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ORIGINAL ARTICLE

A long term feed supplementation based on phosphate binders in Feline Chronic Kidney Disease

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Abstract
Chronic kidney disease (CKD) is a very common disorder in elderly cats. A proper renal diet represents the most efficient therapeutic intervention to improve survival and life quality in feline patients with 3 and 4 International Renal Interest Society (IRIS) stages. Twenty cats were selected in this study. Ten were administered the dietary supplementation for 360 days and the other ten, whose owners did not give consent for any supplemental therapies apart from the renal diet, were selected from a clinical database and used as control group. The present study is a long term study (360 days) aiming to evaluate the efficacy and palatability of a dietary supplementation containing calcium carbonate, calcium-lactate gluconate, chitosan and sodium bicarbonate in cats diagnosed with 3 and 4 IRIS stages of CKD. The owners were asked to fill in questionnaires to get information on the cat's appetite, the palatability of the given supplement, the presence of vomit and/or diarrhoea, general health and vitality. Hematochemical, biochemical and urinary analyses were performed on day 0, 30, 60, 90, 120, 150,180 and 360. GraphPad Prism® software was used to perform statistical analysis. Our study shows that the given dietary supplement reduced serum phosphorus and increased serum bicarbonate values in cats with CKD. In turn, this supplement could be used as a support therapy in cats with advanced CKD improving their clinical conditions without any adverse reaction. Finally, it is important to underline that all the animals completed the study and the owners reported a good palatability of the feed supplement.

Keywords Cat · Chronic kidney disease · Feed supplement · Phosphate binder

Introduction

Chronic kidney disease (CKD) is one of the most common conditions affecting cats that increases with age (Caney 2016). CKD is typically diagnosed on the basis of an increased serum creatinine concentration in combination with inappropriately low urine specific gravity, normally present for several weeks or months, and a clinical history compatible with CKD (Sparkes et al. 2016). Dogs and cats with CKD are staged according to the guidelines developed by the International Renal Interest Society (IRIS) using a four-stage scale of disease progression (International Renal Interest Society 2013). Management of CKD is largely focused on supportive and symptomatic therapy with the aim of improving the quality of life of the affected cats (especially those in CKD stages 3 and 4) (Sparkes et al. 2016).

Renal diets are specifically formulated for the clinical management of cats with CKD. This type of diet has four specific goals: to ameliorate or prevent clinical consequences of CKD and uremia; to slow down progression of CKD and/or prolong animal survival; to minimize derangements of electrolyte, mineral, and acid-base balance, and last to maintain adequate nutrition (Polzin and Churchill 2016). In CKD affected animals, serum phosphate tends to increase and may become more refractory to control using dietary phosphate restriction. Where diet alone is not sufficient, the use of intestinal phosphate binders is recommended (Sparkes et al. 2016). The use of dietary supplements represents another important aspect of nutritional modulation, it is also very common in people, with > 50% of adult Americans taking 1 or more complementary food. Women are greater consumers compared to men, and their use is associated with level of

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education, other health behaviors, and age (Freeman et al. 2006).

The present study provides an additional contribution to a previous research conducted by Vergnano et al. (2016). The aim of our work is to evaluate the efficacy and palatability of a dietary supplementation containing calcium carbonate, calcium-lactate gluconate, chitosan and sodium bicarbonate in cats with 3 and 4 IRIS stages of CKD for a long-term period (360 days).

Table 1 Composition of the feed supplement (Renal)

Analytical constituents	%
Crude ash	28
Crude protein	6.5
Crude fiber	1
Potassium	0.02
Calcium	13.68
Phosphorus	< 0.01
Sodium	0.3

Data are expressed as % on dry matter

Materials and Methods

Twenty cats were recruited from the Veterinary Clinic Napolivet, in Naples (Italy) from 2015 to 2016. The animals were divided in two numerically homogenous groups. Given the written consent from the owners, ten cats belonging to the first group (group T) were fed with a supplementary diet. The second group (group C), was selected from the Clinic's internal database and served as a control group. Owners of the cats belonging to the second group didn't give the consent to administer any supplement in addition to the renal diet during the study period.

Animals included in the study were required to belong to IRIS Stage 3 or Stage 4 CKD according to the International Renal Interest Society (IRIS) system, having a serum creatinine concentration above the reference value (2.9 mg/dl), on at least two different consecutive blood samples. Moreover, they had to show clinical signs of polyuria and polydipsia and have hyperphosphatemia, i.e. a plasma phosphate concentration higher than 5 mg/dl (1.6 mmol/l) for cats in IRIS stage 3 and higher than 6 mg/dl (1.9 mmol/l) for cats in IRIS stage 4.

Cats with evidence of comorbidities including bacterial pyelonephritis, urinary tract obstruction, neoplasia, prerenal or post-renal azotemia, hyperthyroidism, diabetes, chronic heart failure, or other unrelated diseases leading to clinical illness, were excluded from the study. All cats were exclusively fed with the same renal diet (Royal Canin Renal Feline, Royal Canin, Aimargues, France). All animals had been consuming the same diet for at least eight weeks before their inclusion in the study. The amount of food offered was based on the estimated requirements according to FEDIAF Nutritional Guidelines (Fédération européenne de l'industrie des aliments pour animaux familiers 2014). The same diet was maintained for the entire duration of the study in both groups. After the enrollment (T0), a feed supplement (Renal P, Candioli Farmaceutici SpA, Italy) especially designed for cats with CKD (Table 1) was added to the diet. Its dosage was 0.2 g/kg body weight/day divided in two daily administrations mixed with food. The supplement was given for 360 days and analysis were performed at 30 (T30), 60 (T60), 90 (T90), 120 (T120), 150 (T150), 180 (T180) and 360 (T360) days.

Each animal was monitored by a complete physical examination; body weight (BW) and body condition score (BCS, 1–5 point scale) (Thatcher et al. 2010) were also evaluated. Blood pressure (BP) was taken by an indirect Doppler method using the radial pulse, having the cat in sternal decubitus or sitting. During the examination, measurements were taken five times and the mean value was recorded. At each visit a questionnaire was given to the owner to assess: appetite of the cat, palatability of the supplement, presence of vomit and/or diarrhoea, general health and vitality.

Blood and urine samples were obtained by jugular vein puncture and cystocentesis, respectively. Venous haemogas analysis was performed immediately after blood sampling with a standard analytical device[3] in order to assess bicarbonate (HCO3) and ionized calcium (iCA). Urine sediment examination and specific gravity test by refractometry were performed in-house. Urine protein (UP) concentration (pirogallol red method) and creatinine concentration (Jaffè method) were evaluated in urine within 12 h from the collection. Then, urine samples were centrifuged (2 min at 1500 x g), supernatant was removed and stored at + 4 °C. Urine protein/creatinine (UPC) ratio was then calculated.

All procedures, treatments and animal care were in compliance with the guidelines of the Italian Minister of Health for the care and use of animals (D.L. 4 March 2014 n. 26 and D.L. 27 January 1992 n.116) and UE (Directive 86/609/CEE).

Statistical Analysis

GraphPad Prism® software was used to perform statistical analysis. Shapiro–Wilk test established the normality or non-normality distribution of data. One-way ANOVA and Kruskal–Wallis test were used to perform the intra-group comparisons among the experimental times, while the inter-group comparisons between the diets were performed by Student *t* and Mann–Whitney *U* tests. Significance was declared at $P < 0.05$.

Results

Cats included in the study (8 Spayed female and 12 Neutered male) had a mean age of 11.1 ± 2.4. The main breed represented was the European shorthair. The cats were already belonging to IRIS stages 3 (80%) and 4 (20%) of CKD (same proportion in T and C group) at least one month before the beginning of the study. In addition, they had showed hyperphosphatemia despite assuming a renal diet. All the selected animals completed the study. All the owners reported a good palatability of the tested feed supplementation product. Vomit and diarrhoea were observed at T0 in the 80% of the patients, and only two cases of sporadic vomit and diarrhoea were reported at T360. In the C group the percentage of cats with these symptoms (90%) was constant during the study period. No different increase or decrease, of body weight (T group: T0 5,06 ± 0,64 kg; T360 7,18 ± 1,91Kg; C group T0 3,89 ± 0,20 kg; T360 3,29 ± 0,14Kg) or body condition score was observed in both T and C groups.

No significant differences were recorded for blood pressure and hematochemical parameters during the study in both groups (Tables 2 and 3).

Table 3 Blood pressure measured during the study

	T0		T360	
	MIN	MAX	MIN	MAX
Group C	86.67 ± 2.58	174.29 ± 3.09	105 ± 4.69	168.33 ± 4.66
Group T	88.89 ± 1.05	175.56 ± 3.21	93.33 ± 1.63	168.33 ± 4.66

Data are expressed as mean ± standard error of the mean (SEM)

Data on the biochemical and haemogas analysis profile are presented in Tables 4 and 5. Serum phosphorus concentration at days 30, 60, 90, 120, 150 and 180 was lower ($P < 0.001$) in T group than in C (Fig. 1a). Creatinine and BUN, markers of renal function, remained stable and no significant differences between T0 and T360 in the T group were observed. Among the parameters, only creatinine showed a significant increase at T360 in group C. Serum ionized calcium (iCa) at days 60, 90, 120, 150, 180 and 360 was higher ($P < 0.001$) in T group compared with C (Fig. 1b). The increase of iCa fell within the physiological ranges (1.1–1.4 mmol/l). HCO3 at days 60, 90, 120, 150, 180 and 360 was also greater ($P < 0.05$) in T group than in C (Fig. 1c). A decrease (48% at day 360) of serum phosphorus and an increase of iCa (11% at day 360) and HCO3 (10% at day 360) were observed in T group.

Table 2 Ematochemical parameters measured during the study in control and treated group

	Laboratory standard reference range	T0	T30	T60	T90	T120	T150	T180	T360
Parameter group C									
HT %	26.00–45.00	28.8 ± 2.43	27.62 ± 2.71	27.62 ± 2.38	27.98 ± 2.40	26.80 ± 2.29	26.36 ± 2.01	26.48 ± 2.10	22.69 ± 2.03
HG g/dL	8.00–15.00	14.58 ± 1.26	14.39 ± 1.36	14.39 ± 1.17	14.65 ± 1.19	13.89 ± 1.12	13.53 ± 0.92	13.55 ± 0.85	12.29 ± 0.86
RBC 10^6 mm^3	5.00–10.00	7.47 ± 0.50	7.29 ± 0.52	7.25 ± 0.49	7.32 ± 0.52	7.01 ± 0.45	6.86 ± 0.34	6.89 ± 0.36	6.13 ± 0.28
WBC 10^3 mm^3	2.50–19.00	11.51 ± 1.67	10.69 ± 1.47	10.52 ± 1.18	10.33 ± 1.21	11.47 ± 1.61	10.83 ± 1.38	10.02 ± 1.37	6.92 ± 0.91
N 10^3 mm^3	2.50–12.00	8.02 ± 1.43	7.47 ± 1.30	7.44 ± 0.98	6.61 ± 0.82	7.54 ± 1.25	7.11 ± 1.04	6.37 ± 0.94	4.31 ± 0.70
EO 10^3 mm^3	0.1.50	1.02 ± 0.14	0.92 ± 0.13	0.90 ± 0.13	0.93 ± 0.13	1.06 ± 0.14	0.98 ± 0.16	1.00 ± 0.17	0.66 ± 0.12
LYM 10^3 mm^3	1.50–700	1.65 ± 0.13	1.44 ± 0.13	1.36 ± 0.16	1.81 ± 0.24	1.95 ± 0.24	1.89 ± 0.21	1.68 ± 0.18	1.45 ± 0.25
Group T									
HT %	26.00–45.00	27.79 ± 3.12	27.97 ± 2.67	27.98 ± 2.76	28.76 ± 2.33	27.72 ± 2.18	27.60 ± 2.27	26.92 ± 1.65	25.97 ± 1.55
HG g/dL	8.00–15.00	10.98 ± 0.77	10.97 ± 0.56	11.44 ± 0.75	11.89 ± 0.40	11.62 ± 0.63	11.79 ± 0.80	11.60 ± 0.69	11.11 ± 0.69
RBC 10^6 mm^3	5.00–10.00	6.07 ± 0.60	6.11 ± 0.43	6.51 ± 0.50	6.77 ± 0.25	6.42 ± 0.40	6.40 ± 0.46	6.24 ± 0.39	5.87 ± 0.42
WBC 10^3 mm^3	2.50–19.00	8.29 ± 1.38	8.72 ± 1.47	8.26 ± 1.15	8.73 ± 1.07	8.69 ± 1.11	9.09 ± 0.97	8.11 ± 0.87	7.99 ± 1.23
N 10^3 mm^3	2.50–12.00	5.41 ± 1.14	5.75 ± 1.04	5.50 ± 0.98	5.94 ± 0.88	5.50 ± 0.89	5.92 ± 0.92	5.03 ± 0.68	4.52 ± 0.73
EO 10^3 mm^3	0.1.50	1.08 ± 0.12	1.01 ± 0.17	0.91 ± 0.13	0.99 ± 0.12	1.30 ± 0.18	1.38 ± 0.14	1.24 ± 0.15	1.20 ± 0.18
LYM 10^3 mm^3	1.50–700	1.44 ± 0.24	1.51 ± 0.38	1.45 ± 0.21	1.38 ± 0.17	1.30 ± 0.13	1.34 ± 0.18	1.26 ± 0.12	1.69 ± 0.30

Data are expressed as median; T: time in days

Table 4 Biochemical parameters measured during the study

	Laboratory standard reference range	T0	T30	T60	T90	T120	T150	T180	T360
Parameter group C									
BUN mg/dL	20.00–50.00	130.50 ± 10.76	134.80 ± 11.96	135.10 ± 10.30	136.60 ± 8.31	144.40 ± 10.65	148.20 ± 11.68	148.90 ± 10.70	189.50 ± 14.22
CREA mg/dL	0.50-2.00	3.26 ± 0.17^{b}	3.30 ± 0.16^{b}	3.40 ± 0.14^{b}	3.55 ± 0.15^{ab}	3.56 ± 0.14^{ab}	3.68 ± 0.15^{ab}	3.66 ± 0.12^{ab}	4.10 ± 0.13^{a}
P mg/dL	2.70-5.00	7.83 ± 0.23^{b}	8.03 ± 0.17^{b}	8.22 ± 0.18^{ab}	8.35 ± 0.20^{ab}	8.51 ± 0.14^{ab}	8.54 ± 0.18^{ab}	8.53 ± 0.14^{ab}	8.91 ± 0.13^{a}
TP mg/dL	6.00–8.00	7.52 ± 0.34	7.51 ± 0.33	7.46 ± 0.34	7.35 ± 0.34	7.25 ± 0.33	7.18 ± 0.32	7.08 ± 0.28	6.59 ± 0.25
ALB mg/dL	2.20–3.50	3.44 ± 0.13	3.35 ± 0.11	3.34 ± 0.10	3.22 ± 0.08	3.16 ± 0.08	3.05 ± 0.07	2.97 ± 0.05	2.73 ± 0.07
A/G mg/dL	0.80–1.30	0.91 ± 0.03	0.88 ± 0.02	0.89 ± 0.03	0.86 ± 0.04	0.89 ± 0.03	0.89 ± 0.02	0.89 ± 0.03	0.87 ± 0.03
GLU mg/Dl	60.00-120.00	112.60 ± 8.17	106.90 ± 6.13	109.50 ± 8.36	103.30 ± 6.48	98.10 ± 5.53	96.70 ± 5.23	98.70 ± 5.51	95.00 ± 8.59
ALT UI/L	7.00–40.00	45.60 ± 5.05	42.90 ± 4.81	42.10 ± 4.02	42.80 ± 4.86	43.20 ± 4.55	40.70 ± 4.70	42.10 ± 5.03	45.70 ± 5.61
AST UI/L	7.00–40.00	33.00 ± 4.59	31.80 ± 4.25	33.80 ± 4.41	33.20 ± 4.76	35.50 ± 4.82	32.50 ± 3.80	32.80 ± 3.30	35.80 ± 5.45
ALP UI/L	4.00–50.00	79.80 ± 5.02	78.20 ± 5.17	79.20 ± 4.37	79.00 ± 3.67	76.60 ± 2.49	78.20 ± 3.17	79.50 ± 2.07	74.50 ± 5.07
BIL mg/dL	0-0.50	0.13 ± 0.01	0.13 ± 0.02	0.24 ± 0.10	0.13 ± 0.02	0.13 ± 0.02	0.13 ± 0.01	0.13 ± 0.01	0.14 ± 0.02
CHOL mg/dL	70.00-150.00	90.10 ± 7.13	88.70 ± 3.75	85.80 ± 3.60	85.40 ± 3.78	82.80 ± 3.04	81.10 ± 2.54	79.90 ± 3.06	71.00 ± 4.51
Group T									
BUN mg/dL	20.00–50.00	148.89 ± 26.53	142.84 ± 22.51	139.79 ± 21.56	136.01 ± 19.54	136.77 ± 21.60	143.17 ± 21.33	142.38 ± 20.62	186.78 ± 19.48
CREA mg/dL	0.50-2.00	4.08 ± 0.30	3.84 ± 0.32	3.60 ± 0.30	3.67 ± 0.30	3.59 ± 0.27	3.56 ± 0.28	3.54 ± 0.28	4.18 ± 0.22
P mg/dL	2.70-5.00	7.72 ± 0.71^{a}	4.90 ± 0.50^{ab}	3.74 ± 0.26^{ab}	3.54 ± 0.19^{ab}	3.29 ± 0.13^{b}	3.25 ± 0.13^{b}	3.20 ± 0.12^{b}	3.76 ± 0.37^{b}
TP mg/dL	6.00–8.00	6.26 ± 0.20	6.77 ± 0.28	6.83 ± 0.26	6.80 ± 0.24	6.57 ± 0.18	6.48 ± 0.20	6.42 ± 0.16	6.18 ± 0.18
ALB mg/dL	2.20–3.50	2.83 ± 0.22	3.08 ± 0.17	3.18 ± 0.17	3.16 ± 0.11	3.00 ± 0.10	2.98 ± 0.13	2.97 ± 0.10	2.78 ± 0.11
A/G mg/dL	0.80–1.30	0.70 ± 0.09	0.72 ± 0.07	0.82 ± 0.07	0.90 ± 0.04	0.92 ± 0.03	0.88 ± 0.03	0.91 ± 0.03	0.94 ± 0.02
GLU mg/Dl	60.00-120.00	101.11 ± 7.89	103.08 ± 5.54	103.22 ± 5.97	98.63 ± 2.73	100.11 ± 5.45	96.22 ± 4.34	89.67 ± 4.33	92.22 ± 2.99
ALT UI/L	7.00–40.00	32.22 ± 2.92	39.44 ± 6.19	40.33 ± 6.45	37.63 ± 4.59	36.11 ± 2.82	34.78 ± 3.09	35.00 ± 2.08	39.67 ± 2.67
AST UI/L	7.00–40.00	31.44 ± 5.07	27.56 ± 4.18	27.78 ± 3.74	26.13 ± 2.59	29.56 ± 2.66	34.00 ± 3.14	36.33 ± 2.03	39.44 ± 3.87
ALP UI/L	4.00–50.00	60.22 ± 4.04	63.78 ± 6.85	63.22 ± 7.33	70.13 ± 5.64	79.33 ± 4.51	81.44 ± 7.07	81.56 ± 6.04	82.11 ± 7.27
BIL mg/dL	0-0.50	0.19 ± 0.02	0.20 ± 0.03	0.17 ± 0.02	0.15 ± 0.01	0.15 ± 0.02	0.14 ± 0.01	0.13 ± 0.01	0.12 ± 0.01
CHOL mg/dL	70.00-150.00	114.67 ± 12.09	116.44 ± 10.14	121.56 ± 13.09	120.75 ± 14.61	108.67 ± 11.83	102.44 ± 13.46	105.67 ± 12.28	76.38 ± 11.18

Data are expressed as mean and standard error of the mean (SEM); T: time in days. Means with superscript letters (a, b) indicate significant differences ($P < 0.05$) among experimental times within each group

Urinalysis did not show any significant change and UPC, UP and SG remained stable until the end of the study in both groups (Table 6). UPC showed a greater decrease at days 30, 60, 90, 120, 150, and 180 in T group compared with C (Fig. 2) and this trend was still maintained at day 360.

Discussion

The principal aim of the present study was to determine the effect of long-term dietary supplementation in cats with naturally-occurring stable CKD conditions that were already evident before starting our treatment. In general, the management of CKD is largely focused on supportive and symptomatic therapy for improving the quality of life of affected cats (especially those in CKD stages 3 and 4) and, when possible, slowing the progression of the disease (especially in CKD stages 2 and 3) (Sparkes et al. 2016). Palatability is known to be an important factor that influences the final result of a treatment administered to cats with food. In fact, cats' appetite is variable especially when they are sick. In turn, an adequate level of palatability has to be reached when designing a new supplement for CKD cats (Bernachon et al. 2014).

This study showed that although 90% of the cats were anorexic at the first examination (in both T e C groups), the animals belonging to the T group had increased their appetite and practitioners reported a good palatability of supplements, as also reported in Vergnano et al. (2016). Moreover, cats' owners belonging to the T group reported a reduction of vomiting and diarrhea episodes after T60. Animals with poor body condition are destined to decrease their survival (Quimby et la. 2015). In turn, a good nutritional management in combination with medical therapies is very relevant to assure a long-term prognosis for sick animals.

Table 5 Hemogas parameters measured during the study

	Laboratory standard reference range	T0	T30	T60	T90	T120	T150	T180	T360
Parameter group C									
HCO3 mmol/L	16.00–24.00	16.23 ± 0.27	16.15 ± 0.23	15.98 ± 0.21	15.84 ± 0.16	15.63 ± 0.15	15.53 ± 0.11	15.55 ± 0.11	15.21 ± 0.09
iCa mmol/L	1.16–1.30	1.22 ± 0.01	1.22 ± 0.01	1.21 ± 0.01	1.20 ± 0.01	1.19 ± 0.01	1.19 ± 0.01	1.18 ± 0.01	1.16 ± 0.00
Group T									
HCO3 mmol/L	16.00–24.00	16.08 ± 0.28^{b}	16.64 ± 0.31^{ab}	16.86 ± 0.25^{ab}	16.96 ± 0.21^{ab}	17.06 ± 0.20^{ab}	17.08 ± 0.18^{ab}	17.12 ± 0.20^{a}	17.08 ± 0.16^{ab}
iCa mmol/L	1.16–1.30	1.20 ± 0.02^{c}	1.23 ± 0.02^{bc}	1.28 ± 0.02^{abc}	1.30 ± 0.01^{ab}	1.32 ± 0.01^{a}	1.32 ± 0.01^{a}	1.32 ± 0.02^{a}	1.33 ± 0.02^{a}

Data are expressed as mean and standard error of the mean (SEM); T: time in days. Means with superscript letters (a, b, c) indicate significant differences ($P < 0.05$) among experimental times within each group

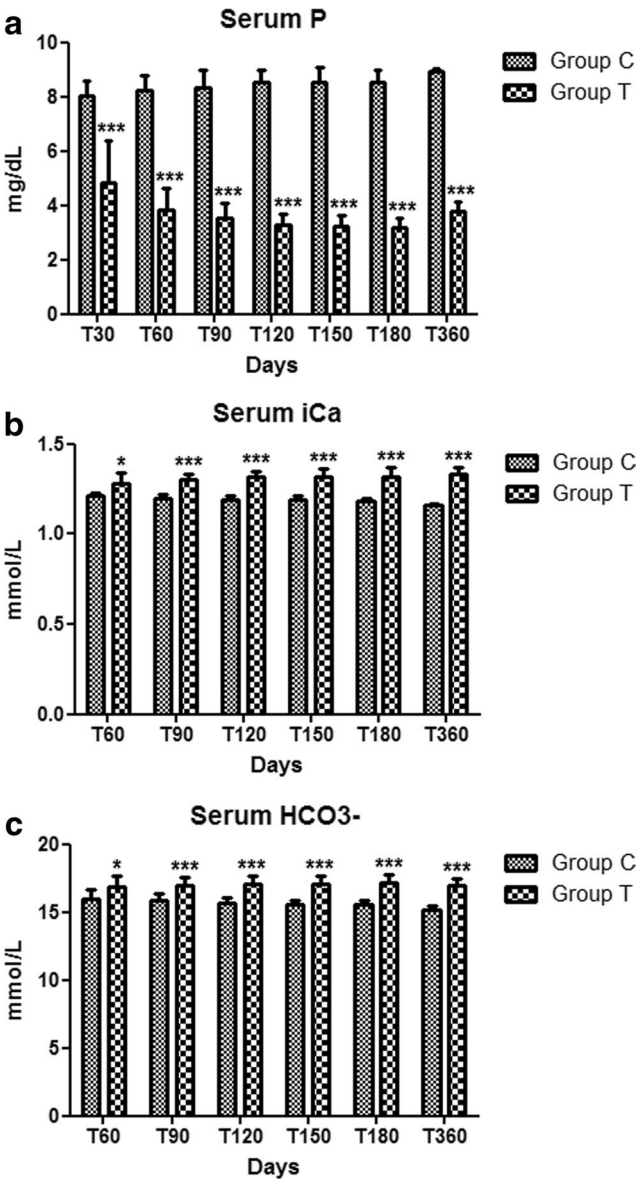

Fig. 1 **a** Serum phosphorus (P) concentration at days 30, 60, 90, 120, 150 and 180 ($P < 0.001$); (**b**) Serum ionized calcium (iCa) concentration at days 60, 90, 120, 150, 180 and 360 ($P < 0.001$); (**c**) Bicarbonate (HCO3) concentration at days 60, 90, 120, 150, 18 ($P < 0.05$)

We would like to underline the improvement of both cats' appetite and palatability of the tested complementary food for the entire duration of our study. This is in agreement with the data published by Vergnano et al. (2016), even if their study lasted for a shorter period of time (60 days). This is an important aspect of our work, because despite the possible benefits of feed supplement containing phosphate binders and alkalinizing agents, the market research studies in Europe show that the first are prescribed in the 41% of CKD patients only (both dogs and cats) (Bernachon et al. 2014). In addition to that, a study performed in the United States on 1089 cats, had shown that the majority of the ones with CKD (78,8%) were not receiving a phosphorus binding agent in their food (Markovich et al. 2015). Practitioners report that the main reasons for adopting the choice of not giving to cats supplements and galenic forms are, respectively, the lack of palatability and the scarce adaptation from cats, resulting in poor compliance. Our results respond in a satisfying way to the problem on the palatability of supplements added to food as also reported by Bernachon et al. (2014). For the sake of completeness, we must add that there is a strong association between CKD and hypertension, cats diagnosed with CKD may often develop this pathology (Bijsmans et al. 2015).

Serum phosphate should be monitored in cats with CKD, and a phosphate-restricted diet should be used in all cats with azotaemic CKD (stages 2–4). Whenever a commercial or home-prepared renal diet cannot be used or turns to be not sufficient to control serum phosphate level, phosphate binders should be added to food. The response should be monitored (eg, 1 month after medication change), and the dose adjusted accordingly (Sparkes et al. 2016). In the present study this strategy has proved to be effective, considering that the Serum phosphorus decreased significantly from T0 to T360 in T group and was lower ($P < 0.01$) in T group than in C.

The monitoring of serum ionized calcium is recommended in cats with renal problems, as hypercalcaemia is an occasional adverse event (International Renal Interest

Table 6 Urinary parameters measured during the study

	Laboratory standard reference range	T0	T30	T60	T90	T120	T150	T180	T360
Parameter group C									
UPC	< 0.50	0.73 ± 0.04	0.74 ± 0.05	0.78 ± 0.04	0.84 ± 0.06	0.82 ± 0.05	0.80 ± 0.04	0.87 ± 0.04	1.09 ± 0.09
UP mg/dL	0-100.00	145.63 ± 32.44	166.88 ± 32.66	186.11 ± 29.75	205.00 ± 31.04	198.89 ± 30.25	177.50 ± 25.17	203.00 ± 28.82	234.50 ± 31.57
SG	1020–1040	1013.13 ± 1.68	1013.75 ± 1.64	1013.33 ± 1.12	1013.13 ± 1.18	1013.33 ± 1.12	1012.50 ± 1.32	1011.50 ± 1.07	1009.00 ± 0.67
Group T									
UPC	< 0.50	0.53 ± 0.06	0.55 ± 0.07	0.56 ± 0.07	0.54 ± 0.06	0.62 ± 0.05	0.62 ± 0.06	0.63 ± 0.06	0.87 ± 0.08
UP mg/dL	0-100.00	322.33 ± 32.37	259.84 ± 37.75	224.73 ± 34.21	202.15 ± 30.35	241.82 ± 34.33	244.93 ± 33.14	235.38 ± 29.55	263.89 ± 17.48
SG	1020–1040	1015.78 ± 1.83	1018.78 ± 2.43	1021.67 ± 2.50	1025.00 ± 2.52	1021.67 ± 2.04	1018.89 ± 1.11	1018.89 ± 0.73	1013.33 ± 1.44

Data are expressed as mean and standard error of the mean (SEM); T: time in days

Society 2013). This happens, in particular, if animals receive phosphate binders containing calcium carbonate. The phosphate binders used in this trial were chitosan, calcium lactate gluconate and calcium carbonate. We found that the serum ionized calcium level was higher in T group compared with C during all the experimental time but the increase of ionized calcium fell within the physiological ranges (1.1–1.4 mmol/l) (Pettifer 2002).

Metabolic acidosis is a common complication in CKD patients. In healthy animals, kidneys serve as the major homeostatic control point for maintaining acid–base balance. In response to acidosis, healthy kidneys increase net reabsorption of bicarbonate and increase secretion of hydrogen ions. In CKD, these homeostatic mechanisms fail, resulting in pronounced acidosis in 53–80% of cats with CKD (Scherk and Laflamme 2016).

In our study, 90% of the patients (group T) at the time of inclusion in the trial had a blood bicarbonate concentration under the normal range (16–24 mmol/l). Interestingly, at the end of the study, the blood bicarbonate concentration in all patients came back to normal, thus reaching the IRIS treatment target.

In conclusion, this research has improved the data from a previous trial reported by Vergnano et al. (2016) in this way: we included a control group and we continued to give to cats the supplementation for a longer period (360 vs 60 days). Our results confirmed that feed supplementation based on phosphate binders reduces the serum phosphorus and increases the serum bicarbonate in cats with CKD, thus improving the clinical conditions of the animals without any adverse reaction. Finally, it is important to underline that all the animals completed the study and owners reported a good palatability of the feed supplement.

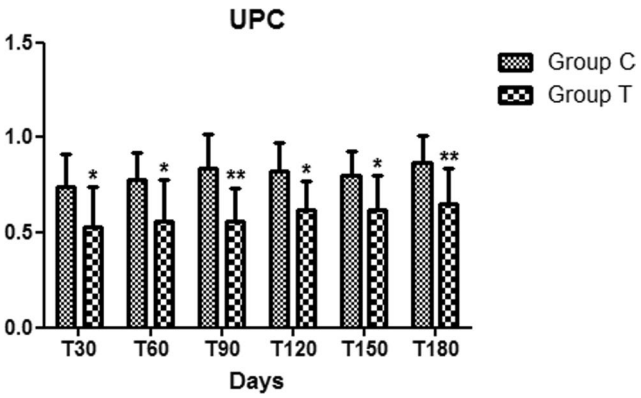

Fig. 2 Urine protein/creatinine (UPC) showed a greater decrease at days 30, 60, 90, 120, 150, and 180

Compliance with Ethical Standards

Ethical approval All procedures, treatments and animal care were in compliance with the guidelines of the Italian Minister of Health for the care and use of animals (D.L. 4 March 2014 n. 26 and D.L. 27 January 1992 n.116) and UE (Directive 86/609/CEE).

Conflict of interest Two of the authors are employees of Candioli Farmaceutici S.p.A.

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