Purina *Research* Report™

Nutrition and Renal Function

This series of articles was adapted from articles presented at the 1998 Purina Nutrition Forum, held June 4-6, 1998, in St. Louis, Mo.

Acid-Base, Electrolytes, and Renal Failure

Adapted from an article by Drs. David J. Polzin, Carl A. Osborne and Kathryn James

Metabolic acidosis is a well-recognized component of chronic renal failure (CRF). Metabolic acidosis in renal failure results primarily from the limited ability of failing kidneys to excrete hydrogen ions and regenerate bicarbonate. In a retrospective case series of cats with CRF, approximately 80 % had metabolic acidosis based on decreased venous blood pH values and bicarbonate concentrations (Lulich, Osborne et al., 1992). In contrast, acidosis appears to occur less consistently in dogs with CRF.

Effects of Dietary Protein Intake on Renal Functions in Dogs

Adapted from an article by Dr. Delmar R. Finco

The effects of proteins on renal functions have been studied extensively in several mammalian species. Early observations (1928) identified harmful effects of protein ingestion on the kidneys of the male gender of a strain of rats predisposed to naturally occurring renal failure.[1] Research conducted between these early studies and the present time has resulted in considerable advancement in our knowledge of protein effects on the kidneys, but many aspects remain controversial or unknown. One caveat to consider in interpretation of results of many of the dietary studies has been failure to control variables other than protein intake. In particular, effects attributed to protein have not always been differentiated from effects of calories, lipids, or inorganic constituents of diets.

Effects of Dietary Lipids on Renal Function in Dogs and Cats

Adapted from an article by Dr. Scott A. Brown

Preliminary studies in our laboratory have established that cats and dogs with induced renal dysfunction exhibit hypercholesterolemia and/or hypertriglyceridemia. We established an association between hyperlipidemia and progressive renal failure in dogs, wherein loss of renal function in dogs with induced renal disease was directly related to plasma triglyceride and total cholesterol concentrations. We have recently observed that the

Acid-Base, Electrolytes, and Renal Failure

Although species-related differences in renal acid excretion may contribute to this apparent difference, it is likely that the high incidence of uremic acidosis in cats relates, at least in part, to the acidifying nature of many cat foods. It has been speculated that routine use of acidifying diets may contribute to the relatively high incidence of CRF observed in cats over the past decade. Further, uremic acidosis may contribute to the chronic wasting typical of CRF.

Chronic metabolic acidosis promotes a variety of adverse clinical effects including anorexia, nausea, vomiting, lethargy, weakness, muscle wasting, and weight loss. Severe acidosis may also

influence carbohydrate and protein metabolism, serum potassium concentrations, and brain metabolism (Androgue and Madias, 1998). Acidemia promotes hyperkalemia through translocation of potassium out of cells, an effect that is more prominent with non-organic acidosis. Severe acidemia impairs brain metabolism and volume

---

... of cats with chronic renal failure, approximately 80% had metabolic acidosis...

---

regulation leading to progressive obtundation and coma.

Protein degradation is stimulated by metabolic acidosis, while protein synthesis is impaired by uremia. The combined effects promoted elevations in blood urea nitrogen, increased nitrogen excretion and negative nitrogen balance. Recent studies have suggested that

correcting even relatively mild acidosis in humans with renal failure may translate to improved nutrition and reduced morbidity (Stein et al. 1997).

Potential benefits of alkalization therapy in patients with CRF include: 1) improving signs of anorexia, lethargy, nausea, vomiting, muscle weakness, and weight loss which may be caused by uremic acidosis, 2) preventing the catabolic effects of metabolic acidosis on protein metabolism in patients with CRF, thereby promoting adaptation to dietary protein restriction, 3) enhancing the patient's capacity to adapt to additional acid stress resulting from such factors as diarrhea, dehydration, or respiratory acidosis, 4) limiting skeletal damage (demineralization and inhibited skeletal growth) resulting from bone buffering, and 5) rectifying the adverse effects of severe acidosis on the cardiovascular system (impaired myocardial contractility and enhanced venoconstriction).

Oral sodium bicarbonate is the most commonly used alkalinizing agent for patients with metabolic acidosis of CRF. Because the effects of gastric acid on

Dietary Protein

Dogs with Renal Dysfunction – Feeding Experiments

Several studies have addressed the issue of effects of protein intake on renal function and morphology in dogs with reduced renal mass. Most of these studies have treated the kidneys as a "black box," and determined the extent of morphologic and functional changes rather than investigating presumed mechanisms of their occurrence. These "black box" studies have served a very useful purpose, because current theories concerning the pathogenesis of progression of renal failure are not restricted to glomerular hypertension and hypertrophy. Mechanisms not yet even postulated may also exist. Should mechanisms other than glomerular hypertension and hypertrophy play a role, they would presumably be uncovered by such "black box" studies.

A few studies have compared diets in dogs with naturally occurring renal diseases.[2-5] In all instances diets varied in several components

other than protein. Since dogs were managed clinically, they sometimes received non-dietary treatments which could have affected disease outcome. The unknown etiology of the naturally-occurring disease also provided potential for considerable variation between dogs in the rate of progression of disease by mechanisms unrelated to diet. These studies have provided some information to veterinarians on clinical responses to various commercially available foods, but they have not provided information to define the role of dietary protein intake on progressive renal injury.

Several studies have examined effects of diet in dogs with "remnant kidneys."[6-11] This model has the advantage of normal renal morphology in the "remnant kidney" at the onset of dietary manipulations. Subsequent changes in renal morphology can then be attributed to the reduction of renal mass, as modified by the diet or other variables being studied. Studies that have used diets formulated so that protein was the only variable (except for carbohydrate sources to maintain the diets isocaloric) are most revealing regarding protein effects. Table 1 on page 4 provides a summary of experiments done to determine diet effects on dogs with

oral sodium bicarbonate are unpredictable, the dosage should be individualized for each patient. The suggested initial dose of sodium bicarbonate is 8 to 12 mg/kg body weight given every 8 to 12 hours.

Potassium citrate is a particularly attractive alternative alkalization agent. Potassium citrate may offer the advantage, at least in cats, of allowing for the simultaneous treatment of both hypokalemia and acidosis with a single drug. Metabolic acidosis when accompanied by potassium depletion or magnesium depletion may respond poorly to alkali therapy alone. There is a risk for over-alkalization, however, in that potassium doses required for adequate correction of hypokalemia may exceed the citrate dose required to correct acidosis. Starting doses of 0.3 - 0.5 meq/kg of potassium every 12 hours are recommended.

Regardless of the alkalinizing agent chosen, administration of several smaller doses is preferred to a single large dose in order to minimize fluctuations in blood pH. The patient's response to bicarbonate therapy should be determined by measuring blood bicarbonate or serum (plasma) total CO_2 concentrations 10 to 14 days after initiating therapy. Ideally, blood should be collected just prior to administration of the drug. The goal of therapy is to maintain blood bicarbonate (or serum total CO_2) concentrations within the normal range. Dosage should be adjusted according to changes in blood bicarbonate (or serum total CO_2) concentrations. Urine pH is often insensitive as a means of assessing the need for or response to treatment and is not routinely recommended for these purposes. ◼

REFERENCES

1. Adrogué HJ and Madias NE: Management of Life-threatening Acid-Base Disorders. New England J Med 338:26-34, 1998.
2. Lulich J, Osborne C, O'Brien T et al.: "Feline renal failure: Questions, answers, questions." Compendium on Continuing Education for the Practicing Veterinarian 14: 127, 1992.
3. Stein A, Moorehouse J, Iles-Smith H, et al.: Role of improvement in acid-base status and nutrition in CAPD patients. Kidney Int 52:1089-1095, 1997.

Dietary Lipids and Renal Function

hyperlipidemia in dogs with induced chronic renal failure can be modified by changes in dietary fatty acid composition. Specifically, animals fed a diet enriched with polyunsaturated fatty acids (PUFA) from either safflower oil or menhaden fish oil exhibited an amelioration of the hyperlipidemia observed in dogs fed a diet containing predominantly saturated fatty acids.

As a potential therapy to slow the rate of progression of renal disease, dietary n-3 PUFA supplementation was hypothesized to exert additional renoprotective effects by altering the critical secondary factors involved in the progressive renal failure: glomerular hypertension, intrarenal inflammation, hyperlipidemia with lipid peroxidation, and intrarenal growth factor elaboration. Critically, long-term studies in our laboratory have shown that a diet supplemented with menhaden fish oil will preserve renal function in dogs with induced renal failure, when compared to

reduced renal mass. When attention is focused on those experiments in which protein has been isolated as the only variable, the data are overwhelmingly indicative of a failure to demonstrate a protein effect on the functional or morphologic deterioration of kidneys of "remnant kidney" dogs.

Older dogs have a higher incidence of chronic renal disease than young dogs, and restricting protein intake in these dogs has been advocated as a renoprotective maneuver. In a study designed to test this hypothesis, experimental dogs seven to eight years of age were divided into two groups. Dogs in both groups had uninephrectomy performed to increase vulnerability of the remaining kidney to any protein effects. One group was fed a low protein diet, and the other group received a high protein diet for the subsequent four years.[12] Results of this study indicated that there were no adverse effects from the high protein diet (Table 1), and mortality was actually higher in the low protein group. A similar study was conducted in another laboratory and likewise no adverse effect from high protein diets was detected.[13] In the latter study, however, increased mortality in dogs receiving the low protein diet did not occur. ◼

REFERENCES

1. Newburgh LH, Curtis AC. Production of renal injury in the white rat by the protein of the diet. Arch Int Med 1928;42:801-821.
2. Polzin D, Leininger J, Osborne C, et al. Development of renal lesions in dogs after 11/12 reduction in renal mass. Lab Invest 1988;58:172183.
3. Finco DR, Brown SA, Crowell WA, et al. Effects of dietary phosphorus and protein in dogs with chronic renal failure. Am J Vet Res 1992; 53:2264-2271.
4. Polzin DJ, Osborne CA, Hayden DW, et al. Influence of reduced protein diets on morbidity, mortality, and renal function in dogs with induced chronic renal failure. Am J Vet Res 1984;45:506517.
5. Barsanti JA, Finco DR. Dietary management of chronic renal failure in dogs. J Am Animal Hosp Assoc 1985; 21:371-376.
6. Hansen B, DiBartola SP, Chew DJ, et al. Clinical and metabolic findings in dogs with chronic renal disease fed two diets. Am J Vet Res 1992;53:326-334.
7. Grandjean D, Paragon BM, Grandjean R, at al. Interer d'une alimentation hypoproteique et hypophosphoree dans i'evolution post seuil critique d'une insuffisance renal chronique chez le chien. Recueil de Medicine Veterinaire 1990;166:865-880.
8. Liebetseder J, Neufeld K. Effects of medium protein diets in dogs with chronic renal failure. J Nutr 1991; 121:S145-S149.
9. Bovee KC, Kronfeld DS, Ramberg C, et al. Long-term measurement of renal function in partially nephrectomized dogs fed 56, 27, or 19% protein. Invest Urology 1979;16:378-384.
10. Robertson JL, Goldschmidt MS, Kronfeld DS, et al. Long-term responses to high dietary protein intake in dogs with 75% nephrectomy. Kidney Int 1986;29:511-519.
11. Polzin DJ, Osborne CA, O'Brien TD, et al. Effects of protein intake on progression of canine chronic renal failure (CRF). Proc 11th Ann Vet Med Forum, 938, 1993.
12. Finco DR, Brown SA, Crowell WA, et al. Effects of aging and dietary protein intake on uninephrectomized geriatric dogs. Am J Vet Res 1994; 55:1282.
13. Churchill J, Polzin D, Osborne C, et al. Influence of diet on renal function and structure in geriatric uninephrectomized dogs. Proc 15th ACVIM Forum 1997:675.

supplementation with safflower oil (a rich source of n-6 PUFA) or a highly saturated fat-source (beef tallow). While further studies are needed to understand the mechanisms responsible for this protection, the use of diets supplemented with menhaden fish oil has become an important consideration in the therapy of chronic renal disease in dogs.

We recently completed studies in cats on the effects of variations in dietary omega-3:omega-6 PUFA on plasma lipoproteins, urinary eicosanoids excretion, systemic arterial pressure and renal function. There was a significant effect of dietary fatty acid composition on plasma total lipoprotein concentrations and on plasma total cholesterol concentration, with a lowering of both plasma concentrations observed only for the diet with the highest omega-3 content, with an omega-6:omega-3 ratio (n-6/n-3) of 1:1.

There was no statisically significant effect of dietary n-6/n-3 to alter urinary prostaglandin E2 excretion. As dietary n-6/n-3 declined from 10:1 to 1:1, there was a statistically nonsignificant trend for this dietary manipulation to lower renal thromboxane A2 production. The hypothesis that dietary n-3 supplementation would lower systemic arterial blood pressure was not supported by our results obtained by radiotelemetry in undisturbed, normal cats. The question remains as to whether or not hypertensive cats would benefit from dietary fish oil supplementation.

Finally, the lower dietary n-6/n-3 PUFA ratio increased glomerular filtration rate in normal cats. There was no significant effect and no discernible trend for effect of dietary PUFA on proteinuria.

Renal disease and dietary fats: Further Recommendations

In cats, dietary supplementation with n-3 PUFA had no apparent deleterious effect on lipid metabolism, immune function, blood pressure, or renal function. At higher levels of supplementation, renal function was actually increased in normal cats. These data support the assertion that this dietary maneuver is safe for normal cats and provides some encouragement for further consideration for dietary n-3 PUFA supplementation in cats with renal disease, systemic hypertension, or hypersensitivity reactions. Further studies will be required, however, to characterize the response of cats with renal disease, systemic hypertension, or hypersensitivity reactions to this dietary manipulation.

Preliminary evidence from recent studies in our laboratory suggests that a dietary trial of menhaden fish oil supplementation could be considered in dogs with renal disease. However, the n-6:/n-3 ratios of the diets in our initial study were <0.2:1 and >50:1; ratios which are difficult to achieve in commercially available preparations. A commercially available diet can be supplemented with PUFA. Commonly available veterinary fatty acid supplements contain a mixture of n-3 and n-6 PUFA, a combination which has not been studied in dogs or cats with renal disease. Results of our studies indicate that n-6 PUFA supplements should be avoided in early renal failure. The diet can be supplemented with available products that supply only n-3 PUFA obtained at health food stores. As with any therapeutic maneuver, baseline values for serum creatinine concentration, the urine protein-to-creatinine ratio, and mean arterial

---

Table 1: Summary of Experiments on Dogs With Reduced Renal Mass That Examined Renal Effects of Diet.

Model	Diets compared	Duration	Conclusions, comments	Ref.
3/4 NX[a]	Three commercial diets varying in many components; protein levels of 44%, 14%, and 7% of metabolizable energy (ME).	Up to 48 months	No evidence of adverse effects of diets on renal function. Histologic trend toward more severe lesions in the highest protein diet. No diet effects demonstrated by electron microscopy. Dogs were non-azotemic for most of the study.	9,10
11/12 NX	Three commercial diets varying in many components; protein levels of 44%, 14%, and 7% of ME.	40 weeks	No evidence of functional deterioration on any diet; no morphologic assessment of kidneys was reported.	8
11/12 NX	Three diets varying in many components; 2 levels of protein; 41% and 15-16% of ME.	8 weeks	Renal lesions developed; severity of lesions was related to decrements in GFR but not to diet.	6
15/16 NX	Two experimental diets designed to vary only in protein levels; 31% and 16% of ME.	24 months	No differences between groups in deterioration of renal function or in severity of renal lesions.	7
11/12 NX	Two experimental diets designed to vary only in protein levels; % of ME unclear; diets were 40% and 14% protein.	100 weeks	No functional deterioration with time with either diet; no difference in severity of renal lesions between diets.	11
1/2 NX Geriatric dogs	Two experimental diets designed to vary only in protein levels; protein levels of 31% and 16% of ME.	48 months	No functional deterioration with time with either diet; no difference in severity of renal lesions between diets.	12
1/2 NX Geriatric dogs	Three experimental diets; protein levels of 34%, 30%, 20% of ME; fat content of 30% diet 2X others.	48 months	No functional deterioration with time with any diet; no difference in severity of renal lesions between diets.	13

[a]NX = functional elimination of nephrons, either by infarction or surgical removal. Fraction represents the portion eliminated.

Variability in urine pH between cats is considerable, even in those fed the same diet.

Variability of Urine Characteristics in Cats Fed a Common Diet as Determined by an Automated Urine pH Collection Device

Urine pH is considered an important physiological parameter in cats which can be influenced by diet as well as by other factors. Typically, collection of urine for measurement of pH has been by cystocentesis, catheterization or manual expression. Some disadvantages to these methods include being limited to a point in time sample rather than continuous monitoring, potential bladder trauma and animal stress – all factors which may influence urine pH. To eliminate these factors, systems were developed to continuously monitor and immediately record the pH of spontaneously voided urine. Studies were conducted with these automated urine pH collection units to estimate the components of variability in urine pH.
Methods: *Experiment 1* – Twelve adult cats (six male and six female) were fed one of two diets differing in urine acidification potential for nine days – each in a crossover design. Urine pH was recorded for all days to determine days to acclimation to a change in diet. *Experiment 2* – Six male and six female adult cats were fed a common, nutritionally complete and balanced diet for 10 days. Urine pH and volume were recorded for the final six days as separate 24-hour collections. Data were analyzed for variation from day, cat and individual urination.
Results: Changes in urine pH in response to a dietary change tended to plateau within the first three to four days feeding in Experiment 1. In Experiment 2, 94% of the variability in urine pH was due to differences between urinations within individual cats. After averaging urine pH values from each cat for each day, cat to cat variability explained 32% of the remaining variability and 68% was explained by day to day variability within cats. Little change in cat to cat variability was found when the number of collection days was increased.
Conclusions: Variability in urine pH between cats is considerable, even in those fed the same diet. Day to day and within day variation may be missed by single urine samples, such as obtained via cystocentesis. This variability should be considered when interpreting urine pH research and clinical data.

J.R. Jackson, D.A. Ritchie, D.P. Laflamme, J.M. Ballam. Ralston Purina Company.

*Research*Abstracts

Agreement Between Urine pH Measurements Made by Dipstrip and pH Meter

To investigate the agreement between urine pH determined by dipstrip and by meter, urine pH measured by both methods was compared in 109 cats and 55 dogs. The cats were either healthy or showing signs of irritative voiding. Urine samples were collected by cystocentesis or metabolic cage. After cystocentesis, urine was stored in the syringe used for collection and pH was measured within two hours. For metabolic cages, 24-hour urine production was collected under USP heavy mineral oil each day in plastic collection bottles connected to pans under the cages. Urine samples were collected by cystocentesis only from 52 healthy dogs and three dogs with urinary tract infections. After cystocentesis, urine was stored in red-topped vacutainers and pH was measured within the hour.

Urine pH was measured using Chemstrip 7 dipstrips. The color reaction was interpolated to the nearest 0.5 pH unit by an experienced clinical laboratory technician. The urine pH also was measured to the nearest 0.01 pH unit using a pH meter. Both correlation coefficients and Bland-Altman plots were used to compare the two methods. The Bland-Altman plot assesses agreement between measurement methods by comparing the difference between the methods against their mean. This method allows the between-method differences to be assessed. It is these differences that must be evaluated when comparing two tests.
Results: The data demonstrates that pH strips provide clinically imprecise estimates of urine pH measured by pH meter. For example, dipstrip pH measurements of 7.0 were associated with urine pHs measured by pH meter ranging from 6.2 to 8.2, a range too broad, for example, to predict the likelihood of struvite precipitation.

Therefore, dipstrip pH determinations may not be sufficiently precise to evaluate systemic disease, or to look for predisposing causes of urinary stone disease. More accurate measurements may be obtained from clinical laboratories by sending urine samples in plain blood collection tubes for pH determination by pH meter.
Conclusions: In our opinion, dipstrip estimates of urine pH should be within 0.25 pH units of the pH meter measurements to be clinically useful. Thus, a urine specimen with a pH meter measurement of 5.75-6.25 should yield a dipstrip pH of 6.0. For the dipstrip tested, this clearly was not the case. We recommend that the agreement between dipstrips and pH meter be assessed before basing therapeutic decisions on any dipstrip pH measurement.

K.J. Heuter, C.A. Tony Buffington, D.J. Chew, College of Veterinary Medicine, The Ohio State University.

Dietary Lipids and Renal Function

continued from page 1

pressure (if available) should be obtained prior to instituting dietary n-3 PUFA supplementation. Generally, a supplement of 0.5 – 1.0 gm of n-3 PUFA/100 Kcal of food is a reasonable starting dose. Based on studies in our laboratory, 2-4 weeks are required to see initial effects of this dietary manipulation. All parameters should be re-evaluated at 2 and 4 weeks and then monthly for 6 months. Therapy with n-3 PUFA should be discontinued if no beneficial effect or an adverse effect is observed during this trial. A key issue will be to define the ideal dietary n-6/n-3 ratio or dose of PUFA for diets with dogs with renal failure. ▧
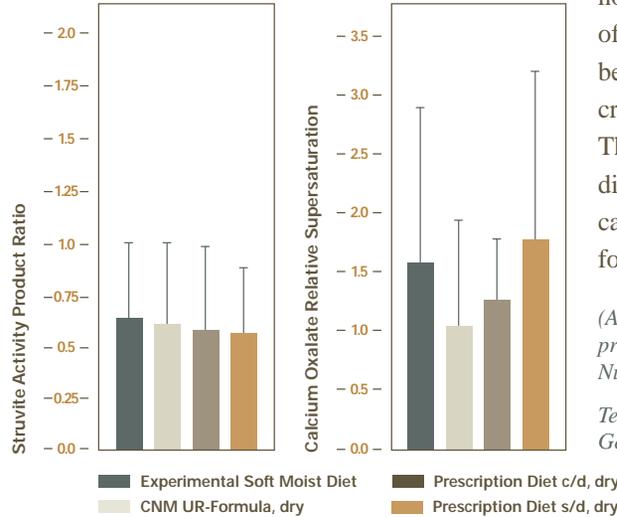
Struvite Activity Product Ratios and Calcium Oxalate Relative Supersaturation in Healthy Cats.

Activity product ratios (APR) are an assessment of the potential for formation or dissolution of urinary crystals or stones. Relative supersaturation (RSS) provides a similar indicator of calculogenic potential. Mean values less than 1.0 suggest stones should dissolve, whereas values greater than 1.0 suggest that conditions are favorable for stone formation. Because APR is influenced by inhibitors and promoters that are not included in the calculation of RSS, APR should provide a better measure of risk for crystal and stone formation. There were no significant differences in struvite APR nor calcium oxalate RSS among the four diets tested. ▧

(Adapted from: Bartges JW, as presented at the 1998 Purina Nutrition Forum, St. Louis, Mo.)

Tests conducted at University of Georgia, January-March, 1997.

Legend:
- Experimental Soft Moist Diet
- CNM UR-Formula, dry
- Prescription Diet c/d, dry
- Prescription Diet s/d, dry

(Y-axis left: Struvite Activity Product Ratio; Y-axis right: Calcium Oxalate Relative Supersaturation)

Purina Research Report ™