content appear to increase the risk of development of hypokalaemia. Although it has been hypothesised that renal potassium wasting occurs in cats with CRF, this has not been proven.

Severe neuromuscular manifestations, once the hallmark of severe hypokalaemia in cats, have become less commonly recognised. Presumably this change is the result of increasing potassium content of manufactured renal failure diets. Decreased renal function and anorexia appear to be common manifestations of hypokalaemia in cats with CRF. In many cats with CRF and hypokalaemia, renal function improves coincident with restoration of normokalaemia by oral or parenteral potassium therapy. This observation suggests that hypokalaemia may induce a reversible reduction in GFR.

Renal function is adversely affected in normal cats fed an acidified, potassium restricted diet (Dow et al 1990). In this study, potassium depletion and acidosis appeared to be additive in impairing renal function. Based on these results, it was hypothesised that a self-perpetuating cycle of excessive urinary potassium loss and whole body potassium depletion may promote a progressive decline in renal function.

Feeding acidifying diets or supplemental oral acidifiers to cats with CRF may exacerbate potassium depletion. If diets designed for cats with CRF do not maintain normal potassium balance, it is logical to recommend that they be supplemented with potassium in order to minimise the risk of hypokalaemia. It is somewhat surprising that results of a recent clinical trial suggest that daily supplementation with potassium gluconate was not demonstrably superior to sodium gluconate in restoring muscle potassium stores in cats with CRF (Theisen et al 1997). However, the number of cats in this study was small and median muscle potassium content increased to near normal.

Further studies are needed to determine the value of enhancing potassium consumption by CRF cats with normal serum potassium concentrations. Likewise, further studies are needed to clarify whether the potassium content of diets fed to cats with CRF is related to development or progression of renal disease.

Dietary salt restriction

It is widely accepted that dietary sodium content should be limited in patients with CRF. The rationale behind this suggestion is that excessive sodium intake might promote arterial hypertension and its various consequences such as hypertensive retinopathy, cardiovascular disease and acute neurological disease. There is also limited data to suggest that sodium restriction may limit progressive renal injury (Dworkin et al 1996). However, evidence linking sodium intake to arterial hypertension is largely drawn from other species, particularly humans. Neither the efficacy of salt restriction in limiting these complications nor the risks of sodium restriction have been critically evaluated in cats with CRF. Seemingly, sodium restriction might decrease extracellular fluid volume, thereby promoting prerenal azotaemia, and adversely influence diet palatability. At present, there is no data on which to base a recommendation for or against limiting dietary sodium intake in cats with CRF.

From theory to practice

In the final analysis, diets designed to minimise the consequences of renal excretory, regulatory and biosynthetic dysfunction will only be of value if the cats with CRF consume them. While diet palatability is an important issue in this regard, many cats are at an advanced stage of renal failure when they become anorexic. At this advanced state of renal dysfunction, reduced appetite may be more a related to uraemia than the palatability the renal failure diets. Modifying diet palatability and administration of 'appetite stimulants' are often ineffective in promoting consumption of a sufficient quantity to maintain an adequate state of nutrition. In these situations, we have had good response by feeding CRF cats renal failure diets via gastrostomy or pharyngostomy tubes. With the aid of these devices, a high quality of life can frequently be sustained for long periods in a cost-effective fashion. They are also invaluable in facilitating oral treatment with phosphorus binding agents, alkalinising drugs and potassium supplements.

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