Renal P

Effectiveness of a dietary supplement in cats affected by chronic renal disease in advanced stage *,**

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BACKGROUND

Chronic kidney disease (CKD) is a very frequent pathology in older cats[13], which may affect up to 50% of cats over 15 years of age[11]. CKD refers to a kidney disease which has been ongoing **for at least 3 months**[25]. Cats and dogs affected by CKD are staged on the basis of the indications developed by the International Renal Interest Society (IRIS)[18] into evolutionary stages indicated by progressive numbers based on severity of the disease.
There is a general consensus with regards to nutritional management of clinically manifest CKD, which includes measures to reduce signs of uraemia and to slow the progression to more advanced stages of the disease[12]. Based on the clinical trial findings, a renal diet is the therapeutic measure that seems most effective in increasing survival rates and quality of life for patients in IRIS stage 3 and 4; consequently, the renal diet should be considered as a treatment standard[2,6,15].
When the diet on its own is not sufficient, nephropathic cats need a dietary supplement containing **phosphate binders** and **alkalising agents**[26].

The aim of this study was to assess palatability, ease of administration and effectiveness of a complementary feed containing calcium carbonate, calcium lactate gluconate, sodium bicarbonate and chitosan in cats with CKD in IRIS stage 3 and 4.

MATERIALS AND METHODS

The study was conducted according to "*good clinical practice*" at the Napolivet Clinic on owned cats, after obtaining written consent from the owners.
From the database of the clinic, 20 cats affected by CKD in IRIS stage 3 (80% of cases) and 4 (20% of cases) were selected, diagnosed via at least two measurements of plasma creatinine with values respectively higher than 2.9 mg/dl (IRIS 3) and 5.0 mg/dl (IRIS 4), and stable for at

least one month (*tab. 2*), according to the indications provided by IRIS[18]. All the cats studied were in dietary therapy with renal diet (Renal Feline Royal Canin) for at least 8 weeks, administered in an appropriate quantity to meet the nutritional requirements indicated by the FEDIAF Nutritional Guidelines 2013, and showed hyperphosphatemia, with plasma phosphorus concentrations >5 mg/dl (1.6 mmol/L) for cats in IRIS stage 3 and >6 mg/dl (1.9 mmol/L) for cats in IRIS stage 4.
Other cats suffering from concomitant diseases such as acute renal disease, prerenal or postrenal azotaemia, genitourinary tract inflammation or infection, urinary obstruction, chronic heart failure, cancer, hyperthyroidism and diabetes were excluded.
10 cats (group T) were administered the complementary feed (Renal P Candioli. tab.1) in addition in addition to the renal diet, starting from the inclusion visit (T0) at the dose indicated by the producer equal to 0.2 g/kg/day, mixed with the therapeutic diet and divided and administered twice daily, continuously for a period of six months.

Renal P - Composition			
Calcium Carbonate	Calcium lactate gluconate	Chitosan	Sodium Bicarbonate

Tab. 1. Composition of the complementary feed evaluated in the study

Another 10 cats (group C) suffering from CKD in stage 3 and 4 (same percentage as group T), the owners of which did not agree to other therapies and which therefore continued with the dietary therapy only for a minimum period of 6 months, were selected from the database of the clinic as control group.
With the exception of the renal diet, administered for at least 8 weeks before the initial examination which determined inclusion in the study (inclusion visit), no other treatments were administered, pharmacological or supporting, aimed at either directly or indirectly influencing on kidney function.

List of cats included in the study

Case	Name	Breed	Gender	Age	IRIS	Creatinine (mg/dL)	Phosphatemia	Weight	BCS (1-5)	
1	Bice	European	Female	8	3	4,4	10,8	3,2	2	Goup T
2	Tommy	European	Male	9	3	3,1	6,4	8,7	5	
3	Macchia	European	Female	12	3	3,6	8,3	6,3	4	
4	Bella	European	Female	8	4	6,1	8,7	3,8	3	
5	Pat	European	Male	11	3	3,8	7,7	4,2	3	
6	Topo	European	Male	12	4	5,1	8,7	3,1	3	
7	Lucia	Persian	Female	14	3	3,4	7,4	4,2	3	
8	Miki	European	Male	7	3	4,6	9,6	6,2	4	
9	Skinny	Persian	Male	14	3	3,47	8,0	2,4	2	
10	Silvestro	European	Male	11	3	4,2	7,4	2,7	2	
11	Isotta	European	Female	12	3	2,9	8,1	3,8	3	Group C
12	Lolita	European	Female	12	3	2,8	8,0	4,2	4	
13	Lolly	European	Male	9	3	3,3	8,3	3,9	3	
14	Mino	European	Male	13	2	2,4	6,0	4,2	3	
15	Mussillo	European	Male	15	3	3,7	8,8	3,2	2	
16	Pablito	European	Male	11	3	2,9	7,7	3,8	3	
17	Piccolo	European	Male	10	3	3,4	7,9	4,5	4	
18	Sofia	European	Female	7	3	3,8	7,6	4,4	4	
19	Sonny	European	Male	15	3	3,2	8,2	5,3	4	
20	Titina	European	Female	11	3	4,2	7,7	3,2	2	

Tab. 2. List of cats included in the study: in green the cats of the treated group (T), in white the cats of the control group (C). The clinical and laboratory data refer to the inclusion visit

On days 0 (inclusion visit), 30, 60, 90, 120, 150 and 180 the following check-ups were conducted on each animal (*tab. 3*):

- Complete clinical examination with assessment of bodyweight and BCS (body condition score – scale from 1 to 5). The systemic blood pressure was taken at each examination (average of 5 determinations), using an indirect Doppler method on the radial pulse with the subject in sternal recumbency or sitting. During each examination, the owner was given a questionnaire to determine: cat's appetite, product palatability, presence of vomiting or diarrhoea, general health conditions and degree of vitality.
- Urinalysis, taken from spontaneous urination, with UPC ratio;
- Blood cell count and biochemical examination taken from the jugular vein after fasting, with venous blood gas analysis.

Laboratory parameters

Parameters	CAT physiological range		
	min	max	u.m
BP (pressure)	<95	<150	mm Hg
HT (haematocrit)	26	45	%
HG (haemoglobin)	8	15	g/dl
RBC (Red blood cells)	5	10	10^6 mm^3
WBC (White blood cells)	5,5	19	10^3 mm^3
UPCR (urinary proteinuria / urinary creatinine)		0,4	
UP (urinary protein)	0	100	mg/dl
sg (specific weight)	1020	1040	
Bun (blood ureic nitrogen)	20	50	mg/dl
crea (creatinine)	0,5	1,8	mg/dl
P (phosphorus)	2,7	5	mg/dl
p. tot (total protein)	6	8	mg/dl
alb (albumins)	2,2	3,5	mg/dl
A/G (albumins / globulins)	0,8	1,3	mg/dl
Glu (glucose)	60	120	mg/dl
ALT (alanine transaminase)	7	40	UI/lt a 25 °C
AST (alanine aminotransferase)	7	40	UI/lt a 25 °C
ALP (alkaline phosphatase)	4	50	UI/lt a 25 °C
BIL (bilirubin)	0	0,5	mg/dl
CHOL (cholesterol)	70	150	mg/dl
HCO_3 (bicarbonate)	16	24	mmol/l
Ionised calcium	1,16	1,4	mmol/l

Tab. 3. Laboratory parameters assessed during clinical examinations with physiological values of reference

The collected data underwent statistical analysis using the Graphpad Prism® software (version 5.03, GraphPad Software, Inc, San Diego CA USA), and analysed with the tests ANOVA, Kruskall-Wallis, Student and Mann-Whitney U, considering as statistically significant p values <0.05.

RESULTS

All the owners of cats belonging to group T reported good palatability of the product, which was eaten by all the animals during the study.
All 10 cats selected in group T completed the study. 9 out of 10 (90%) of them showed decreased appetite; 66% showed an improvement starting from day 30 ($p<0.05$). 8 out of 10 (80%) cats of group T showed vomiting/diarrhoea, which disappeared starting from day 30 ($p<0.05$).
Cats in group C with poor appetite, vomiting and diarrhoea did not show clinical improvements during the study.
BCS and body weight kept constant during the study for group T, while they progressively dropped in group C.
The cats of the two groups T and C remained in the same IRIS stage of chronic renal disease for the entire duration of the study.

With regards to the main parameters concerning kidney function covered by the study, i.e. **phosphatemia**, **ionised calcium** and **bicarbonates** in the serum, the graphs below show the trends over time of the two groups C and T, as well as the statistical significance assessment.

serum P (mg/dl) v. n. 2,7-5

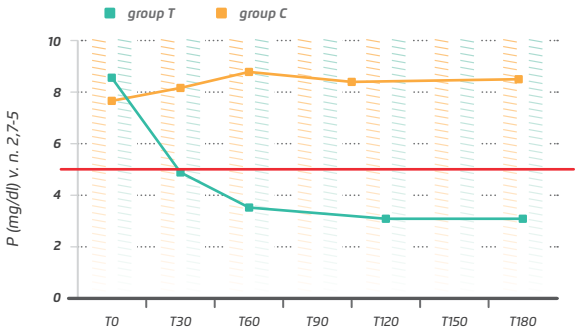

Fig. 1 Graph showing the trends of the average phosphatemia values of Group C and Group T starting from T0.
The red line indicates the upper physiological phosphatemia level

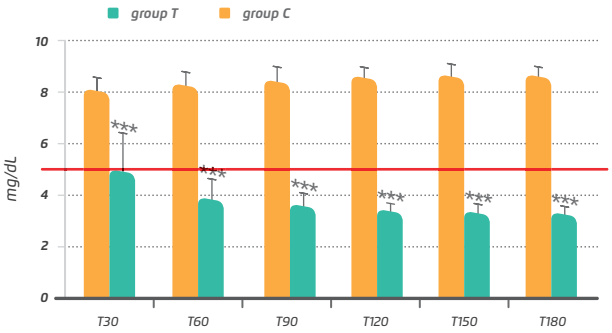

Fig. 2 Statistically significant difference ($p<0.001$) of average phosphatemia values between the two groups C and T

Average phosphatemia values of group T significantly decreased ($p<0.001$) compared to those of the control group on days 30, 60, 90, 120, 150 and 180 (fig. 2). Phosphatemia reduction in group T was 41% on day 180. It should be noted (fig. 1) that the average phosphatemia values of group T fall back within the physiological range already from day 30 (< 5 mg/dl) and progressively decrease during the study, while in group C they remain constantly high and increase progressively during the study.

With regards to the trends of ionised serum calcium (iCa), the average values of group T were significantly higher ($p<0.05$) starting from day 60 compared to the control group, with greater significance ($p<0.001$) on day 90, 120, 150 and 180 (*fig. 4*).
The average of group T values was consistently within the physiological values of reference (<1.4 mmol/L) throughout the duration of the study (*fig. 3*). In group T the increase in ionised calcium on day 180 was 10%.

Ionised serum Ca (mmol/lt) v. n. 1,16-1,4

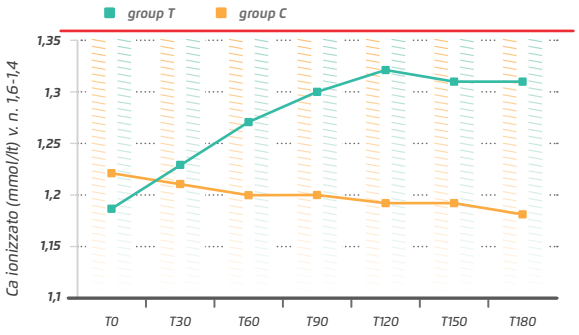

Fig. 3 Graph showing the trends of the average ionised serum calcium values of Group C and Group T starting from T0.
The red line indicates the upper physiological ionised serum calcium level

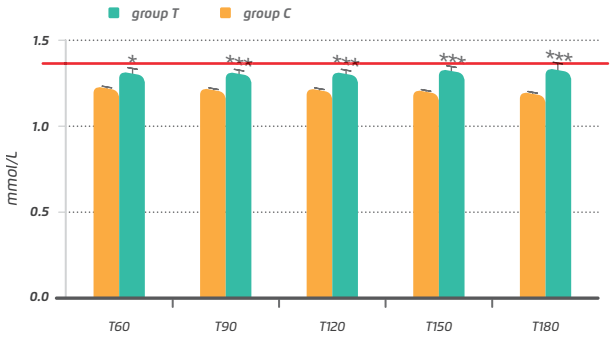

Fig. 4 Statistically significant difference at T60 (p<0.05) and starting from T90 (p< 0.001) of the average serum ionised calcium levels between the two groups

With regards to the trends of the average blood bicarbonate levels, on day 30 those of group T fell back within the normalcy range, while those in group C dropped below the physiological minimum values (16 mmol/L) (*fig 5*).
The statistical assessment between the two groups (*fig. 6*) shows significant differences starting from day 60 (p<0.01) and even greater (p<0.001) on days 90, 120, 150 and 180. The increase in serum bicarbonate rates in group T was 7% on day 180.

serum bicarbonate (mmol/lt) v. n. 16-24

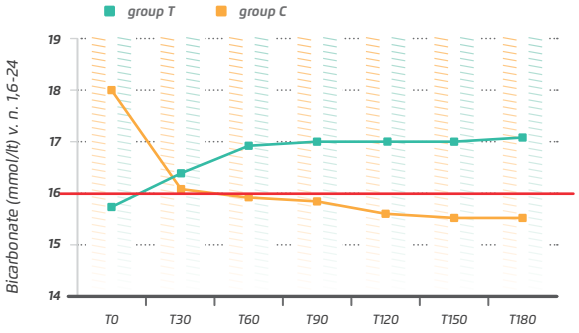

Fig. 5 Graph showing the trends of average serum bicarbonate values of the two groups T and C starting from T0.
The red line indicates the upper physiological serum bicarbonate level

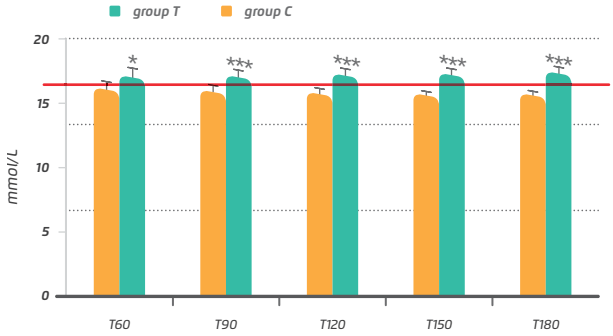

Fig. 6 Statistically significant difference at T60 (p<0.05) and starting from T90 (p< 0.001) of the average serum bicarbonate levels between the two groups

Among the various laboratory parameters taken into consideration during the study to monitor the evolution of CKD, although not included in the objectives of the study, are also plasma creatinine and UPC ratio.

While no differences were highlighted between the two groups with regards to trends in the average values of plasma creatinine, **statistically significant differences (p<0.05) were found between the two groups on day 180 (fig. 7) for the UPC ratio.**

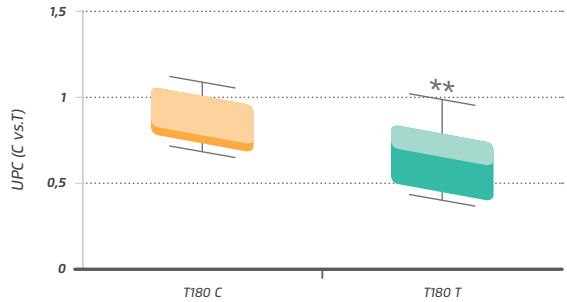

Fig. 7 Statistically significant difference (p<0.05) for average UPC ratio values between the two groups at the end of the study

DISCUSSION

In most CKD cases it is not possible to treat the specific cause, often multiple, hence the objective of the treatment is to manage secondary metabolic complications in the best possible way, with the aim of improving quality of life and to slow down progression of the disease[8]. Various markers have been associated to lower survival rates in cats suffering from CKD, including proteinuria, anaemia and hyperphosphatemia[4]. Furthermore, both in humans and cats, a significant correlation has been reported between the increase in plasma phosphorus concentrations and the reduction in survival time[20].

Phosphorus is freely filtered at glomerular level, so its plasma concentration may be objectively considered a marker of glomerular filtration rate (GFR)[4]. The mechanisms involved in phosphorus homoeostasis are complex and still not completely understood[7]. It is known that it depends on the balance between the proportion of phosphorus take in with food, the phosphorus exchange between the intracellular and extracellular compartment, deposit in the bone tissue and renal excretion[14]. Furthermore, it is also strongly related to calcium homoeostasis, since the plasma levels of both these minerals are modulated by calciotropic hormones, parathyroid hormone (PTH) and calcitriol: an increase in plasma phosphorus concentrations causes reciprocal decrease in ionised calcium due to the law of mass action[14].

In humans it has been shown that hyperphosphatemia is associated to vascular calcification and nephrocalcinosis, resulting in a more rapid progression of kidney disease[19]. The situation in cats seems different. In fact, in the only scientific publication connecting kidney damage with clinicopathological parameters in cats suffering from spontaneous CKD, phosphatemia has been associated with interstitial fibrosis, but not tubular mineralisation[4].

This suggests that hyperphosphatemia in cats may not induce parenchymal mineralisation, but may contribute to renal fibrosis through another mechanism, thus promoting progression of CKD[22]. This highlights the need for keeping hyperphosphatemia in check as well as secondary hyperparathyroidism, more aggressive in cats suffering from CKD.

Dietary restriction of absorbable phosphorus is nowadays regarded as one of the main factors that may be used in slowing the progression of the disease and in increasing the survival rate[2]. IRIS guidelines recommend in fact to keep phosphatemia within specific ranges of reference, which change according to the CKD stage, via reduction of the dietary phosphorus intake, often in combination with the use of chelating agents of dietory phosphorus. In this study this strategy has been found to be effective and the phosphorus levels in cats in group T significantly decreased from T0 to T180 (41%), achieving the plasma phosphorus concentration objectives indicated by IRIS in stage 3 (2.7-5.0 mg/dl) after 30 days of administration (average value at T30: 4.83 mg/dl). Cats belonging to the control group showed plasma phosphorus levels above the limits indicated by the IRIS guidelines throughout the study.

The phosphate binders are also able to bind to phosphorus in the intestine, forming insoluble compounds that are eliminated with the faeces, thus reducing plasma phosphorus levels[27].

The phosphate binders in the product tested during this study were chitosan, calcium lactate gluconate and calcium carbonate.

Chitosan is a deacetylated glucosamine formed by chitin and acetylglucosamine[23]. Previous studies on humans and cats suffering from CKD have demonstrated the effectiveness of chitosan, on its own or in combination with calcium carbonate, in controlling hyperphosphatemia and in reducing azotaemia[2,29,30].

Calcium lactate gluconate is a calcium salt used as intestinal phosphate binder in human medicine, in association with calcium carbonate[9].

Calcium Carbonate is widely used, both in human and veterinary medicine, thanks to its availability, ease of use and low cost, compared to other binders[16].
In human medicine, it has been speculated that in addition to chelating food phosphorus, calcium carbonate may prevent and even reverse a negative balance of skeletal calcium, thereby reducing the risk of bone fractures, which is typically found in CKD[16].
The use of calcium-based phosphorus chelating agents has the side effect of increasing the risk of hypercalcaemia in human medicine[27], although few data are available in veterinary medicine[7], especially in cats.
In this study, serum ionised calcium levels were significantly higher both during the study and at its end (T180), nevertheless without ever exceeding the physiological levels of reference (1.1-1.4 mmol/L)[24]. In any case, the possible risk of hypercalcaemia is the reason why it is important to monitor plasma calcium concentrations (preferably the ionised fraction), in the course of check-ups of a patient undergoing a phosphate restriction regime using calcium-based phosphorus chelating agents[7,26].
Another important recommendation for CKD treatment is to promote alkalinization when there is metabolic acidosis[17]. It has been reported that metabolic acidosis is found in 15% of cats in IRIS stage 3 and in over 50% of cats in IRIS stage 4[21]. The conditions of the patient's plasma acidity or basicity should therefore be monitored, if possible by blood gas analysis, and metabolic acidosis should be treated on the basis of laboratory test findings[25].
IRIS provides guidelines for the treatment of metabolic acidosis in cats suffering from CKD in IRIS stage 2-4. If this condition is confirmed (blood bicarbonate or total CO2 <16 mmol/L) sodium bicarbonate should be administered orally to keep blood bicarbonate or total CO2 between 16 and 24 mmol/L.
The complementary feed tested in this study also contains **sodium bicarbonate**. In our study, at the inclusion examination 90% of the patients in group T showed lower plasma bicarbonate concentrations than the range of reference (16-24 mmol/L), thus indicating a condition of metabolic acidosis. **At the end of the study, the same concentration of all group T patients was within the range of reference, thus achieving the therapeutic objective indicated by IRIS**. In the control group, at the inclusion visit 7 cats out of 10 showed blood bicarbonate values within standard, and at the end of the study all 10 cats showed a lower blood bicarbonate level than 16 mmol/L, thus indicating a condition of metabolic acidosis.
In human patients suffering from CKD, chronic metabolic acidosis has been associated with bone metabolic disorders, insulin resistance, reduction in the energy share of protein origin, and acceleration in renal disease progression. Also in medicine, bicarbonate dietary supplementation has been put forth as a nephroprotective strategy[1]. The evidence from clinical trials suggests that the alkalising therapy may delay progression of CKD[5].
According to the authors, no previous study has been effected on cats in order to assess the nephroprotective properties of sodium bicarbonate. Further studies are deemed necessary to strengthen the preliminary results achieved. Appetite disturbances are frequently found in cats in general, and more specifically in cats suffering from CKD[2]. It has also been reported that in uraemic cats the addition of a phosphorus chelating agent may reduce the intake of food[3]. **The latter effect has not been noticed in this study, where 66% of cats in group T has shown an increase in appetite, probably due to an improvement in clinical conditions**. No changes in appetite have been observed in cats in the control group.

CONCLUSIONS

The preliminary results arising from this study, although requiring further confirmations, extending the observation time of patients and increasing the number of patients included in the two groups T and C, make it possible to highlight the importance of specific dietary supplementation when the mere diet formulated for cats suffering from CKD is not sufficient to improve patients' metabolic conditions. **The product tested was found to be effective in reducing blood phosphorus levels and increasing blood bicarbonate levels, thus improving the clinical condition of treated cats throughout the duration of the study, without showing any adverse side effect**.

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Renal P

CALCIUM CARBONATE AND CALCIUM LACTATE-GLUCONATE

CHITOSAN

SODIUM BICARBONATE

PROPER USE

Add **Renal P** to the usual feed ration in a proportion of 0.2 g powder per kg of body weight per day, corresponding to the following daily dosages:

Powder per day

1 small levelled measuring spoon every 2.5 kg of b.w.

1 large levelled measuring spoon every 10 kg of b.w.

Complementary feed for dogs and cats.

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