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Acceptance and effects of a therapeutic renal food in pet cats with chronic kidney disease

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ABSTRACT

Introduction: Renal foods are used to manage chronic kidney disease (CKD) in dogs and cats, but their effectiveness may be limited by the ability to transition animals to them.

Material and Methods: In a prospective study, pet cats with previously undiagnosed kidney disease (20 International Renal Interest Society (IRIS) 1, 61 IRIS 2, 14 IRIS 3/4, 33 at risk for CKD) were transitioned to a renal food. Markers of renal function were measured and owners answered questionnaires about their pet over one year.

Results: All but eight cats (120/128; 94 per cent) successfully transitioned to the renal food. Most of the time, cats moderately or extremely liked the food (89 per cent), ate at least half (73 per cent) and were moderately or extremely enthusiastic while eating (68 per cent). Cats rarely disliked the food (2 per cent) or refused to eat it (1 per cent). Markers of renal function were unchanged in IRIS 1 and 2 cats and changed little in IRIS 3/4 cats. In all groups, owner-assessed quality of life improved initially and then remained stable. Mean bodyweight did not change in cats with CKD.

Conclusions: Most cats with CKD successfully transitioned to the renal food. The results also support previous studies that the renal food can help stabilise cats with CKD.

INTRODUCTION

Chronic kidney disease (CKD) occurs mostly in older cats and may affect as many as one in three cats aged >15 years (White and others 2011). Complications include a variety of metabolic disorders, dehydration, anaemia, proteinuria and arterial hypertension (Polzin 2011). Conservative management of CKD focuses on correcting and maintaining fluid, electrolyte, acid-base, endocrine and nutritional balance (Roudebush and others 2009). Nutritional management, in particular feeding therapeutic renal foods, is an important part of this. When compared with typical feline maintenance foods, therapeutic renal foods feature reduced protein, phosphate and sodium and increased buffering capacity, soluble fibre, B-complex vitamins, antioxidants and omega-fatty acids. Because changing cats to a new food can be challenging, recommendations are to transition gradually to a renal food over at least seven days, although some cats may need as much as three to four weeks (Polzin 2013, Roudebush and others 2009).

Prescription Diet k/d feline renal health (Hills Pet Nutrition, Topeka, Kansas, USA) is a low-phosphate renal food that has been used to manage CKD in cats for more than 40 years. In a 24-month randomised controlled trial in cats with CKD, it significantly reduced the number of uraemic episodes and reduced renal-related mortality when compared with a maintenance diet, without inducing significant adverse events (Ross and others 2006). The current study examined the ability to transition pet cats with CKD to the dry formulation of this renal food and assessed its effects on quality of life and markers of renal function.

MATERIALS AND METHODS

Study design

This was a prospective study to assess the palatability and ability to transition pet cats with CKD to a renal food (Prescription Diet k/d feline renal health) and to validate its use for managing feline CKD. The study was conducted at 38 sites in the USA between April 13, 2010 and July 22, 2011.

Ethics

All aspects of this study were conducted in accordance with the Hill's Pet Nutrition Global Animal Welfare Policy. The study was approved by the Hill's Institutional Animal Care and Use Committee. Procedures were designed to avoid or minimise discomfort, distress and pain to the subjects. Study subjects were monitored for any signs of disease. For adverse events, the subject's health took precedence over continuation in the trial. Owners had to sign an informed consent form before enrolment of their cat and had

to agree to comply with the instructions given by the veterinarian and listed in the consent form.

Study population

Pet cats at least two years of age were considered for enrolment if they had a serum creatinine concentration ≥1.0 mg/dl and at least one of the following: abnormal kidney on palpation or ultrasound, dilute urine (urine specific gravity (USG) <1.035) or a urine protein/creatinine (UPC) ratio >0.4. The cats could not be emaciated and had to otherwise be in good health as determined by a physical examination and laboratory analysis. Cats were excluded if they would not consume dry food only during the study, had been fed a renal therapeutic food within the previous three months, had a planned surgery, were pregnant or likely to become pregnant during the study period, were fractious, were in a multi-cat household and could not be segregated or had participated in another clinical trial within the previous six months.

Cats could be removed from the study if they had an adverse reaction, injury or illness that warranted treatment or surgical intervention; if the investigator determined that the cat was unable to continue in the study due to progression of CKD or other concurrent medical conditions; if the cat was uncooperative with study procedures; or if the owner did not comply with the study guidelines.

Study conduct

Cats were housed with their owners. One to two weeks after the screening visit, cats were offered the test food (Prescription Diet k/d feline renal health dry formulation; Hills Pet Nutrition, Topeka, Kansas, USA). The cats were transitioned by their owners to the test food over a seven-day period by progressively increasing the ratio of test food to the cat's usual food. Amounts offered were based on the resting energy requirement, which was estimated as $70\times(\text{bodyweight in kilograms})^{0.75}$. The food was provided in bags that were marked with tracking codes but no other indications of the contents. Cats were considered to have accepted the food if they fully transitioned to it by the end of the seven-day period.

On day 0 and at 1, 3, 6, 9, and 12 months, the cats were fasted overnight and brought in by their owners for a visit with the investigating veterinarian. During the visit, the investigator took a blood and urine sample, obtained a complete history and performed a physical examination.

At all visits, owners completed a questionnaire assessing palatability of the renal food (the cat's food consumption and appetite) and the cat's overall health, quality of life, energy level, youthfulness/vitality, desire for attention and socialising with other animals.

Cats that refused to eat two or more consecutive meals within a 36-hour period were dismissed from the study and offered a choice of two other renal therapeutic foods. For suspected adverse events, the pet owner was instructed to contact the investigator immediately. The investigator was required to report details of the event within 24 hours.

International Renal Interest Society staging

During the study, the severity of CKD was staged according to the 2006 version of the International Renal Interest Society (IRIS) system (Polzin 2013) by an independent, blinded veterinarian. The IRIS stage is assigned based on the serum creatinine concentration and whether an abnormal kidney on palpation or ultrasound, dilute urine or elevated UPC ratio is present. IRIS stage 1 corresponds to mild CKD, IRIS stage 2 to moderate CKD and IRIS stage 3 and 4 to severe CKD. To be assigned an IRIS stage, a cat had to have these signs of kidney disease at multiple consecutive assessments. Cats that had intermittent evidence of kidney disease were considered to be 'at risk for CKD' and were not assigned an IRIS stage. Veterinarians shared results from physical exams and renal health assessments with their clients, but pet owners were not made aware of the specific IRIS classification of their cats during the study.

Statistical analysis

Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA). A P value <0.05 was considered to indicate statistical significance. The analyses included all cats at all time points for which data were available. IRIS 3 and IRIS 4 cats were combined in a single group for the analyses.

To determine whether mean responses in the health and vitality components of the pet owner questionnaires were significantly different from 'no change' or 'about the same', all scores were first centred around zero by subtracting four (for overall health change and quality of life change) or three (for all other questions). Data were analysed using a linear mixed model for a repeated measures design with disease group and month as fixed effects in the model. A compound symmetry covariance structure was fit to the data to account for the correlation between the repeated measurements (months). The Kenward and Roger procedure was used to adjust the error degrees of freedom and SE for the fixed effects for downward bias in the test statistics. A *t* test was used to determine whether the response mean was significantly different from 0.

Bodyweight, blood urea nitrogen (BUN), serum creatinine concentration, UPC ratio and USG were analysed using the same model. Several different covariance structures were initially fit to the data and Akaike information criterion corrected (AICC) and Bayesian information criterion (BIC) fit statistics were used to select the best structure. UPC ratio was log-transformed before analysis. Linear and quadratic trends over time were analysed using orthogonal polynomial contrasts for unequally spaced intervals. The orthogonal polynomial coefficients for the contrasts were calculated as described previously (Snedcor 1958). A *t* test was used to determine whether the mean change between day 0 and month 12 was significantly different from 0.

TABLE 1: Baseline characteristics of the cats enrolled

Characteristic	At risk for CKD	IRIS 1	IRIS 2	IRIS 3/4
N	33	20	61	14
Age (years), mean±sd	9.5±2.4	11.6±3.0	11.9±3.8	12.6±2.2
Weight (kg), mean±sd	5.5±1.4	5.3±1.5	4.7±1.4	5.0±1.2
Body condition score*	3.61±0.79	3.25±0.91	3.31±0.89	3.14±0.53
Sex, n (%)				
Male	16 (48.5%)	12 (60.0%)	25 (41.0%)	10 (71.4%)
Female	17 (51.5%)	8 (40.0%)	36 (59.0%)	4 (28.6%)

*As described previously, body condition score was 1 for emaciated, 2 for underweight, 3 for normal weight, 4 for overweight and 5 for obese (Toll and others 2010)
CKD, chronic kidney disease; IRIS, International Renal Interest Society

RESULTS

One hundred and twenty-eight cats met the selection criteria and were enrolled in the study. Twenty cats were classified as IRIS 1, 61 as IRIS 2, 12 as IRIS 3, 2 as IRIS 4 and 33 as at risk for CKD. Sex distribution, body condition scores and weights were similar in the four groups (at risk, IRIS 1, IRIS 2 and IRIS 3/4), but age increased with IRIS stage (Table 1).

A total of 112 cats remained in the study at month 1, 101 at month 3, 76 at month 6, 75 at month 9 and 70 at month 12 (Table 2). The most common reason for leaving the study before month 12 was that, in 21 cases, the owners had originally agreed to enrol their cat in a three-month study but the study was later extended to 12 months, so they were given the option to withdraw their cat after three months. In another eight cases, the cat refused to eat the study food or did not eat enough of it to maintain its bodyweight. In seven cases, the cat was dismissed because the owner did not follow feeding guidelines or wanted to feed non-study foods. In one case, the cat was dismissed because the owner became aware of the nature of the study food.

Seven cats died or were euthanased during the study (one due to respiratory distress, one due to stroke, one due to progression of CKD, two due to cardiovascular disease, one for no assignable cause and one due to a neurological disorder). Another seven cats were dismissed before the end of the study because of a deteriorating condition (i.e. worsening CKD), three were dismissed for concurrent medical conditions (inflammatory bowel disease, cardiovascular disease, anal sac abscess), two were lost to follow-up and two were dismissed for adverse events (diarrhoea).

Palatability and acceptance of the renal food

Of the 128 cats enrolled in the study, only eight (6.3 per cent) refused to eat the food. This included two cats in the at-risk group, five in the IRIS 2 group and one in the IRIS 3/4 group. The remaining 120 (93.7 per cent) successfully transitioned to the renal food and continued eating it until the last assessment available.

Owners reported that their pets liked the test food 89 per cent of the time (384/431 total assessments; Fig 1). They also reported that their pets ate at least half the

TABLE 2: Disposition of the cats enrolled

Category	Normal	IRIS 1	IRIS 2	IRIS 3/4	Total
Enrolled	33	20	61	14	128
Remaining in the study					
Baseline (day 0)	33	20	61	14	128
Month 1	31	19	52	10	112
Month 3	28	18	47	8	101
Month 6	16	16	37	7	76
Month 9	16	16	36	7	75
Month 12	16	14	35	5	70
Reasons for not completing to month 12					
Adverse event	0	1	0	1	2
Concurrent medical condition	0	1	2	0	3
Deteriorating condition	0	1	4	2	7
Death or euthanasia	0	1	2	4	7
Did not eat the test food or did not eat enough to maintain bodyweight	2	0	5	1	8
Owner compliance	3	0	4	1	8
Owner withdrawal	10	2	9	0	21
Lost to follow-up	2	0	0	0	2

IRIS, International Renal Interest Society

food offered 73 per cent of the time (314/431) and that their cats were moderately or extremely enthusiastic while eating 68 per cent of the time (292/431). Cats were reported as disliking the food only 2 per cent of the time (7/431), not at all enthusiastic while eating it only 5 per cent of the time (21/431) or frequently refusing to eat the food <1 per cent of the time (1/431). These palatability assessments were similar to those at baseline when the cats were consuming their usual food, although cats more frequently ate all or most of the test food (55 per cent) than their usual food (43 per cent).

Owner assessment of health and quality of life

At each visit, owners were asked to rate changes since the previous visit in overall health, quality of life, energy level, youthfulness/vitality, desire for attention and socialising with other animals (Fig 2). Owners reported that overall health and quality of life significantly improved since the previous visit at months one and three in cats with the most severe CKD (IRIS 2 and IRIS 3/4). Energy level, youthfulness and vitality and socialising with other animals were reported as significantly improved since the previous visit in all groups at most visits up to month 6. Finally, desire for attention significantly improved in at-risk, IRIS 1 and IRIS 2 cats at most visits.

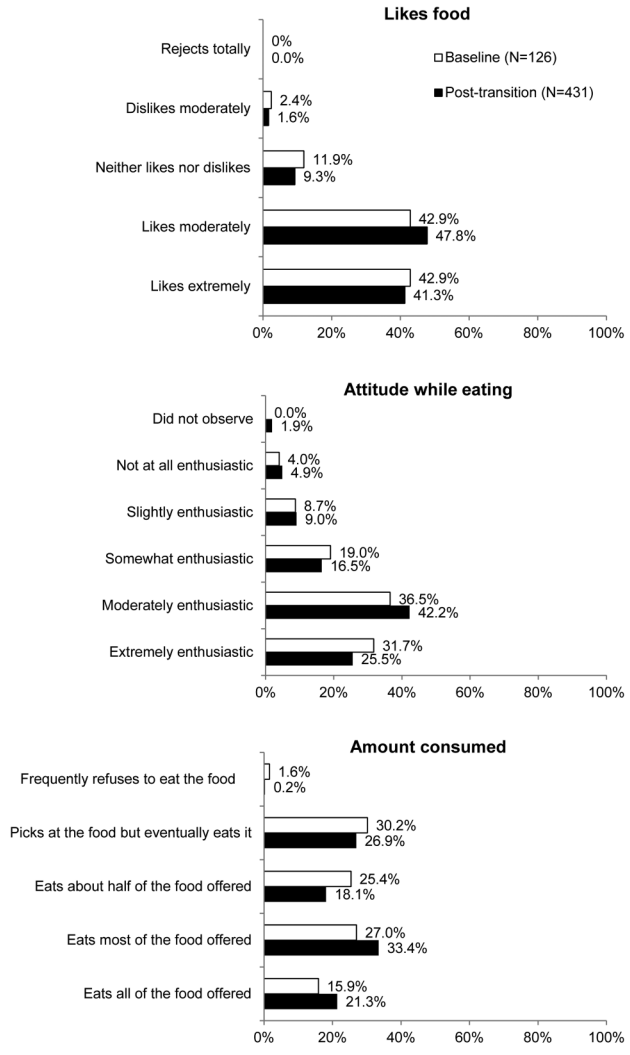

FIG 1: Owners' assessment of their cat's consumption of the test food. At months 0, 1, 3, 6, 9 and 12, owners were asked about their cat's consumption of the food during the previous period. Shown are the per cent in each category of for all cats at baseline (n=126 assessments) and for all visits (months 1–12) after they transitioned to the test food (n=431 assessments).

Bodyweight

In IRIS 3/4 cats, mean bodyweights initially increased and then progressively decreased, so that at the end of the study there was no net change. In IRIS 1 and 2 cats, mean bodyweight remained stable (Fig 3 and Table 3). In at-risk cats, mean bodyweights increased slightly over time (mean change=0.29±0.11 kg (P=0.013)).

Markers of renal function

Few changes in markers of renal function were detected in this 12-month study. Serum creatinine and blood urea nitrogen (BUN) concentrations remained stable in at-risk, IRIS 1 and IRIS 2 cats (Fig 4 and Table 3). In IRIS 3/4 cats, mean serum creatinine and BUN concentrations decreased during the first six months of the study and then increased during the remaining six months, resulting in a significant quadratic trend over time (P=0.002) but no difference between day 0 and month 12 (Fig 4 and Table 3). UPC ratios also did not significantly change over time in at-risk, IRIS 1 or IRIS 2 cats, but they increased linearly over time in IRIS 3/4 cats (P=0.03 for trend over time; P=0.0012 for month 12 v day 0). USG did not significantly change in any group.

DISCUSSION

Prescription Diet k/d feline renal health has been used for more than 40 years to treat cats with CKD. The most difficult aspect of using renal foods may be transitioning cats to them (Roudebush and others 2010). For example, Elliott and others reported that of 50 cats with CKD, only 29 successfully transitioned to a renal food (Elliott and others 2000). Accordingly, recommendations are to make the transition to a renal food over a period of at least seven days (Roudebush and others 2010). The authors followed these recommendations to transition pet cats with CKD to the dry formulation of Prescription Diet k/d feline renal health. The authors found that the cats transitioned well to this food: 94 per cent accepted the food and continued eating it until the last assessment available, and owners reported that their cats liked it as much or more than their original food.

Ross and others (2006) reported a 24-month randomised, double-blinded, controlled trial comparing the renal effects of Prescription Diet k/d feline renal health and a maintenance food. When compared with the maintenance food, the renal food significantly reduced the number of uraemic episodes (from 26 per cent to 0 per cent) and reduced renal-related mortality (from 22

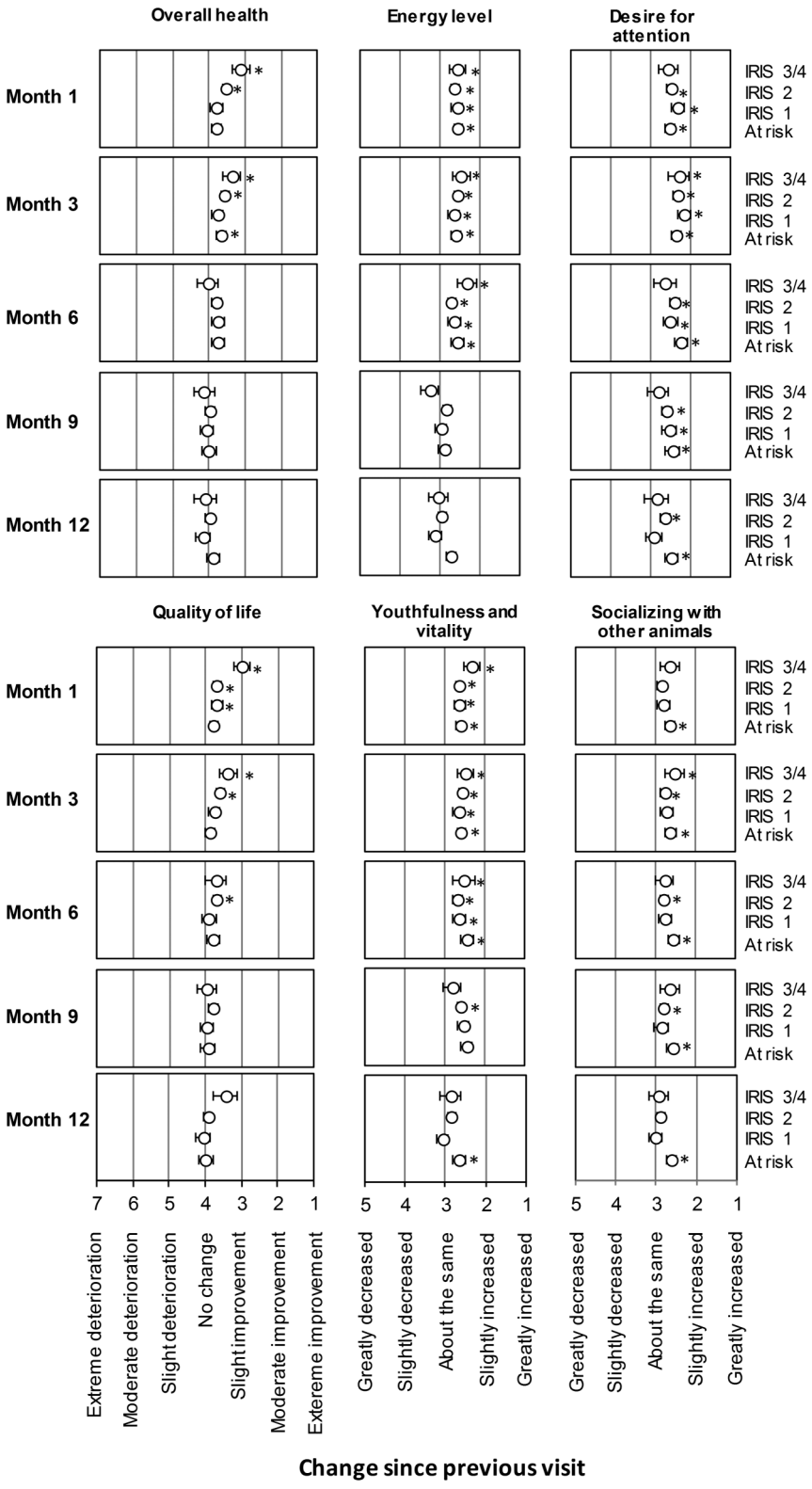

FIG 2: Change in overall health and quality of life at each visit. At each visit, owners were asked about changes in their cat's health and quality of life since the previous visit. Mean values±se are plotted according to severity of chronic kidney disease for all cats at all time points for which data were available. *Significantly different (P<0.05) versus "no change" (score=4) or "about the same" (score=3). IRIS, International Renal Interest Society

per cent to 0 per cent), with no significant adverse events reported. In addition, a retrospective analysis of data on deceased cats in The Netherlands by Plantinga and others (2005) showed that cats with CKD survived longer when fed the dry formulation of Prescription Diet k/d feline renal health than when not fed a renal food (median survival=16 v 7 months, P<0.001).

The results of this study agree with and extend these findings. In cats with CKD, most owner-reported quality of life measures improved during the first six months and then remained stable. Also, blood and urine markers of renal function remained stable over the 12 months of the study in cats with mild to moderate CKD (IRIS 1 and 2). In cats with severe disease (IRIS 3/4), serum creatinine

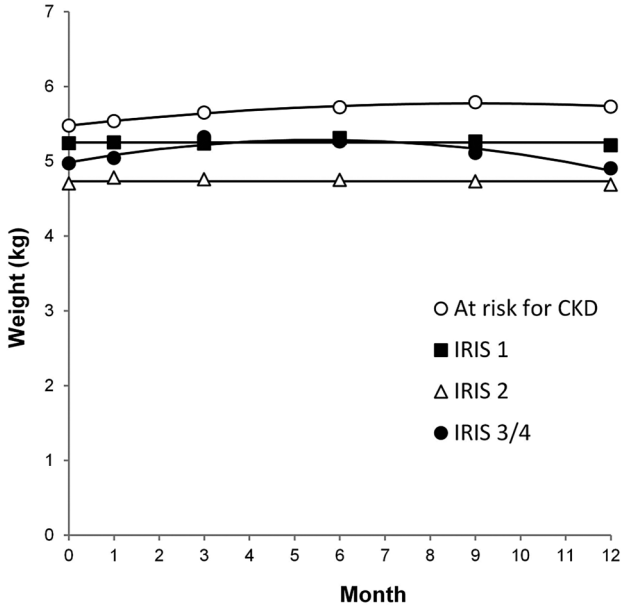

FIG 3: Bodyweight. Mean bodyweights at each visit are plotted according to the severity of chronic kidney disease (CKD) for all cats at all time points for which data were available. Symbols indicate the observed means, and the lines indicate the mean values predicted by regression analysis using a linear mixed model. IRIS, International Renal Interest Society

and BUN concentrations initially improved and then returned to pretreatment levels, while USG remained stable and UPC ratios slowly increased. In agreement with this, mean bodyweight did not change in any of the IRIS groups. Together, these findings, along with those of Ross and others and Plantinga and others suggest that Prescription Diet k/d feline renal health can stabilise renal function in cats with CKD.

Because this study did not include a control group, the authors could not adjust for subjectivity in the owner assessments. However, 94 per cent of the cats transitioned to and continued eating the test food, an objective finding that supports the owners' assessment that the food was well accepted. Other objective measures—serum and urine markers of renal function and the change in bodyweight—agreed with owners' quality of life assessments, suggesting stabilisation of CKD. Direct confirmation of stabilised or improved renal function, however, would require measuring the glomerular filtration rate, which was not feasible in this study of pet cats.

Of the 128 cats starting the study, 61 did not complete the study until month 12. Most of these were because of lack of owner compliance or owner withdrawal of consent for reasons other than the cat not eating the food, and only eight (including one death) were because of worsening CKD.

A study of risk factors for CKD found that owners of cats with CKD were approximately three times more likely to report decreased appetite at the time of diagnosis as owners of cats without CKD (Greene and others 2014). Also, according to a survey of owners of cats with CKD, 43 per cent of the cats had an abnormal appetite (Elliott and others 2000). According to baseline assessments, on average, the cats in this study had a good appetite both before and after transitioning to the renal food. This may be because the population was skewed more towards early stages of CKD. However, even cats with more advanced stages of CKD (IRIS 3/4) transitioned to the renal food with little problem.

Conclusions and recommendations

This study showed that pet cats with CKD or at risk for CKD transition to Prescription Diet k/d feline renal health with little or no problem. Furthermore, in agreement with previous findings (Plantinga and others 2005, Ross and others 2006), the results of this study suggest that that this food can help slow or stabilise CKD in this population. These results support the recommendation that the standard of care for feline CKD includes feeding a renal food (Polzin 2013).

TABLE 3: Mean change in bodyweight and renal markers between day 0 and month 12

Measure	Value	At-risk for CKD	IRIS 1	IRIS 2	IRIS 3/4
Weight (kg)	Mean change±se	0.29±0.11	0.04±0.11	−0.10±0.07	−0.04±0.19
	P value*	0.013	0.72	0.16	0.83
Serum creatinine (g/dl)	Mean change±se	0.04±0.17	−0.04±0.17	−0.15±0.11	0.40±0.29
	P value*	0.81	0.84	0.17	0.17
BUN (g/dl)	Mean change±se	−1.3±2.1	−1.3±2.2	−0.1±1.4	0.2±3.7
	P value*	0.55	0.56	0.92	0.96
UPC ratio	Mean change±se	0.04±0.05	−0.02±0.05	0.03±0.03	0.29±0.09
	P value*	0.46	0.70	0.33	0.0012
USG	Mean change±se	0.002±0.003	−0.003±0.003	0.001±0.002	0.002±0.005
	P value*	0.55	0.33	0.53	0.75

*v no change (0)
BUN, blood urea nitrogen; CKD, chronic kidney disease; IRIS, International Renal Interest Society; UPC ratio, urine protein/creatinine ratio; USG, urine specific gravity

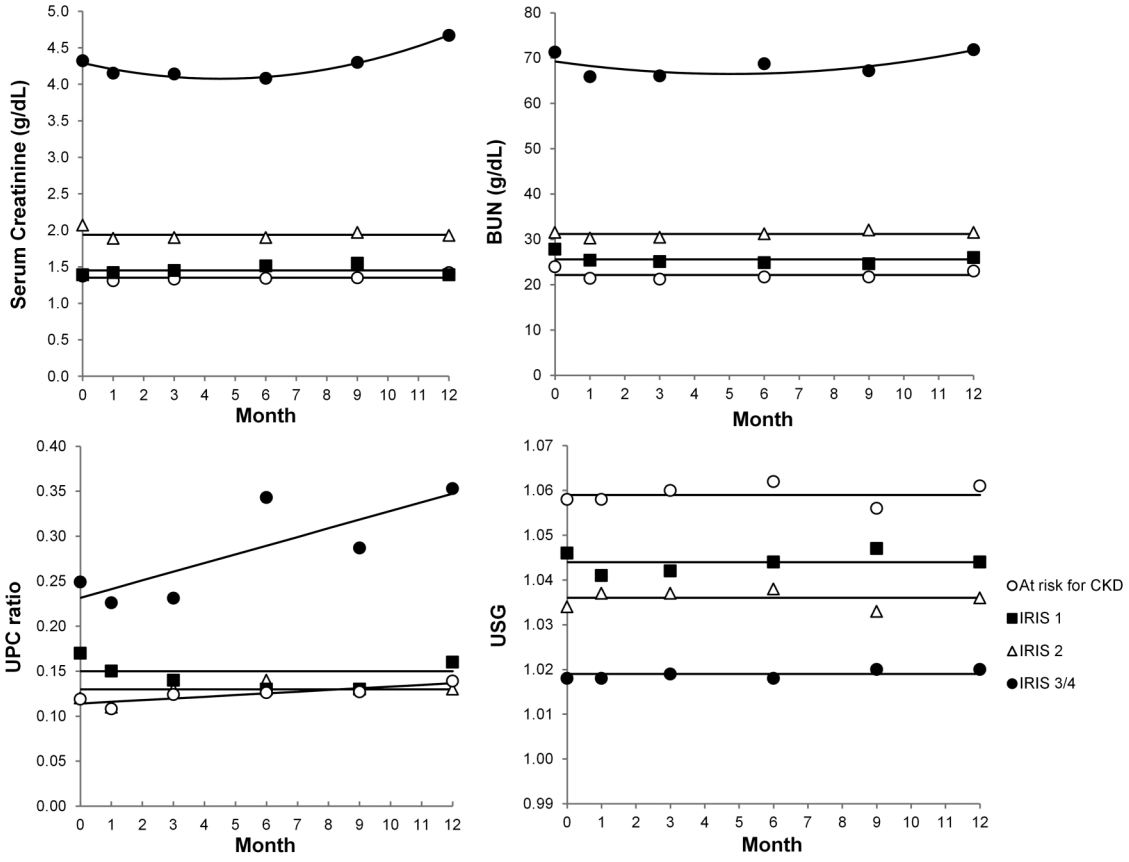

FIG 4: Markers of renal function. Mean serum creatinine, blood urea nitrogen (BUN), urine protein/creatinine (UPC) ratio, and urine specific gravity (USG) concentrations at each visit are plotted according to severity of chronic kidney disease (CKD) for all cats at all time points for which data were available. Symbols indicate observed mean values, and the lines indicate the mean values predicted by regression analysis using a mixed model. IRIS, International Renal Interest Society

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Collaborators DF: Project management, guarantor; DJ: data interpretation, manuscript review; P S Leventhal: medical writing; J Brejda: statistical analysis; N W Ahle: veterinary oversight; H M Schiefelbein: data management and S D Forrester: manuscript review.

Contributors DF: Project management, guarantor; Neil Ahle and Linda Melindez: veterinary oversight; John Brejda: statistical analysis; Phillip Leventhal: scientific writing; Heidi Schiefelbein: data reporting.

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Data sharing statement Summaries tables of the veterinary dermatological evaluations and pet owners assessment of skin and coat quality are available upon request through the corresponding author.

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