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Effect of a high phosphorus diet on indicators of renal health in cats

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Abstract

Objectives High phosphorus intake may further impair renal health in cats with chronic kidney disease (CKD). The hypothesis that a high phosphorus (HP) diet might be nephrotoxic for healthy animals was tested in cats, a species with a high incidence of naturally occurring CKD.

Methods Thirteen healthy adult cats were fed a phosphorus excess diet (about five times maintenance requirements), and this HP group was compared with cats on a balanced control diet (CON). The trial lasted for 29 days (10 days of faeces and urine collection). Endogenous creatinine clearance was determined towards the end of the trial. Fresh urine was tested for glucose and proteins.

Results Glucosuria and microalbuminuria were observed exclusively in the HP group in 9/13 cats. Creatinine clearance was significantly decreased after feeding HP. In the HP group phosphorus was highly available (apparent digestibility around 60%). Renal phosphorus excretion was significantly increased in the HP group (115 mg/kg body weight/d vs 16 mg/kg body weight/d in the CON group).

Conclusions and relevance The intake of a diet with an excessive content of highly available phosphorus may have adverse effects on parameters of kidney function in healthy cats.

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Introduction

Chronic kidney disease (CKD) is a major cause of death in cats.[1] A large number of elderly cats develop clinical signs of CKD, with a reported prevalence in the general feline population of 1–3%, and as high as 35% in geriatric feline populations presenting to referral centres.[2] The aetiology mostly remains unclear.

The majority of cats in Germany are fed complete prepared cat foods.[3] Complete prepared cat foods, especially moist foods, provide, on average, 4–5 times the phosphorus maintenance requirements according to the National Research Council (NRC) and the European Pet Food Industry Federation.[4,5] The maximum concentration of phosphorus observed in complete cat foods covers nine times the maintenance requirement.[6,7]

MacKay and Oliver demonstrated long ago that excess dietary phosphorus can cause phosphate nephritis in rats.[8] Since then, the detrimental effect of an excessive intake of highly available phosphorus on renal function has been demonstrated in different species, such as dogs,[9] rats[8,10–12] and humans.[13–15] Pastoor et al investigated the effect of phosphorus excess in young healthy cats.[16] They fed diets with a phosphorus content of 870 mg/MJ metabolisable energy (ME). This amount corresponds to about five times the maintenance requirements of the NRC.[4] After 28 days of feeding such a diet, endogenous creatinine clearance was significantly reduced. It is unequivocally agreed upon that a diet high in phosphorus accelerated the progression of kidney diseases in cats like in other species,[17,18] whereas the restriction of dietary phosphorus prolonged mean survival times in patients with naturally occurring CKD.[19] It is only a small step from there to hypothesise that high-phosphorus diets might be involved in the aetiology of CKD in cats. In the present study the effect of the excessive intake of phosphorus from a highly available source on indicators of renal health was investigated.

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Table 1 Composition of diets

Diet		CON	HP
DM	g/kg	338	356
Gross energy	MJ/kg DM	23.1	22.1
Crude protein	g/kg DM	418	393
Crude fat	g/kg DM	192	180
Crude fibre	g/kg DM	27	27
Calcium	g/kg DM	7.3	6.5
Phosphorus	g/kg DM	5.6	16.0
Calcium/ phosphorus ratio	g/g	1.3	0.4
Potassium	g/kg DM	7.5	10.8
Magnesium	g/kg DM	0.9	0.9
Sodium	g/kg DM	2.3	9.6
Chloride	g/kg DM	9.0	5.4
CAB	mmol/100g DM	−12.5	−31.4

CON = control; HP = high phosphorus; DM = dry matter; CAB = cation–anion balance

Materials and methods

A total of 13 European Shorthair cats from our cat colony (approved experimental cat breeding and housing faculty [Betriebsnummer at Kreisverwaltungsreferat Munich, the proper authority: KVR-I/221-TA-0131/13]) were included in the study. Body weight (BW) ranged from 2.5–6.1 kg and age was between 1 and 8 years. There were two intact and five neutered males, and six neutered females. Cats were visually checked on a daily basis; a more detailed examination was carried out once a week (weight control, body condition score, mouth, ears, palpation, body temperature, auscultation). There was permanent veterinary supervision at the cat facility by a veterinarian specially trained for experimental animal supervision. In addition, during the trial the cats were checked closely every day by a veterinarian. After a clinical examination at the end of the trials all cats remained in the cat colony. None of them had a clinical kidney problem. They were rehomed following the normal schedule of the cat colony. All animals were clinically healthy with serum parameters such as urea, creatinine and phosphorus, indicative of kidney diseases, within the reference intervals before the start of each experiment, during the trial, as well as some time after the end of the trial. All procedures and protocols were conducted in accordance with the guidelines of the Protection of Animals Act and the study was approved by the representative of the Veterinary Faculty for animal welfare, as well as the Government of Upper Bavaria (reference number 55.2.-1-54-2532.3-48-11).

The study investigated the effects of a phosphorus excess diet (HP) in comparison with a balanced control diet otherwise identical to the HP diet (CON). The HP and CON diet are shown in Table 1. All cats were fed the control diets for 29 days (pre-trial) to gauge base values of parameters (overall mean ± SD serum creatinine 134.9 ± 15.0 µmol/l; endogenous creatinine clearance 2.8 ± 0.9 ml/kg BW/min; serum calcium 2.5 ± 0.3 µmol/l; serum phosphorus 1.8 ± 0.3 µmol/l; blood urea nitrogen 3.7 ± 0.4 mmol/l) and to make sure that all cats taking part in the study had no abnormalities of either kidney function or phosphorus metabolism before they were either switched to the HP diet or remained on the control diet. After the switch the animals were on the control or the HP diet for 18 days, and then a balance trial of 10 days was carried out with the respective diet. On the day following the balance trial (ie, after 29 days on the diet) blood samples were taken before the morning meal. After a break of 1 year (reasons unrelated to the study, cats taking part in other trials during this time) the experiment, including the pre-trial period to ensure the cats were healthy before the experiment, was repeated with the cats from the previous HP group in the control group and vice versa.

Control and HP diet were identically composed of 84% cooked beef (heart, steak), 14% cooked rice, 1% cellulose and 2% rapeseed oil. The rice and meat compounds were cooked in water in a big pot at our facilities – a process comparable to home cooking. The cooked compounds were minced after cooling, then the other compounds were added and the product was thoroughly mixed and stored at −15°C. The amount needed per day was thawed before feeding. The analysed nutrient profile is given in Table 1.

All diets were supplemented with minerals and vitamins according to the recommended allowance suggested by the NRC on a metabolic body weight basis.[4] Vitamin D supply was 7 IU/kg $BW^{0.67}$. Major mineral content is given in Table 1. No phosphorus was added to the control diet, whereas phosphorus was added to the HP diet as monophosphate to make it highly available. In the HP diet, 5/6 of the added monophosphate originated from calcium monophosphate and the rest from sodium monophosphate. To ensure high phosphorus availability no other calcium was added to the HP diet, which resulted in a low Ca/P ratio. To avoid struvite crystalluria in the HP diets or a strongly acidifying effect, a urine pH between 6.5 and 7 was targeted. Sodium bicarbonate was added in amounts to ensure the corresponding cation–anion balance in all diets. The mean cation–anion balance (for calculations see below) amounted to −18 ± 10 mmol/100 g dry matter (DM) in all diets. The cats were fed individually twice a day with at least 1 h of access to the food. Food allowances were calculated according to the NRC (0.42 MJ ME/kg $BW^{0.67}$).[4] The mean intake was slightly lower, with 0.36 MJ ME/kg $BW^{0.67}$ in the CON group and 0.39 MJ ME/kg $BW^{0.67}$ in the HP group.

Table 2 Dry matter (DM) intake, water balance, urine pH and urine specific gravity (USG)

Diet	n	DM intake (g/kg BW)	Total water intake (g/kg BW)	Faecal water excretion (g/kg BW)	Insensible water losses (g/kg BW)	Urine volume (ml/kg BW)	Urine pH	USG (g/cm^3)
CON	13	12.3 ± 2.4^a	29.8 ± 5.5^a	2.5 ± 1.2^a	13.4 ± 3.1^a	13.9 ± 3.9^a	6.68 ± 0.25^a	1.046 ± 0.006^a
HP	13	13.6 ± 1.3^b	34.8 ± 4.6^b	2.8 ± 1.3^a	16.6 ± 4.1^b	15.4 ± 3.8^a	6.69 ± 0.11^a	1.062 ± 0.008^b

Data are mean ± SD. Means in the same column not sharing a superscript letter differ significantly (P <0.05)
BW = body weight; CON = control; HP = high phosphorus

During the 10 day collection period the cats were housed individually in metabolic cages (length × width × height = 120 cm × 60 cm × 53 cm and 90 cm × 80 cm × 75 cm) equipped with a litter box filled with inert polyethylene granules to ensure separate collection of faeces and urine. The urine was preserved with thymol and paraffin until measuring and storage at −30°C. It was collected repeatedly during the day with a maximum period in between of 8 h (during the night). The stability of the measured pH values under the preservation method carried out was verified repeatedly for a period of 12 h under actual conditions by measuring fresh urine samples, then preserving them as described above and measuring the pH again. Proximates in food and faeces were determined using the Weende method,[20] and gross energy using an adiabatic bomb calorimeter. Total water intake was calculated by adding the amount of moisture from food to the amount of drinking water consumed. When faecal and renal water excretion was subtracted from total water intake, the remainder, including possible water retention, was defined as insensible losses. Urine pH was measured using an electric pH meter (WTW pH 325), and specific weight with a pycnometer (Superior). For semi-quantitative measurement of blood, bilirubin, protein, glucose, nitrate and ketone bodies in the urine a diagnostic medical dipstick (Urispec VET 10 Plus; Henry Schein) was used on fresh urine. At day 10 of each collection period (day 28 of the trial) fresh urine was used to test for microalbumins using a semi-quantitative dipstick (ERD HealthScreen, Feline Urine Test; Heska) at a standardised specific urine weight of 1.020 (detection limit for albumin <1 mg/dl). Creatinine in urine and serum was measured with the Jaffé method. Phosphorus in faeces and urine was measured after acid hydrolysis and microwave disintegration by photometry with molybdate-vanadate.

The cation–anion balance in food was calculated as suggested by Kienzle and Wilms-Eilers:[21] cation–anion balance (mmol/kg DM) = (49.9 × Ca) + (82.3 × Mg) + (43.5 × Na) + (25.6 × K) – (64.4 × P) – (13.4 × methionine) – (16.6 × cysteine) – (28.2 × Cl) (nutrients in g/kg DM). The calculation of the creatinine clearance normalised by BW was completed using the following equation: endogenous creatinine clearance [ml/kg BW] = (urine volume [ml/kg BW/24 h] × urine creatinine [µmol/l])/(1440 [mins]/serum creatinine [µmol/l]). For absolute creatinine clearance the same equation without division by BW was used. The apparent digestibility of minerals was calculated as follows: (intake – faecal excretion)/intake × 100.

Data of the trial and control periods (pre-trial data not shown) are expressed as means ± SD. Statistical analysis was performed with IBM SPSS 23.0. The data were tested for normality using the Kolmogorov–Smirnov test. If no statistically significant difference to a normal distribution was found, a paired t-test was used to test for significant differences between CON and HP. Discrete data were tested by the Fisher's exact test. Differences were considered significant at P <0.05.

Results

DM intake was higher in the HP group than in the CON group (Table 2). There was also a higher water intake, and an increase in urine specific gravity (Table 2). There was no significant effect of HP diet on faecal water excretion, urine volume and urine pH (Table 2).

Glucosuria and microalbuminuria were observed exclusively in the HP group in 9/13 cats each (P <0.05). Creatinine clearance differed significantly between the HP and the CON group: when the cats were eating the CON diet mean creatinine clearance amounted to 3.12 ± 1.11 ml/kg BW/min. Creatinine clearance decreased to 2.39 ± 0.86 ml/kg BW/min during the HP trial. The difference was significant (P = 0.01). The corresponding values without normalisation by BW were 12.9 ± 5.6 and 10.1 ± 4.8 ml/min (P <0.05). Blood urea nitrogen content was significantly higher (P = 0.002) in the HP group (4.8 ± 1.0 mmol/l) than in the CON group (4.0 ± 0.6 mmol/l). For comparison, the protein intake amounted to 5.3 and 5.4 g/kg BW, respectively.

Preprandial serum calcium, phosphorus, sodium and potassium values remained within the reference intervals in all trials. There was a significant difference (P = 0.001) in serum calcium (CON 2.34 ± 0.14mmol/l, HP 2.50 ± 0.09 mmol/l) but not in serum phosphorus (CON 1.65 ± 0.24 mmol/l, HP 1.52 ± 0.32 mmol/l).

The balance data on phosphorus showed that in the HP trial faecal phosphorus excretion was higher than in

Table 3 Phosphorus balance

Diet	n	Intake (mg/kg BW)	Faecal excretion (mg/kg BW)	Renal excretion (mg/kg BW)
CON	13	72 ± 11[a]	45 ± 11[a]	16 ± 8[a]
HP	13	214 ± 22[b]	82 ± 16[b]	115 ± 20[b]

Data are mean ± SD. Means in the same column not sharing a superscript letter differ significantly ($P<0.05$)
BW = body weight; CON = control; HP = high phosphorus

the CON group (Table 3). This corresponds to an apparent phosphorus digestibility of about 60% in the HP group vs a digestibility of around 40% in the controls. Renal phosphorus excretion was significantly increased in the trial HP (Table 3).

Discussion

In our study the intake of excessive phosphorus in a highly available chemical form led to a high absorption from the gastrointestinal tract and a corresponding high renal excretion of phosphorus. Endogenous creatinine clearance decreased significantly during HP feeding. In cats, creatinine in blood is filtered by the glomerula and excreted via urine without being reabsorbed and re-excreted by renal tubules, and therefore the creatinine clearance represents the glomerular filtration rate.[22,23] Glomerular filtration rate is currently considered to be the best marker of renal function.[24]

The present study confirms the results of Pastoor et al;[16] that is, that the intake of excesses of highly available phosphorus can cause kidney damage or dysfunction in cats.

In the HP group of the present study, markers of renal damage (microalbuminuria, glucosuria) showed a significantly positive reaction. Phosphate nephrotoxicity in the case of excessive intake of highly available phosphorus has been shown to induce tubular damage in humans,[13–15] dogs[9] and rats.[8,10–12] The nephrotoxicity of an increased phosphorus consumption in modern societies through processed food frequently 'enhanced' by the addition of PO_4 additives (convenience products, fast food, prepared diets) is discussed intensively.[25,26] Excessive intake of highly available phosphorus significantly disrupts the hormonal regulation of phosphate, calcium and vitamin D, specifically by the secretion and action of fibroblast growth factor 23 and parathyroid hormone (PTH). Both PTH and fibroblast growth factor 23 decrease tubular phosphorus reabsorption,[27] which results in increased phosphorus concentration in the tubuli, potentially leading to tubular damage. Thus, the concentration of phosphorus in the primary urine is influenced by the phosphorus uptake from the gastrointestinal tract.

To answer questions regarding food safety, it may not be sufficient to determine the total amount of phosphorus in a diet, because the organic (mainly protein sources) and inorganic (additives) sources of phosphorus probably differ in their effects, owing to a higher bioavailability of inorganic sources.[27,28]

Given the above-described hypothesis of high phosphorus concentration in renal tubuli as a precondition of phosphorus nephrotoxicity, the Ca/P ratio in the food is highly likely to play an important role. The digestibility of phosphorus decreases with increasing Ca/P ratio.[29] The low Ca/P ratio in the present study was chosen as a method to prove the principle of phosphorus toxicity in cats and to allow comparison to the results of Pastoor et al.[16] In addition, there are prepared cat foods on the market with a low Ca/P ratio plus a high phosphorus content.[6,7]

The increase in urine specific gravity in the HP group is likely to be due to the increased phosphorus content in urine in these groups, because phosphates have a considerably higher specific gravity than water.

Conclusions

Taking into account the outcome of the study of Pastoor et al[16] and the results of the present study, a phosphorus content of 870 mg/MJ ME (ie, an intake of about five times the maintenance requirements, according to the NRC[4]) cannot be considered unconditionally safe. More studies on the safety of a high phosphorus intake that consider various factors such as Ca/P ratio, phosphorus source and other potential co-factors that may alleviate or enhance the effect of high phosphorus intake on renal health, and long-term studies on chronic phosphorus excess are clearly necessary. In addition, more sensitive urinary markers of kidney damage or dysfunction, especially of tubular origin such as *N*-acetyl-beta-D-glucosaminidase, cystatin C or retinol binding protein, have been identified[30] that might be used in the future. In summary, the present study confirmed that the intake of a large amount of highly available phosphorus can affect parameters of kidney damage or dysfunction in healthy cats.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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