Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs

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Objective—To determine whether a diet used for dogs with renal failure (renal food [RF]) was superior to an adult maintenance food (MF) in minimizing uremic crises and mortality rate in dogs with spontaneous chronic renal failure.

Design—Double-masked, randomized, controlled clinical trial.

Animals—38 dogs with spontaneous chronic renal failure.

Procedure—Dogs were randomly assigned to a group fed adult MF or a group fed RF and evaluated for up to 24 months. The 2 groups were of similar clinical, biochemical, and hematologic status. The effects of diets on uremic crises and mortality rate were compared. Changes in renal function were evaluated by use of serial evaluation of serum creatinine concentrations and reciprocal of serum creatinine concentrations.

Results—Compared with the MF, the RF had a beneficial effect regarding uremic crises and mortality rate in dogs with mild and moderate renal failure. Dogs fed the RF had a slower decline in renal function, compared with dogs fed the MF.

Conclusions and Clinical Relevance—Dietary modifications are beneficial in minimizing extrarenal manifestations of uremia and mortality rate in dogs with mild and moderate spontaneous chronic renal failure. Results are consistent with the hypothesis that delay in development of uremic crises and associated mortality rate in dogs fed RF was associated, at least in part, with reduction in rate of progression of renal failure. (*J Am Vet Med Assoc* 2002;220: 1163–1170)

For the past 5 decades, the mainstay of therapy for extrarenal manifestations of chronic renal failure in dogs has been dietary modification. Presently, there is a general consensus of opinion that dietary modification is of benefit to patients with renal failure.[1-6] However, opinions vary about the types of dietary modifications that will safely and effectively ameliorate uremic signs in dogs with naturally occurring disease.[2,7-9] Understandably, these varied opinions have prompted questions from practicing veterinarians about the risks and benefits of manufactured renal failure diets. To resolve these questions, there is clearly a need for recommendations established on the basis of randomized, double-masked, controlled clinical studies in dogs with spontaneous chronic renal failure.

To examine the impact of dietary therapy on development of uremic crisis, mortality rate, and progression of renal failure, we chose to incorporate a combination of dietary modifications commonly recommended to manage chronic renal failure. Results of such a study may provide a more informative and efficient evaluation than a series of clinical trials in which the therapeutic efficacy of individual dietary components are studied singly.[10] In addition, studying a combination of dietary modifications encompasses evaluations of the overall interactions of various dietary components. The purpose of the study reported here was to test the hypothesis that a diet used in dogs with renal disease (**renal food [RF]**) would be superior to an adult **maintenance food (MF)** in minimizing uremic episodes and mortality rate in dogs with spontaneous chronic renal failure of various degrees of severity.

Materials and Methods

Dog selection—Dogs with chronic renal failure were recruited by mailing a description of the study to veterinarians practicing in the Minneapolis-St. Paul, Minn region. On the basis of results of medical histories, physical examinations, CBC, serum biochemical profiles, urinalyses, and indirect blood pressure measurements, 38 dogs of 16 breeds (mixed breed [n = 9], Shetland Sheepdog [6], Soft Coated Wheaten Terrier [3], Boxer [3], Labrador Retriever [3], Golden Retriever [2], German Shepherd Dog [2], Samoyed [2], Bernese Mountain Dog [1], Dalmatian [1], Lhasa Apso [1], Miniature Pinscher [1], Miniature Poodle [1], Shih Tzu [1], American Springer Spaniel [1], and West Highland White Terrier [1]) ranging in weight from 4.2 to 46.4 kg (9.2 to 102.0 lb; mean, 19.5 ± 12.0 kg [42.9 ± 26.4 lb]) met the following inclusion and exclusion criteria and were subsequently enrolled in the study. Included were dogs > 1 year of age (mean, 8.0 ± 4.2 years; range, 1 to 16 years) with stable renal function characterized by serum creatinine concentrations between 2.0 and 8.0 mg/dl. Stable renal function was confirmed by determining that serum creatinine concentrations did not increase or decrease by > 20% within 5 to 15 days of determination of the initial value. Excluded were dogs expected to die of nonrenal illnesses before the study

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was completed; dogs with diabetes mellitus or hyperadrenocorticism; dogs with overt signs of uremia (eg, anorexia, vomiting, and lethargy); and those currently treated with corticosteroids, H_2-blocking drugs, antiemetic drugs, antihypertensive drugs, parenterally administered fluids, vitamin supplements, phosphate binders, alkalinizing agents, potassium supplements, recombinant human erythropoietin, or vitamin D supplements.

Diets—This study was designed to compare a typical adult dry MF formulated to mimic 10 popular commercial adult MF with a dry RF designed specifically for treatment of canine renal failure[a] (**Table 1**). Both diets provided complete and balanced nutrition for the maintenance of adult dogs as substantiated by the **Association of American Feed Control Officials (AAFCO)** feeding trials (RF) or by exceeding the minimum AAFCO nutrient profile for a canine adult MF. The digestibility of each diet was similarly based on ingredient digestibility testing. Fat and carbohydrate sources were identical between the 2 diets. Protein digestibility was 80% for the MF and 93% for the RF. As with most contemporary manufactured diets for management of canine renal failure, principal characteristics of the RF were reduced quantities of protein, phosphorus, and sodium, compared with the MF.[b] Dietary lipid content was higher in the RF than in the MF. Also, the RF was supplemented with omega-3 **polyunsaturated fatty acids (PUFA)**, whereas the MF was not.

Feeding protocol—After qualifying for the study, all dogs were initially fed a mixture of their regular diet and a diet composed of an equal combination of the MF and RF. The goal was to gradually decrease consumption of the amount of regular diet while increasing the amount of combination diet so that dogs would be consuming at least 80% of the combination diet prior to randomization. Dogs were fed this combination diet to minimize variability that would have been associated with consumption of the variety of diets being fed by owners prior to enrollment in the study. This strategy was also chosen to minimize abrupt changes in dietary ingredients at the time of random assignment to the MF or RF group.

Throughout the study, owners were asked to continue the method of feeding (free-choice or meal fed) used prior to entry into the study. Owners were advised to give a sufficient quantity of diet with the goal of maintaining adequate nutrition based on serial assessments of body weight, body condition score, and physical examination. When body weight decreased, the owners were asked to increase the amount of food given to the patient. In dogs that developed partial anorexia, owners were advised to use flavoring agents (eg, warming the food, adding water, adding diluted chicken broth) to enhance food intake.

Table 1—Compositions of a renal food and a maintenance food fed to dogs with spontaneous chronic renal failure

Nutrient	Renal food	Maintenance food
Protein (% [ME {%}])	14 (12)	25 (23)
NFE (% [ME {%}])	60 (50)	53 (50)
Fat (% [ME {%}])	19 (39)	12 (27)
ME (kcal/g)	4.2	3.7
Calcium (%)	0.8	1.60
Phosphorus (%)	0.28	1.00
Sodium (%)	0.17	0.40
Potassium (%)	0.35	0.71
Vitamin D (U/g)	2.0	1.1
Crude fiber (%)	3.2	2.7
Moisture* (%)	11	12
n6 FA (%)	33	3.3
n3 FA (%)	1.60	0.22
n6:n3 ratio*	2.0:1	15.1:1

*Indicates percentage as fed or ratio; all other units are on a dry-matter basis.

ME = Metabolized energy (by calculation). NFE = Nitrogen free extract; represents carbohydrate fraction of the food. n6 FA = Omega-6 series fatty acids. n3 FA = Omega-3 series fatty acids.

Study design—A randomized, double-masked, controlled clinical trial was performed. After ascertaining that the dogs met all inclusion and exclusion criteria, owners were asked to review and sign an informed consent form approved by the University of Minnesota Institutional Animal Care and Use Committee. For the next 2 months, all dogs were acclimated to a diet composed of an equal combination of the 2 study diets. After 2 months and immediately prior to random assignment to either the MF or RF, each dog was reevaluated by use of a defined medical history, physical examination, indirect blood pressure measurement, and evaluation of results of urinalysis, urine protein-to-creatinine ratio, CBC, and serum biochemical profile. Random allotment to 1 of the 2 study diets was performed by use of a table of random numbers. Identical packaging material was used to mask the identity of the diets, which were identical in physical appearance, from all individuals directly involved with the evaluation of each dog.

On the first and second month after assignment to the RF or MF groups, the status of each dog was evaluated by use of history, physical examination, limited serum biochemical profile (consisting of serum urea nitrogen, creatinine, inorganic phosphate, and total CO_2 concentrations), and PCV and total plasma protein concentration determinations. Throughout the study, indirect blood pressure was also measured if the previously measured systolic blood pressure was > 150 mm Hg.

For the next 2 years, dogs were scheduled to be reevaluated at 3-month intervals or if signs indicative of a uremic crisis developed. During these scheduled visits, the status of each dog was evaluated by use of history, physical examination, indirect blood pressure measurements, serum biochemical profile, CBC, urinalysis, and bacteriologic culture of urine. Telephone interviews of clients were performed monthly when on-site examinations were not scheduled. The same veterinary technician performed all telephone interviews.

Blood acquisition and assay—Owners were instructed not to feed their dog for 12 hours prior to scheduled reevaluations. During each visit, a blood sample was collected from the jugular vein, and serum was obtained within 30 minutes for biochemical profiles; if analyses could not be performed the same day, serum was stored at 4 C and evaluated the next day. An aliquot of serum was also frozen (–70 C) for future determinations of other analytes. A CBC and serum biochemical analyses (ie, serum urea nitrogen, creatinine, glucose, inorganic phosphorus, calcium, sodium, potassium, chloride, total CO_2, albumin, total bilirubin, and total protein concentrations and serum amylase, alanine transaminase, and alkaline phosphatase activities) were serially performed by use of standard procedures. Serum magnesium concentration was determined by use of dye-binding methodology.[c] Although all these analytes were evaluated throughout the clinical trial, only analytes relevant to renal failure (ie, serum creatinine, serum urea nitrogen, inorganic phosphorus, calcium, parathormone, total CO_2, and albumin concentrations) were compared between diet groups.

Urine acquisition and analysis—Urine was collected via cystocentesis. Urinalyses were performed by use of a

refractometer for urine specific gravity determinations, commercial reagent strips[d] for chemical determinations, and standard technique for sediment evaluation. Quantitative bacteriologic urine cultures for aerobic bacteria were performed on all urine samples. Urine protein concentration was determined by use of Coomassie brilliant blue dye precipitation[e] and spectrophotometry.[11] Urine creatinine concentrations were determined by an autoanalyzer-based kinetic Jaffe reaction.[12] Urine samples for protein and creatinine determination were stored at 4 C and analyzed within 24 hours of collection.

Blood pressure measurement technique—Systolic blood pressure measurements were obtained by use of oscillometry[f] techniques.[13,14] In 3 of 38 dogs, an ultrasonic Doppler[g] monitor was used, because it was not possible to obtain reliable blood pressure measurements by use of oscillometry.[13,14]

Patient management—With the exception of diet, the protocol used to manage chronic renal failure was the same for all dogs. Likewise, the same protocol was used to manage nonuremic events. Treatments conformed to predetermined criteria of intervention as described in detail elsewhere[h] and summarized as follows.

Gastrointestinal tract bleeding—Three dogs (RF, [n = 2]; MF, [1]) with suspected gastrointestinal tract bleeding (suspected on the basis of hematemesis, melena, abruptly reduced PCV, microcytic hypochromic anemia, or increased serum urea nitrogen-to-creatinine ratio) were treated with ranitidine[i] and sucralfate[j] PO. One dog with suspected gastrointestinal tract bleeding (microcytic hypochromic anemia) in the MF group was treated with ranitidine alone. Administration of these drugs was discontinued when evidence of bleeding ceased.

Anemia—Three dogs (RF [n = 2], MF [1]) with PCV < 18% unassociated with blood loss were given sufficient recombinant human erythropoietin[k] SC to maintain PCV between 30 and 40%. Ferrous sulfate[l] was concurrently administered PO with erythropoietin.

Systemic hypertension—Five dogs (RF [n = 2], MF [3]) with sustained systolic blood pressure > 180 mm Hg during 3 successive visits were treated orally with antihypertensive drugs to decrease systolic blood pressure to a value < 170 mm Hg as determined by use of indirect blood pressure measurements. Four dogs (RF [n = 2], MF [2]) were initially treated orally with the angiotensin-converting enzyme inhibitor enalapril.[m] When systolic blood pressure remained > 170 mm Hg, enalapril was administered PO with diltiazem[n] or amlodipine.[o] Two dogs received combined treatment with enalapril and diltiazem or amlodipine. In the MF group, 1 dog with gastrointestinal tract signs was treated with amlodipine only.

Urinary tract infections—Five dogs (RF [n = 2], MF [3]) with bacterial infections of the urinary tract were treated for 3 weeks with an appropriate antimicrobic, as determined by use of susceptibility tests. Response to treatment was evaluated via urinalysis and quantitative bacteriologic culture.

Metabolic acidosis—Six dogs (RF [n = 4], MF [2]) with serum total CO_2 concentrations < 14 mEq/L were evaluated by determining venous blood HCO_3 concentrations. Dogs with venous blood HCO_3 concentrations < 17 mEq/L were treated with sodium bicarbonate or potassium citrate[p] administered PO. Response to sodium bicarbonate was determined by measuring serum total CO_2 concentrations 10 to 14 days after beginning treatment, with the goal of maintaining values between 18 and 24 mEq/L.

Anorexia, emesis, or diarrhea—Vomiting thought to be unrelated to development of an uremic crisis was treated with antiemetics. Eleven dogs (RF [n = 7], MF [4]) were initially treated PO with H_2-blockers (ranitidine or cimetidine[q]). Four dogs (RF [n = 2], MF [2]) with persistent anorexia and vomiting during treatment with H_2-blockers were also administered metoclopramide[r] PO. Metronidazole[s] was given PO to 1 dog in the MF group with biopsy-confirmed gastric-duodenal lymphocytic-plasmocytic inflammatory bowel disease and to 2 dogs in the RF group with intermittent large bowel-related diarrhea.

Hyperphosphatemia—Nine dogs (RF [n = 3], MF [6]) with serum phosphorus concentration > 7 mg/dl were treated with aluminum carbonate[t] mixed with the food. Treatment with aluminium carbonate was adjusted to maintain serum phosphorus concentration < 7 mg/dl.

Extrarenal causes of uremic crisis—One dog in the RF group was temporarily withdrawn from the study because of a uremic crisis attributed to an extrarenal cause. One month after successful treatment of this dog with IV administration of fluid and other concurrent medications (eg, ranitidine, metoclopramide, nutritional support), the dog reentered its group at the point at which it had been temporarily withdrawn from the study.

Patient management after uremic crisis—Dogs that reached the primary end point of the study (eg, uremic crisis) were treated parenterally with fluids and appropriate medical care but were not reintroduced in the study. However, the commercially available RF was fed to all dogs after the development of a uremic crisis, including dogs that had previously been fed the MF. In our judgment, continuing to feed an adult MF after onset of an uremic crisis would be unethical. Ten dogs died within 30 days of the onset of uremic crisis (MF [n = 5], RF [5]). Three dogs (all fed MF) survived > 30 days after uremic crisis. Because of the type of analysis used for this clinical trial (ie, intention-to-treat study), all surviving dogs were evaluated until death as if belonging to their initial randomly assigned diet groups.

Diagnosis of uremic crisis—A diagnosis of uremia (the primary end point of the study) was established by 2 clinicians unaware of the diet being fed and uninvolved in patient management. A diagnosis of uremic crisis was established when all 3 of the following criteria were evident: owner's observation of at least 2 clinical signs consistent with uremia including signs of depression, lethargy, anorexia, vomiting, uriniferous breath odor, or uremic stomatitis; serum urea nitrogen concentration at least 20% greater than the previously determined value when uremic signs were not detected; and no plausible alternative for these clinical signs as determined by use of medical history and physical examination, serum biochemical profile, CBC, urinalysis, aerobic bacteriologic urine culture, abdominal radiography, and indirect blood pressure determinations.

In 1 dog, an extrarenal cause was unequivocally determined to have precipitated the episode of uremia (the dog consumed a substantial quantity of meat). Treatment for this prerenal cause was successful, and the dog was allowed to remain in the study. With the exception of that dog, all dogs that developed a uremic crisis that did not appear to be extrarenal in origin reached the primary end point of the study. Therefore, all dogs that developed a uremic crisis were subsequently fed the commercially available RF. They were also given appropriate medical care, and their survival was monitored.

Establishing causes of death—By use of results from the medical history, physical examination, laboratory tests,

criteria defining uremic crisis, and necropsy (when available), causes of death were categorized as definitely not renal, possibly renal, probably renal, or definitely renal. Patients classified in the first or second category were considered to have died from a nonrenal event. Patients classified in the third or fourth category were considered to have died from a renal event.

Termination of the study—Based on the assumption that 60% of the MF group would develop uremic crisis during the study and seeking at least a 35% reduction in development of uremic crisis in the RF group, this study was initially designed to evaluate 46 dogs with a statistical power of 80% (1-β) and type-1 error of 5% ($\alpha = 0.05$). However, during the study, an unexpectedly high number of deaths seemingly unrelated to renal failure was observed. Because of these unexpected complications and the masked nature of the study, we questioned whether 1 of the diets was associated with these deaths. In order to answer this question without invalidating the blind design of the study, an external review of the data was performed by a clinician and 2 statisticians not involved in the study, without knowledge of group assignments. However, they were provided with our assessment as to whether deaths or uremic crises were renal-related or nonrenal-related. Kaplan-Meier survival curves were analyzed to assess associations between diet and uremic crises and deaths of all causes. Because diet assignment had a significant association with uremic crisis rate ($P = 0.006$) and deaths of all causes ($P = 0.004$), the clinician and statisticians stated that those associations would probably not be modified by enrolling 8 additional dogs as originally planned; therefore, the study was terminated after inclusion of 38 dogs.

Statistical analyses—At the time of diet assignment, clinical characteristics of dogs in the RF and MF groups were compared by use of the Mann-Whitney nonparametric test.[15] Kaplan-Meier survival curves with logrank test (Mantel-Cox) were used to compare the rates of development of uremic crisis and death in both diet groups.[16] In addition, the Cox proportional hazard regression model was used to evaluate the effect of diets on the **relative risk (RR)** of development of uremic crisis. The same model was used to estimate the influence of covariates (age, sex, systolic blood pressure, PCV, and serum creatinine, urea nitrogen, phosphorus, total CO_2, and albumin concentrations) on the development of uremic crisis in the RF versus the MF group.[17] **Relative risk reduction (RRR)** was calculated by computing [1- RR] × 100%.

Means of hematocrits, urine-to-protein creatinine ratios, and serum creatinine, urea nitrogen, phosphorus, calcium, parathyroid hormone, and total CO_2 concentrations were compared between MF and RF groups during 12- and 24-month intervals. Because of differences related to dates of enrollment and deaths, it was not possible to collect data from all patients at the intervals specified by study design. To permit comparison between groups with incomplete data at the 12- and 24-month intervals, the mixed model procedure for analysis of repeated measures was used.[18]

For each diet group, the mixed model procedure for analysis of repeated measures was used to generate means for reciprocal of serum creatinine values for each time interval. By use of these means, computer-generated best-fit curves[u] were derived for each diet group by use of the least-squares method. The mixed model of procedure of analysis was also used to compare the overall mean of reciprocals of serum creatinine concentration up to 12- and 24-month intervals. Terminal data that could coincide with a uremic crisis were not included in these analyses.

Statistical analyses were performed with the aid of computer software packages.[v,w] Significance was defined as $P < 0.05$.

Results

Clinical characteristics of patients—At the time the study was terminated, the control group consisted of 17 dogs fed the dry MF, whereas the treatment group consisted of 21 dogs fed the dry RF. At the time of diet assignment, there was no statistical difference in overall clinical (age, weight, systolic blood pressure), hematological, or serum biochemical characteristics of the 2 groups. Furthermore, mean values for CBC and serum biochemical analytes were within the reference range for each group except for serum urea nitrogen, creatinine, and parathyroid hormone concentrations and urine-to-protein creatinine ratios (**Table 2**). Fourteen males were in the RF group (1 sexually intact male; 13 neutered males) and 7 in the MF group (2 sexually intact males; 5 neutered males). Seven females were in the RF group (4 sexually intact females; 3 neutered females), and 10 were in the MF group (1 sexually intact female; 9 neutered females).

Results of ELISA tests for *Dirofilaria immitis* were negative in 37 of the 38 dogs, which were receiving monthly treatment with ivermectin or milbemycin oxime. Prior to random assignment to the RF or MF, 1 dog had positive test results for *D immitis* on 2 consecutive occasions. Because this dog was successfully treated with melarsomine during the combination diet period and prior to assignment of study diets, it was

Table 2—Mean ± SD values for hematologic, serum, and urinary variables obtained at baseline and during 12- and 24-month intervals in dogs with spontaneous chronic renal failure that were fed a renal food (RF) or a maintenance food (MF)

	Baseline		During 12-month interval		*P* value	During 24-month interval		*P* value
	RF	MF	RF	MF	(RF vs MF)	RF	MF	(RF vs MF)
Hct (%)	37.4 ± 9.5	37.7 ± 8.3	37.0 ± 1.9	34.8 ± 2.4	0.48	35.7 ± 2.0	33.2 ± 2.6	0.45
SUN (mg/dl)	65 ± 26	69 ± 38	63 ± 8	89 ± 9	0.04	68 ± 8	99 ± 10	0.002
Albumin (g/dl)	3.2 ± 0.4	3.0 ± 0.5	3.1 ± 0.1	3.0 ± 0.1	0.64	3.0 ± 0.1	3.1 ± 0.1	0.74
Total CO_2 (mmol/L)	20.3 ± 2.1	21.0 ± 3.8	19.6 ± 0.6	21.1 ± 0.7	0.12	19.5 ± 0.6	20.8 ± 0.8	0.18
Calcium (mg/dl)	11.5 ± 0.9	10.7 ± 1.5	11.2 ± 0.2	11.0 ± 0.2	0.4	11.0 ± 0.2	11.0 ± 0.2	0.74
Creatinine (mg/dl)	3.3 ± 1.1	3.7 ± 1.7	3.5 ± 0.4	4.6 ± 0.4	0.06	3.7 ± 0	5.1 ± 0.4	0.016
Phosphorus (mg/dl)	4.6 ± 1.5	5.5 ± 1.5	5.1 ± 0.4	6.2 ± 0.5	0.07	5.3 ± 0	6.6 ± 0.5	0.39
PTH (pmol/L)	14.2 ± 11.3	22.9 ± 18.1	25.2 ± 4.7	24.7 ± 7.0	0.95	25.7 ± 6.2	28.3 ± 8.3	0.80
UPUC ratio	1.12 ± 0.96	1.76 ± 1.74	1.41 ± 0.32	1.17 ± 0.45	0.67	1.39 ± 0.33	1.11 ± 46	0.096

SUN = Serum urea nitrogen. PTH = Parathyroid hormone. UPUC = Urine protein to urine creatinine.

included in the study. Baseline diagnostic values were obtained for this dog after therapy for *D immitis* but prior to diet assignment.

Association between diets and serum biochemical values—Evaluation of serum urea nitrogen concentrations at 1, 2, 3, 6, 9, and 12 months after diet assignment and grouped together to derive overall mean values revealed significantly higher mean values in the MF group than in the RF group (Table 2). Mean serum urea nitrogen and creatinine concentrations evaluated at 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months after diet assignment and grouped together to derive overall mean values were significantly higher in the MF group than in the RF group. When the mean serum concentrations of phosphorus, albumin, total CO_2, calcium, and parathormone of the MF group evaluated throughout the study were compared with those of the RF group, significant differences were not detected.

Association between diets and uremic crisis—Onset of uremic crisis was significantly delayed in the RF-group dogs, compared with the MF-group dogs **(Fig 1)**. The RF group was associated with a RRR of 72%, compared with the MF group. At the time the study was terminated, 33% of dogs in the RF group had developed uremic crises, compared with 65% of dogs in the MF group **(Table 3)**. A median of 615 days elapsed before uremic crises developed in the RF group. In contrast, a median of only 252 days elapsed before development of uremic crises in the MF group.

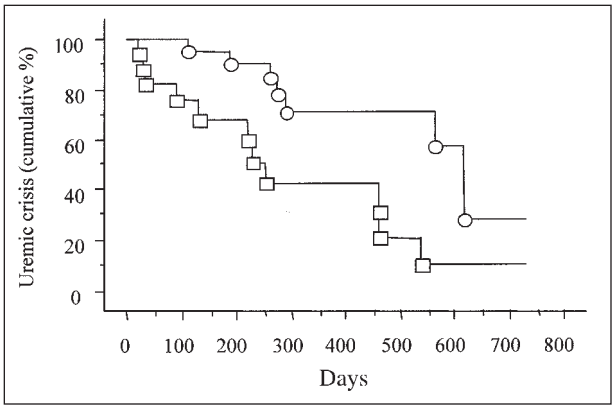

Figure 1—Development of uremic crises in dogs with spontaneous chronic renal failure that were fed a renal food (circles; n = 21) or a maintenance food (squares; 17).

Table 3—Proportions (number of affected dogs/number of dogs per group) and relative risks (RR) of uremic crisis or death in dogs with spontaneous chronic renal failure that were fed RF or MF

Events	RF	MF	RR	95% CI	*P* value
Uremic crises	7/21 (33)	11/17 (65)	0.28	0.11–0.74	0.006
Serum creatinine					
2.0–≤ 3.0 mg/dl	5/11 (45)	8/9 (89)	0.19*	0.04–0.98	0.027
≥ 3.1–7.6 mg/dl	2/10 (20)	3/8 (37.5)	0.31*	0.09–1.14	0.064
All cause mortality	11/21 (52)	16/17 (94)	0.34	0.16–0.73	0.004
Renal mortality	7/21 (33)	11/17 (65)	0.31	0.12–0.79	0.010
Nonrenal mortality	4/21 (19)	5/17 (29)	0.4	0.11–1.54	0.172

*No significant difference ($P = 0.58$).
CI = Confidence interval.

After adjustment for the influence of covariates on development of uremic crises, RR for uremic crises (RR refers to the risk of uremic crises and death for the RF group, relative to the risk for the MF group) continued to be significantly reduced in the RF group, compared with the MF group (Table 3).

From the initial population of 21 dogs in the RF group and 17 dogs in the MF group, a subpopulation of dogs with serum creatinine concentrations between 2.0 and 3.1 mg/dl was evaluated (RF [n = 11]; MF [9]). Kaplan-Meier analysis revealed a significantly longer time to onset of uremic crises among dogs in the RF group, compared with dogs in the MF group **(Fig 2)**. For this subgroup, RR of developing uremic crises was significantly reduced in dogs in the RF group, compared with dogs in the MF group (Table 3). After assignment to the RF group, a median of 615 days elapsed before uremic crises developed in dogs with serum creatinine values between 2.0 and 3.1 mg/dl. In the MF group, a median of 461 days elapsed prior to development of uremic crises. When the study was terminated, 55% of the dogs in the RF group had not yet developed the end point (uremic crisis), compared with only 11% of dogs in the MF group (Table 3). A similar comparison in dogs with moderate to severe azotemia (serum creatinine concentration, 3.1 to 7.6 mg/dl) revealed a 3-fold reduction of the RR of developing a uremic crisis in the RF group, compared with the MF group (Table 3). The RR of developing uremic crises was similar between the subgroup with mild azotemia and the subgroup with moderate to severe azotemia.

Association between diets and death—Kaplan-Meier analysis revealed a significant difference between the RF and MF groups in renal-related deaths **(Fig 3)** and all causes of death **(Fig 4)**. When the influence of diets on all causes of death was evaluated by use of the Cox proportional hazard model, a RRR of 66% was detected in the RF group, compared with the MF group (Table 3). At the time the study was terminated, 52% of dogs in the RF group had died. During the same interval, 94% of the dogs assigned to the MF group had died. After assignment to the RF group, a median of 594 days elapsed before deaths occurred. In contrast, a median of 188 days elapsed before deaths occurred in the MF group.

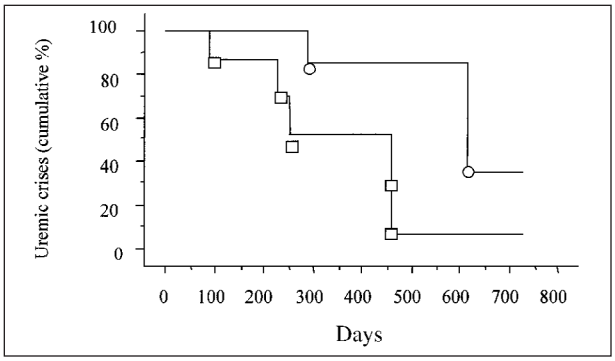

Figure 2—Development of uremic crises in dogs with mild chronic renal failure that were fed a renal food (circles; n = 11) or a maintenance food (squares; 9).

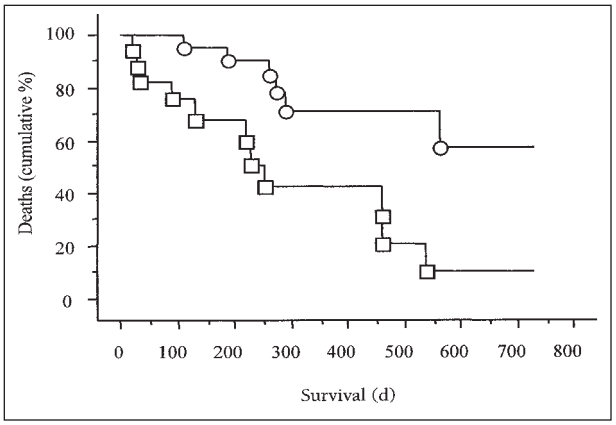

Figure 3—Survival curves for death from renal causes in dogs with chronic renal failure that were fed a renal food (circles; n = 21) or a maintenance food (squares; 17).

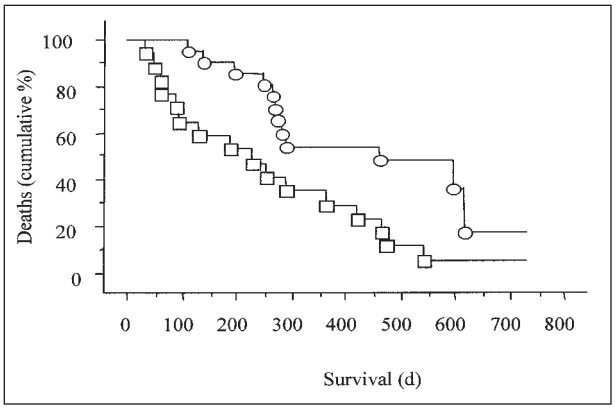

Figure 4—Survival curves for death from all causes in dogs with chronic renal failure that were fed a renal food (circles; n = 21) or a maintenance food (squares; 17).

When the influence of diets on mortality rate related to renal failure was evaluated, a RRR of 69% was detected in the RF group, compared with the MF group (Table 3). When the study was terminated, 65% of dogs in the MF group had died from renal causes, compared with 33% of dogs in the RF group. Nonrenal causes of death or euthanasia in the RF group included peripheral vestibular disease (n = 1), splenic hemangiosarcoma (1), generalized seizures (1), and CNS thromboembolism (1). In the MF group, causes of death or euthanasia included peripheral vestibular disease (n = 1), aspiration pneumonia (1), tumor of the right atrium (1), and gastric dilatation-volvulus (2). Nonrenal disease deaths did not differ significantly between the RF (19%) and the MF group (29%).

Progression of chronic renal failure—Although serum creatinine concentrations were not significantly different at the beginning of the study, during the 24-month interval, serum creatinine concentrations became significantly greater in the MF group, compared with the RF group (Table 2). In addition, the magnitude of decline in reciprocal of serum creatinine concentration was greater in the MF than in the RF group **(Fig 5)**. This difference approached significance ($P = 0.06$) during the 12-month interval and was significant ($P = 0.036$) during the 24-month interval.

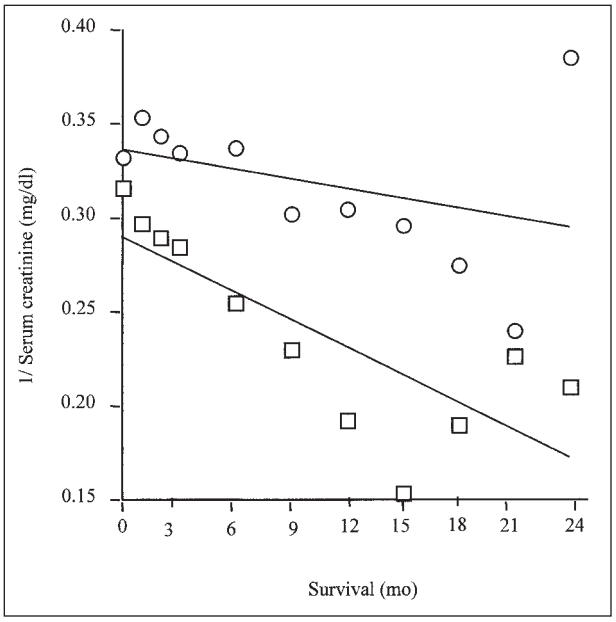

Figure 5—Inverse of serum creatinine concentrations in dogs with chronic renal failure that were fed a renal food (circles; n = 21) or a maintenance food (squares; 17). Solid lines are computer-generated best-fit curves.

Discussion

Results of our trial support the hypothesis that a RF is superior to an adult MF in minimizing uremic episodes and death in dogs with spontaneous chronic renal failure of various severities. Our results parallel observations derived from experimentally induced chronic renal failure in dogs[19-28] and some prospective clinical studies.[29-31] The 75% RRR in dogs with various degrees of azotemia persisted after potential confounding effects were considered. In addition, the median interval before development of uremic crisis in dogs fed the RF was twice as long as that observed in dogs fed the MF.

In our study, the risk of death irrespective of the cause was reduced by at least two thirds when dogs were fed the RF, compared with dogs fed the MF. Dogs in the RF group lived at least 13 months longer than dogs in the MF group did. When nonrenal causes of death were eliminated from both study groups, a similar RRR of death (70%) was observed in the RF group. Results of experimental studies[21,23,28] and a clinical study[29] performed by other investigators also revealed increased survival in dogs fed RF.

Criteria for timing of dietary intervention in dogs with spontaneous chronic renal failure have been based on empirical observations. A cited guideline has been to initiate dietary therapy when serum creatinine concentration exceeds 2.5 mg/dl or the serum urea nitrogen concentration exceeds 60 to 80 mg/dl.[3,32,33] One investigator recommended a staged approach whereby dietary phosphorus restriction and omega-3 PUFA dietary supplementation be implemented when azotemia is mild to moderate without clinical signs attributable to uremia.[9] When clinical signs attributable to uremic toxins accompany the azotemia (ie, serum creatinine concentration > 4.0 mg/dl or serum urea

nitrogen concentration > 80 mg/dl), dietary modifications are combined with protein restriction. Our observation that feeding a RF to dogs with a lesser degree of azotemia (serum creatinine concentration, 2.0 to 3.1 mg/dl) delayed the onset of uremic crises by approximately 5 months is noteworthy. In addition, the RF reduced the risk of uremic crises by 75%, compared with that observed in dogs fed an adult MF. We conclude that initiation of treatment with the RF examined in this study would be beneficial in dogs with serum creatinine concentration ≥ 2 mg/dl.

An unexpected finding was the short interval between uremic crises and renal-related death in many of the dogs. We expected that with treatment, duration of survival after uremic crises would typically have been longer than was observed. However, because these dogs were enrolled in a clinical study in a university setting, clinical manifestations of renal failure were often managed to the limits possible with conservative management. In this context, it is not surprising that the duration of survival after a uremic crisis, even with treatment, was short. Also, in clinical practice, prerenal causes of complications commonly contribute to development of uremic crises. When the prerenal component is corrected, patients often return to a state of compensated renal failure for a substantial period. However, in this study, prerenal components did not significantly contribute to development of uremic crises.

Of the 3 dogs that survived more than 1 month after onset of uremic crises, all were initially fed the MF. At first, this appears to be a paradox. However, in context of the likelihood that dogs fed the RF were treated to the limits possible by conservative management, a beneficial effect would not be expected by switching them to a manufactured RF of similar composition. In contrast, a comparably better response would be expected of dogs fed a RF following development of a uremic crisis while they were fed a MF.

Our clinical impression and those of other investigators suggest that spontaneous chronic renal failure in most dogs is slowly progressive and leads to uremia and, ultimately, death.[34,35] Progressive decline in the reciprocal of serum creatinine concentration was the most common pattern of change in renal function observed in our study, regardless of diet group. One mechanism by which diet therapy may delay the development of uremic crises and associated death is by slowing this inexorable progression of renal failure. Our results are consistent with the hypothesis that the delay in development of uremic crises and associated death observed in dogs fed the RF was associated, at least in part, with reduction in the rate of progression of renal failure. Whereas renal function continued to decline in most dogs regardless of diet fed, renal function assessed by evaluation of serially measured reciprocal of serum creatinine concentrations declined to a significantly greater degree in dogs fed the adult MF, compared with dogs fed the RF. One group of investigators recommended that appropriate caution be used in interpreting isolated measurements of serum creatinine concentration or the calculated reciprocal of serum creatinine concentrations, because they are not a sensitive index of glomerular filtration.[35,36] Whereas isolated measurements of serum creatinine concentration or the reciprocal of serum creatinine concentrations may not be a reliable index of specific values for glomerular filtration rate, serially performed measurements in the same dog are of value in establishing trends in renal function.[35] In this context, a plausible interpretation of our results is that dietary modification ameliorated the rate of progression of renal dysfunction.

Our study was designed to evaluate the composite effects of modifications of several dietary components in dogs with spontaneous chronic renal failure. Our results are consistent with results of several studies designed to evaluate the influence of specific dietary components on the rate of progression of induced renal failure in dogs. For example, reduction of dietary phosphorus reduced the rate of progression of chronic renal failure and decreased mortality rate in canine remnant kidney models.[25,28,37] The beneficial effect associated with restriction of dietary phosphorus was thought to be related, at least in part, to reduction in the severity of renal-related hyperphosphatemia, which in turn reduced deleterious effects caused by hyperparathyroidism and deposition of calcium-phosphate within the renal parenchyma.[25] Likewise, addition of menhaden fish oil, a rich source of omega-3 PUFA, to diets fed to dogs with induced renal failure preserved renal function.[26] In the same study, addition of safflower oil, a rich source of omega-6 PUFA, to dogs with induced renal failure resulted in progressive decline in renal structure and function. Dietary omega-3 PUFA may minimize progression of renal failure by improving renal hemodynamics and by suppressing mediators of inflammation and coagulation.[38] Individually or in combination, similar dietary modifications in our study may have contributed to the RF ameliorating the rate of progression of renal failure.

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[a]HILL'S PRESCRIPTION DIET Canine K/D brand dry pet food (3861TP), Hill's Pet Nutrition Inc, Topeka, Kan.

[b]Details regarding the diets' ingredients, nutritional profile, and vitamin-mineral content are available from D. J. Polzin, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St Paul, Minn.

[c]Gemstar, Electro-nucleonics Inc, Fairfield, NJ.

[d]Multistix, 10 SG, Bayer Corp, Elkhart, Ind.

[e]Lancer Microprotein Rapid Stat Diagnostic kit, Sherwood Medical, St Louis, Mo.

[f]Dinamap, model 33614, Critikon Inc, Tampa, Fla.

[g]Ultrasonic Doppler flow detector model 811, Park Medical Electronics Inc, Ahoha, Ore.

[h]Jacob F. *Beneficial effects of dietary modification in dogs with spontaneous chronic renal failure: a clinical trial*. PhD thesis, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St Paul, Minn, 2002.

[i]Zantac, Novopharm USA Inc, Schaumburg, Ill.

[j]Carafate, Blue Ridge Laboratories Inc, Kansas City, Mo.

[k]Epogen, Amgen, Thousand Oaks, Calif.

[l]Fer-In-Sol, Silarx Pharmaceuticals Inc, Springvalley, NY.

[m]Enacard, Merck & Co Inc, Rahway, NJ.

[n]Cardizem, Lederle Laboratories, Pearl River, NY.

[o]Norvasc, Pfizer Inc, New York, NY.

[p]Polycitra-K Syrup, Pharmaceutical Associates Inc, Greenville, SC.

[q]Tagamet, Novopharm USA Inc, Schaumburg, Ill.

[r]Reglan, Watson Laboratories Inc, Corona, Calif.

[s]Flagyl, Sidmark Laboratories Inc, East Hanover, NJ.

[t]Basalgel, Wyeth Laboratories Inc, Philadelphia, Penn.
[u]Cricket Graph, Computer Associates International Inc, Islandia, NY.
[v]Statview 4.1, Abacus, Berkeley, Calif.
[w]PROC MIXED, PROC PHREG, PROC LIFETEST, SAS Institute, Cary, NC.

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