

Evaluation of the Effects of a Therapeutic Renal Diet to Control Proteinuria in Proteinuric Non-Azotemic Dogs Treated with Benazepril

O. Cortadellas, J. Talavera, and M.J. Fernández del Palacio

Background: Angiotensin-converting enzyme inhibitors (ACEIs) are currently used to control proteinuria in dogs with chronic kidney disease. Renal diets (RDs) have beneficial effects in the management of azotemic dogs, but its role in proteinuric non-azotemic (PNAz) dogs has been poorly documented.

Hypothesis: Administration of a RD to PNAz dogs treated with benazepril (Be) improves proteinuria control compared with the administration of a maintenance diet (MD).

Animals: Twenty-two PNAz (urine protein/creatinine ratio [UPC] >1) dogs.

Methods: Randomized open label clinical trial design. Dogs were assigned to group-MD (5.5 g protein/100 kcal ME)/Be or to group-RD (3.7 g protein/100 kcal ME)/Be group during 60 days. Dogs with serum albumin (Alb) <2 g/dL received aspirin (1 mg/kg/12 hours). A physical examination, systolic blood pressure (SBP) measurement, complete blood count (CBC), biochemistry panel, urinalysis, and UPC were performed at day 0 (D0) and day 60 (D60).

Results: At D0, there were no significant differences between groups in the evaluated variables. During the study, logUPC (geometric mean (95% CI) and SBP (mean±SD mmHg) significantly decreased (paired *t*-test, *P* = 0.001) in Group-RD (logUPC_{D0} = 3.16[1.9–5.25]; UPC_{D60} = 1.20 [0.59–2.45]; SBP_{D0} = 160 ± 17.2; SBP_{D60} = 151 ± 15.8), but not in Group-MD (UPC_{D0} = 3.63[2.69–4.9]; UPC_{D60} = 2.14 [0.76–6.17]; SBP_{D0} = 158 ± 14.7; SBP_{D60} = 153 ± 11.5). However, RM-ANOVA test did not confirm that changes were consequence of dietary modification. Weight and Alb concentration did not change significantly in any group.

Conclusion and Clinical Relevance: The administration of a RD to PNAz dogs treated with Be might help to control proteinuria and SBP compared with the administration of a MD, without inducing clinically detectable malnutrition, but more studies are warranted.

Key words: Azotemia; Canine; Kidney; Protein.

Evaluation of proteinuria in dogs with chronic kidney disease (CKD) has generated great interest in the last decade, as a diagnostic marker of both renal disease and progressive renal injury.^{1–6} Renal proteinuria mainly results from glomerular or tubular pathology or both, but it can also be caused by inflammatory or infiltrative renal diseases.^{2,6–9} In the clinical setting, proteinuria is generally quantitated by measuring the urine protein/creatinine ratio (UPC). Values persistently >0.5 (>0.4 in cats) and associated with inactive urine sediment are abnormal and indicative of CKD.^{2,6–10} Studies in humans and animals have demonstrated that proteinuria can promote progression of kidney disease.^{11,12} Furthermore, persistent proteinuria has extrarenal consequences including sodium retention, edema, ascites, hypercholesterolemia,

Abbreviations:

Alb	serum albumin
ACEIs	angiotensin-converting enzyme inhibitors
Be	benazepril
BUN	blood urea nitrogen
CBC	complete blood count
CKD	chronic kidney disease
D0	day 0
D60	day 60
DE	digestible energy
MD	maintenance diet
ME	metabolizable energy
OC	observed change
PNAz	proteinuric non-azotemic
PUFAs	polyunsaturated fatty acids
RCV	reference change value
RD	renal diet
RM-ANOVA	repeated measures ANOVA
SBP	systolic blood pressure
SCr	serum creatinine
UPC	urine protein/creatinine ratio
X-LHN	X-linked hereditary nephritis

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hypertension, hypercoagulability, muscle wasting, and weight loss.¹³ These consequences prompted research into novel therapeutic approaches aimed at reducing proteinuria, including identification and treatment of underlying disorders, pharmacologic management, and dietary modifications.^{2,7,9} The pharmacologic management of dogs with proteinuria comprises administration of angiotensin-converting enzyme inhibitors (ACEIs) and low doses of aspirin.^{7,13–17} Benazepril

(Be) administration slows the rate of disease progression in humans with various renal disorders.¹⁸ Furthermore, ACEIs (enalapril, benazepril) have efficacy in the treatment of proteinuria and hypertension in dogs with kidney disease.^{13,14,17} Enalapril delays the onset of azotemia and increased survival in Samoyed dogs with X-linked hereditary nephritis (X-LHN).¹⁴ Dietary modifications for dogs with proteinuria include protein restriction and supplementation with omega-3 polyunsaturated fatty acids (PUFAs).⁷

However, the level of protein restriction or fatty acids supplementation necessary to control proteinuria without causing adverse effects remains unclear. One study in Samoyed dogs with X-LHN demonstrated that a diet designed for the treatment of renal failure delayed the onset and decreased the severity of glomerular and tubulointerstitial lesions compared with a regular diet. Dogs fed the renal diet (RD) survived longer (53%) than dogs fed the regular diet. However, proteinuria was not evaluated in this study.¹⁹ A small study in proteinuric dogs (n = 5) reported a nonsignificant reduction in proteinuria in 3 dogs after dietary protein restriction (3.77–4.71 g protein/100 kcal).^a Finally, non-azotemic dogs with X-LHN²⁰ fed a diet with 6.02 g of digestible protein/100 kcal increased proteinuria, whereas diet with 1.83 g of digestible protein/100 kcal reduced it, but caused malnutrition. Dietary supplementation with omega-3 PUFAs reduced proteinuria and prevented deterioration of glomerular filtration rate in remnant-kidney model dogs,²¹ but the benefits of this supplementation in dogs with spontaneous proteinuria are not well documented. Compared to maintenance diets (MDs), therapeutic RDs may be modified in some or all of the following ways: reducing protein, phosphorus, and sodium content; increasing B-vitamin content, caloric density, and soluble fiber; a neutral effect on acid-base balance; supplementing with omega-3 PUFAs and potassium (feline diets); and adding antioxidants.^{22,23} These diets reduce the incidence of uremic crisis and mortality in dogs and cats with azotemic CKD compared with MDs.^{24,25} Although RDs have been used in the management dogs with proteinuria,^{13,19,20} their possible benefits in the control of proteinuria in non-azotemic dogs are unknown.

In this study, we investigate whether a RD combined with an ACEI (Be) improved proteinuria in proteinuric non-azotemic (PNAz) dogs compared with a MD and Be, and whether feeding a RD to dogs with spontaneous renal proteinuria has a deleterious effect on their nutritional status.

Materials and Methods

Dogs

The study was conducted on privately owned dogs attending the Clínica Veterinaria Germanías (Gandía-Valencia, Spain) and Veterinary Teaching Hospital of the University of Murcia (Murcia, Spain) between January 2010 and September 2011.

The inclusion criteria for this study were serum creatinine (SCr) <1.4 mg/dL and persistent renal proteinuria. For the purposes of this study, persistent renal proteinuria was defined as a

UPC >1 occurring twice in a 2-week period in samples with inactive urine sediment, after excluding pre- and postrenal causes of proteinuria. Urine samples were obtained by cystocentesis for routine urinalysis (specific gravity measurement, dipstick testing, and sediment examination) and UPC assayed in duplicate at a reference laboratory.^b

The exclusion criteria included the presence of a correctable cause of proteinuria identified by obtaining a complete history and performing clinical and laboratory evaluation and abdominal ultrasound.

The laboratory evaluation of dogs considered for inclusion comprised a complete blood count (CBC) assessment,^c biochemical analysis (alanine aminotransferase, albumin [Alb], alkaline phosphatase, calcium, cholesterol, SCr, globulins, glucose, phosphorus, total proteins, and blood urea nitrogen [BUN])^d obtained after ≥12 hour fast, serologic testing for vector borne diseases,^{e,f} and complete urinalysis.

Dogs were randomly allocated (1 : 1 ratio)^g by a person that was independent of the research team into 2 groups: group-MD^h or group-RD.ⁱ Average dietary analysis is shown in Table 1. Dogs were fed twice daily the amount of the corresponding diet recommended by the manufacturer. Owners were encouraged to contact the attending clinician if problems arose related to the assigned diet. Dogs not consuming the assigned amount of the diet were excluded from the study. Dogs in both groups were treated with Be.^j The recommended dose was 0.5 mg/kg/day, administered once daily, but the attending clinician was permitted to increase (up to 1 mg/kg) or decrease (to 0.25 mg/kg) the dose according to the severity of proteinuria. In addition, in both groups, dogs with Alb <2 g/dL received a compounded formulation of 1 mg/kg aspirin, twice daily.

Dietary changes, supplementation of any kind, and treats were not allowed during the study. The use of drugs that could affect proteinuria was not permitted and owners were asked to contact the investigator before any medicine was given to the dog.

The study lasted 2 months and the dogs were evaluated twice: at inclusion (D0) and at the end of the study (D60). Evaluation consisted of a complete physical examination, body weight recording, systolic blood pressure (SBP) measurement,^k CBC

Table 1. Nutritional analysis of diets used in the study.

Nutrient	Average Analysis (g) per 100 kcal/ME		Average Analysis (%) per 1000 g of Food	
	Adult maintenance diet (MD) ^h	Renal diet (RD) ⁱ	Adult maintenance diet (MD) ^h	Renal diet (RD) ⁱ
Moisture	–	–	8	8
Protein	5.5	3.7	23	16
Fat	3.8	4.2	16	18
Carbohydrate	9.5	10.7	39.7	46.2
NFE	10.8	11.9	45	51.1
Dietary fiber	1.6	1.7	6.7	7.3
Crude fiber	0.3	0.6	1.4	2.4
Minerals	1.6	1.0	6.6	4.5
Calcium	0.26	0.16	1.1	0.7
Phosphorus	0.19	0.05	0.8	0.2
Magnesium	24	16	0.1	0.07
Sodium	0.05	0.05	0.2	0.2
Potassium	0.17	0.16	0.7	0.7
Chloride	0.1	0.2	0.5	0.65
EPA+DHA	0.07	0.1	0.3	0.42
ME (kcal/100 g)	416.0	430.4	416.0	430.4

assessment,^b biochemistry analysis,^b urinalysis of a sample obtained by cystocentesis, and UPC calculation.^b A 12-hour fasting period was required before testing in all dogs.

Changes in UPC were considered significant if the observed change (OC) between both UPC measurements was greater than the calculated reference change value (RCV) according to Nabity et al.²⁶

$$\text{OC}\% = 100 \times (\text{UPC}_{\text{D0}} - \text{UPC}_{\text{D60}}) / \text{UPC}_{\text{D0}};$$

$$\text{RCV}\% = (2.77 \times (0.24 \times \text{UPC}^{0.74}) / \text{UPC}) \times 100$$

Nonsignificant changes, either above or below the initial UPC value, were interpreted as indicators of stable disease.

For this study, malnutrition was considered when significant changes in weight or Alb concentration occurred between D0 and D60.

Statistical Analysis

Statistical analysis was performed by a statistical software package.¹ Variables were evaluated for normality using the Shapiro-Wilk test. If necessary to achieve normality, data were natural logarithm-transformed. Parametric tests were used once data were normally distributed. Baseline variables were compared between treatment groups using the unpaired two-tailed Student's *t*-test. The paired *t*-test was used to investigate changes in the evaluated variables in each group throughout the study. A separated analysis was performed using a two-way repeated measures analysis of variance (RM-ANOVA) with diet as a between (grouping) variable and time as a within (repeated) variable. Statistical significance was assigned for values of $P < .05$.

Results

Thirty-five dogs were considered for inclusion in this study (Fig 1). Of them, 7 were excluded after the initial evaluation disclosed a potentially correctable cause of proteinuria. Consequently, 13 dogs were enrolled

into group-MD and 15 into group-RD. During the study, 2 dogs from group-MD and 4 from group-RD were excluded from the final analysis. Causes of exclusion were as follows: not eating the diet ($n = 3$), use of drug that can affect proteinuria magnitude ($n = 2$), and missing D60 visit ($n = 1$) (Fig 1). Finally, 22 dogs completed the study: 11 from group-MD (6 mongrel dogs, 2 American Staffordshire Terrier, 1 Boxer, 1 Beagle, and 1 Miniature Schnauzer) and 11 from group-RD (2 Miniature Pinscher, 2 mongrel dogs, and one of each of the following breeds: Chow-Chow, Giant Schnauzer, West Highland White Terrier, Beagle, Doberman, Beagle, and Bull Terrier).

At baseline (D0), there were no significant differences between the groups in the evaluated variables (Table 2). Doses of benazepril (mean \pm SD) did not differ significantly between the groups ($P = .57$); group-MD, 0.55 ± 0.2 mg/kg; group-RD 0.5 ± 0.2 mg/kg. In group-MD, there were not significant changes in any of the evaluated variables between D0 and D60, whereas in group-RD, there was a significant decrease ($P = .001$) in log UPC (Fig 2, Table 2) and SBP (Fig 3, Table 2).

The data were analyzed individually: in group-MD, 4 dogs exhibited a significant reduction in UPC, 2 a nonsignificant decrease, 3 a nonsignificant increase, and 2 a significant UPC increase. In group-RD, 7 dogs exhibited a significant reduction in UPC, 3 a nonsignificant decrease, and 1 a significant increase.

Regarding SBP, in group-MD, SBP decreased in 6 dogs, remained unchanged in 2, and increased in 3. The changes ranged between -20 and 10 mmHg. In group-RD, SBP decreased in 9 dogs and remained unchanged in 2. In this group, the changes ranged between -5 and -15 mmHg. The observed percentage of change in each dog ranged from a 6.1% increase to an 11.8% decrease.

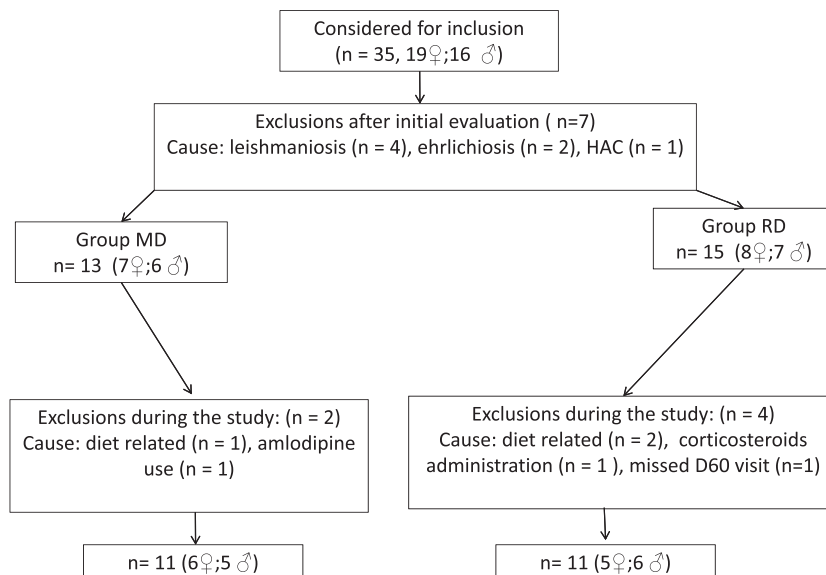


Fig 1. Distribution of the studied population. HAC, hyperadrenocorticism.

Table 2. Data (mean ± SD)* from the evaluated variables in both groups at inclusion (D0) and at the end of the study (D60).

	Day 0				Day 60			
	Reference range	Group-MD (n = 11)	Group-RD (n = 11)	P-value	Group-MD (n = 11)	Group-RD (n = 11)	P-value	Group-RD (n = 11)
Age (years)	NA	6.4 ± 2.3	7.5 ± 3.2	.35	NA	NA	NA	NA
Weight (kg)	NA	16.6 ± 8.7	18 ± 11.4	.76	17.1 ± 9.1	18.4 ± 11.8	.09	18.4 ± 11.8
Alb (g/dL)	2.7-4.1	2.4 ± 0.6	2.5 ± 0.5	.7	2.5 ± 0.5	2.7 ± 0.5	.49	2.7 ± 0.5
SCr (mg/dL)	0.7-1.4	0.8 ± 0.3	0.9 ± 0.2	.26	0.9 ± 0.3	0.9 ± 0.3	.19	0.9 ± 0.3
Log Urea (mg/dL)	NA	28.8 (24-33.9)	29.5 (25.1-35.5)	.69	30.2 (24.5-40.7)	27.5 (1.33-1.46)	.56	27.5 (1.33-1.46)
Log UPC	NA	3.63 (2.69-4.90)	3.16 (1.9-5.25)	.59	2.14 (0.76-6.17)	1.20 (0.59-2.45)	.28	1.20 (0.59-2.45)
SBP (mmHg)	< 150	158 ± 14.7	160 ± 17.2	.74	153 ± 11.5	151 ± 15.8	.14	151 ± 15.8

NA, not applicable.

*Data that were log transformed are expressed as geometric mean and 95% confidence intervals (between brackets).

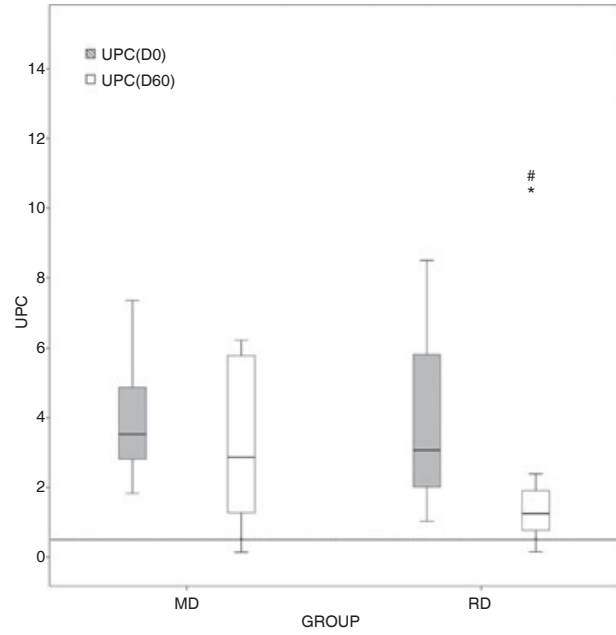


Fig 2. Box and whisker plots of UPC in both groups at day 0 (D0) and day 60 (D60). Each box-and-whisker plot illustrates the median, quartiles, and extreme values (*).#: statistically significant difference ($P \leq .05$). Dashed line indicates lower normal value.

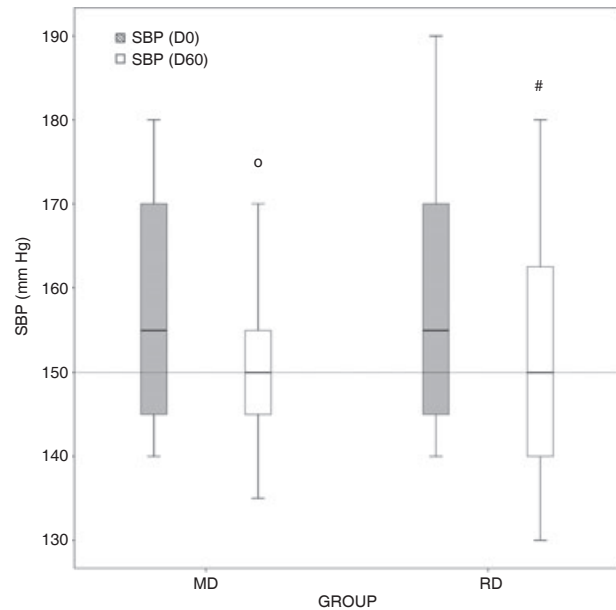


Fig 3. Box and whisker plots of SBP in dogs of group MD and RD at D0 and D60. Each box-and-whisker plot illustrates the median, quartiles, and outliers (°).(*). #: statistically significant difference ($P \leq .05$). Dashed line indicates upper normal value.

Although weight and Alb did not significantly change in any of the groups, the trend for increased weight was greater in group-MD ($P = .09$) than in group-RD ($P = .22$) (Fig 4, Table 2). Conversely, the

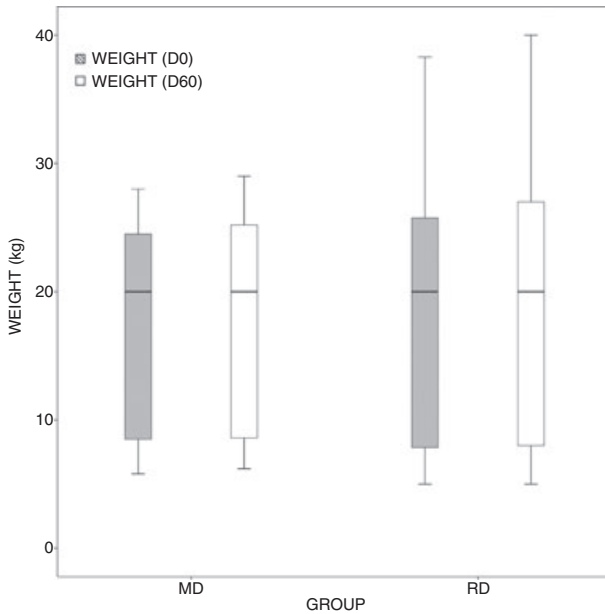


Fig 4. Box and whisker plots of weight in dogs of group MD and RD at D0 and D60. Each box-and-whisker plot illustrates the median and quartiles.

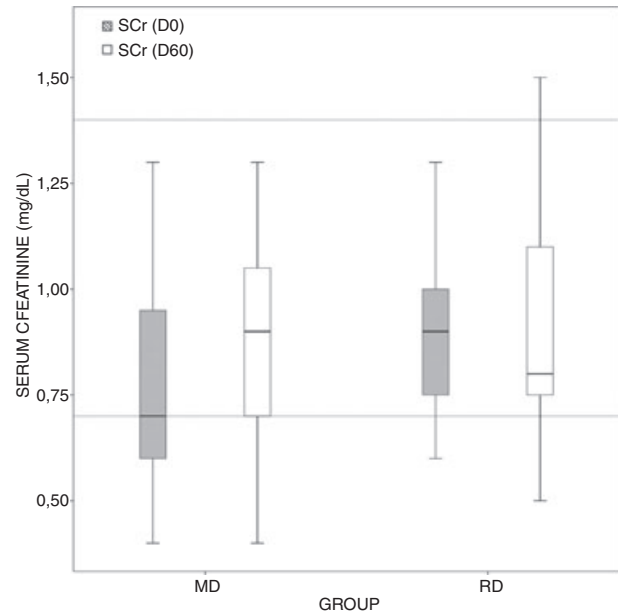


Fig 6. Box and whisker plots of serum creatinine concentration in dogs of group MD and RD at D0 and D60. Dashed lines indicate reference range.

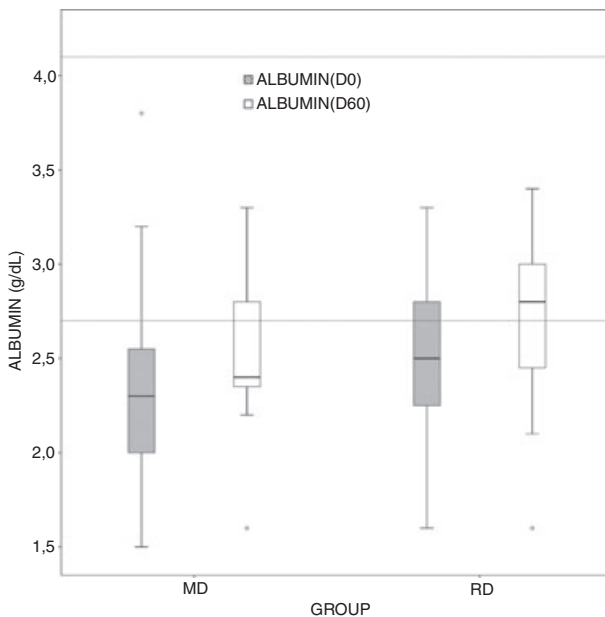


Fig 5. Box and whisker plots of serum albumin concentration in dogs of group MD and RD at D0 and D60. Each box-and-whisker plot illustrates the median, quartiles, and outliers (°). Dashed lines indicate reference range.

trend for increased Alb was greater in group-RD ($P = .06$) than in group-MD ($P = .49$) (Fig 5, Table 2). In group-MD, 7 dogs exhibited increased weight (5/7 increased Alb too, whereas Alb did not change in 2/7), 1 exhibited decreased weight (Alb also decreased in this dog), and 3 dogs exhibited no

changes between D0 and D60 (Alb did not change in 1/3 dogs and decreased in 2/3 dogs). In group-RD, weight decreased in 2 dogs (Alb did not change in 1 and decreased in the other dog), increased in 3 (Alb also increased in 2/3 dogs and did not change in 1), and remained stable in 6 dogs (Alb increased in 4/6 dogs, remained constant in 1, and decreased in the other dog).

In group-MD, hypoalbuminemia (Alb < 2.7 g/dL) was present in 9 dogs at D0 and, of them, 3 exhibited Alb < 2 g/dL. At D60, 8 of the 9 dogs remained hypoalbuminemic, and, of them, 2 had Alb < 2 g/dL. In group-RD, 8 dogs were hypoalbuminemic at D0 (of them, 2 had Alb < 2 g/dL), whereas only 4 were hypoalbuminemic at D60 (of them 1 had Alb < 2 g/dL).

All dogs included in the study except 1 dog from group-RD remained non-azotemic at D60 (Table 2; Fig 6). In the exception, azotemia was mild (SCr = 1.5 mg/dL, urea = 62 mg/dL), the urine was normally concentrated (USG = 1,032), and the dog did not show clinical signs of kidney disease.

RM-ANOVA revealed a significant decrease in log UPC ($P = .005$) and SBP ($P = .001$) and a significant increase in weight ($P = .038$) throughout the study, but these changes could not be attributed to the diet used for any of the variables (Table 3).

Discussion

The results of this study suggest that the administration of a RD and benazepril to PNAz dogs could contribute to control proteinuria and SBP without causing clinically detectable malnutrition. However, these results should be interpreted with caution.

Table 3. Repeated measures ANOVA of variables evaluated in the study at D0 and D60.

	Time Effect (<i>P</i> -value)	Diet Effect (<i>P</i> -value)	Interaction Effect (<i>P</i> -value)
Weight (kg)	.038	.77	.796
Albumin (g/dL)	.12	.714	.714
SCr (mg/dL)	.40	.47	.202
Log urea	.63	.32	.104
Log UPC	.005	.39	.394
SBP (mmHg)	.001	.942	.321

NA, not applicable.

Although the initial statistical analysis (paired *t*-test) identified significant changes in log UPC and SBP in group-RD not evident in group-MD, RM-ANOVA did not attribute these differences to the diet administered. This discrepancy could be a consequence of small sample size and characteristics of the statistical tests.

Available evidences indicate that dietary modification has beneficial effects in the management of glomerular diseases.¹⁹ Protein restriction is a common dietary modification in therapeutic RDs,^{22–25} and can reduce proteinuria in dogs with glomerulopathies.²⁰ However, if protein restriction is too severe (1.83 g of protein/100 kcal of digestible energy), protein malnutrition can occur.²⁰ According to the manufacturer's information, the RD used in this study provides 3.7 g of protein/100 kcal of ME. Our results showed that this level of dietary protein could result in a significant reduction in proteinuria compared with dogs fed a MD with a protein content of 5.5 g/100 kcal of ME.

In this study, changes in the nutritional status were evaluated by measuring weight and Alb concentration. These parameters are considered insensitive and late markers of malnutrition in humans,^{27,28} so maybe a more complete evaluation of the nutritional status of the dogs, including monitoring of food intake and body and muscle condition, had been desirable. However, weight and Alb concentration were monitored in a study evaluating dietary changes in dogs with X-LHN and proved to be good markers of malnutrition, showing a prompt response to dietary changes.²⁰

Considering the evaluated parameters, protein malnutrition was not observed in any of the dogs administered the RD. Only 2 dogs in group-RD lost weight during the study and 50% (*n* = 4) of dogs with hypoalbuminemia at inclusion had normal Alb at D60.

Different results were obtained by the paired *t*-test and RM-ANOVA in the evaluation of weight changes. Although the former identified a nonsignificant trend toward increased weight in group-MD but not in group-RD, RM-ANOVA results indicated statistically significant changes in weight between D0 and D60, independent on the diet administered. In this study, which features a small sample size, with only 2 groups of dogs and only 2 checkpoints, it is possible that the paired *t*-test was a more suitable than the

RM-ANOVA. In the authors' opinion, future studies with a more robust design (larger samples and more checkpoints) could elucidate whether the differences detected using the paired *t*-test are also detected by RM-ANOVA.

Supplementation with omega-3 PUFAs is recommended in the management of proteinuric dogs.⁷ The RD used in this study provides a higher percentage of omega-3 PUFAs than the MD, and it is possible that this contributed to the control of proteinuria evident in group-RD. Although some authors recommend a daily dose of 1–5 g of omega-3 PUFAs,²⁹ the effects of this level of supplementation in dogs with spontaneous proteinuria are unknown.

ACEIs are efficacious in the treatment of proteinuria and hypertension in dogs with kidney disease.^{13,14,17} In Samoyed dogs with X-LHN, enalapril decreases proteinuria, improves renal excretory function, decreases glomerular basement membrane splitting, and prolongs survival compared with control dogs.¹⁴ Enalapril reduces proteinuria and SBP, and delays the onset or progression of azotemia in dogs with idiopathic, naturally occurring glomerulonephritis.¹³ Benazepril reduces proteinuria and improves the health status and glomerular filtration rate of a group of dogs with spontaneous CKD compared with dogs receiving placebo.¹⁷ Dogs included in this study received Be, but proteinuria did not significantly decrease in the group-MD. However, this apparent lack of efficacy of Be must be reviewed carefully. Four dogs in group-MD showed a significant reduction in UPC at the end of the study, and two exhibited a decrease in the UPC value, but without statistical significance (stable disease).

Comparison of our results with those of previous studies evaluating the effects of ACEIs in dogs with glomerular proteinuria is complicated, owing to differences in studies design. In addition, because the kidneys of the dogs included in this study were not biopsied, it is possible that those with a UPC <2 did not have a glomerulopathy, but suffered instead from a tubular disease.² Although ACEIs have demonstrated an antiproteinuric effect in dogs with various renal conditions,^{13,14,17} it is possible that their efficacy varies depending on the cause and severity of the disease. Moreover, the drug used and its dose also contribute to the clinical effectiveness of ACEIs. Although the benefits of ACEIs are believed to be a property of the drug class, differences exist between ACEIs that could influence their efficacy.³⁰ In humans, it was suggested that using higher doses of ACEIs increases their antiproteinuric and renoprotective effects³⁰ and this could also be the case in dogs. Thus, we cannot exclude the possibility that some dogs would have experienced a significant reduction in proteinuria if a higher dose of benazepril had been administered. To confirm this hypothesis, a study investigating the antiproteinuric effects of ACEIs used at different doses is warranted.

Dogs with Alb <2 g/dL received low doses of aspirin. Aspirin can be of benefit on the management of

proteinuria in dogs with glomerulonephritis,^{7,13} so the possibility that at least some of the beneficial effects observed in these dogs were attributable to the concurrent effect of aspirin therapy cannot be excluded.

The use of ACEIs in patients with kidney disease can also cause renal excretory function to decrease.^{13,16,31,32} SCr and urea did not change significantly in group-MD or RD and remained within the reference range in all but 1 dog in group-RD, which presented with mild azotemia and concentrated urine at D60. The treatment of this dog was not changed and later follow-up found concentrations of SCr and urea to be within the reference range (data not shown). In the authors' opinion, the transient character of azotemia in this dog combined with normal urine concentration suggests a prerenal origin, perhaps caused by a subclinical dehydration. However, the dogs were not kept in a controlled environment, and therefore other possibilities (for example, the dog may not have been fasted when the blood was obtained) should be considered. The authors consider that at the doses used in this study, Be is a safe drug to use in hemodynamically stable PNAz dogs.

The paired *t*-test identified a significant reduction in SBP in group-RD that was not detected in group-MD. This suggests a benefit of dietary modification, additionally to the expected ACEIs effect in reducing blood pressure. However, considering that RM-ANOVA did not confirm the results of the *t*-test, further studies are required to evaluate this possibility.

This study has several limitations. Probably, the most important is the small sample size, which could explain the apparent discrepancies in the results obtained from the statistical tests. The study was designed as a pilot study to investigate the potential benefits of using a therapeutic RD in the management of PNAz dogs. A larger sample size was desirable, but recruitment of dogs was complicated, and we decided to perform the study with fewer animals than the initially planned. Thus, the results should be interpreted with caution. In all cases, renal biopsy was proposed once the presence of persistent proteinuria of unknown origin was confirmed. As most owners did not accept the procedure, we were unable to use biopsy results in the study. This fact did not allow to classify dogs according to the presenting renal lesion, which would have contributed to the findings of the study. Finally, the study lasted for just 2 months: it is unknown whether or for how long the observed benefits would have persisted or whether delayed disease progression or improved survival time was achieved in these dogs. A future study with a larger sample size and a longer follow-up is indicated.

In summary, this study suggests that the administration of a RD combined with Be to non-azotemic dogs with renal proteinuria may improve proteinuria and SBP control compared with the administration of a MD and Be without causing significant clinically detectable malnutrition, but more studies are warranted.

Footnotes

- ^a Hopwood-Courville RM, Vaden SL, Huerley KJ, et al. Dietary protein modification in dogs with non-azotemic protein-losing nephropathy. *J Vet Intern Med* 2003; 17:404 (abstract)
- ^b IDEXX-Vetlab, Barcelona, Spain
- ^c MS4s, Melet Schloesing Laboratoires, Osny, France
- ^d Dri-Chem 4000i, Fujifilm, Japan
- ^e SNAP 4Dx test kit, IDEXX Laboratories, Westbrook, ME
- ^f SNAP Leishmania test kit, IDEXX Laboratories, Westbrook
- ^g www.randomizer.org. Last accessed 01/15/2012
- ^h Adult Royal Canin SAS, Amargues, France
- ⁱ Renal Royal Canin SAS
- ^j Fortekor, Novartis Santé Animale SAS, Huingue, France
- ^k Parks-Medical Electronics, model 811-BL, Aloha, OR
- ^l SPSS 15.0 for Windows; Chicago, IL
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Conflict of Interest: Dr Oscar Cortadellas' expenses for travel and accommodation to present this study at the 2012 ACVIM Forum were covered or reimbursed by Novartis Sanidad Animal and Royal Canin Ibérica.

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