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### Summary

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## Effects of a dietary chitosan and calcium supplement on Ca and P metabolism in cats

*Effekte der Zufütterung einer Chitosan- und Kalziumkombination auf den Kalzium- und Phosphorstoffwechsel der Katze*

Elisabeth Wagner<sup>1</sup>, Ilse Schwendenwein<sup>2</sup>, Jürgen Zentek<sup>1</sup>

The aim of the present study in cats was to investigate the potential effects of a calcium carbonate and chitosan supplement on blood parameters in aged cats with moderate chronic renal failure and on the mineral balance in adult healthy cats. For the trials, 10 neutered cats 2–4 years of age were fed for 21 days and six neutered cats (2 male and 4 female), 14 years of age, with elevated urea and phosphorus level in the plasma were fed for 35 days with a supplement. The apparent digestibility of phosphorus was ( $p < 0.05$ ) reduced in the treatment period. Plasma urea inorganic phosphate decreased significantly ( $p < 0.05$ ) in the old cats after 35 days of treatment. The treatment had a significant effect on the phosphorus, gross energy, dry matter, crude ash, crude fiber and crude protein digestibility in adult healthy cats. The practical implication could be an alternative treatment option for cats refusing to ingest veterinary renal diets.

**Keywords:** chronic renal failure, chitosan, cat, plasma urea, plasma phosphate, phosphorus binder, digestibility

Das Ziel der Studie war der Nachweis des Einflusses eines Supplements mit Kalziumkarbonat und Chitosan auf die Blutparameter bei Katzen mit erhöhten Harnstoff- und Phosphatgehalten im Plasma und auf den Mineralstoffhaushalt bei gesunden Katzen. Für die Studie wurden 10 kastrierte Katzen (2–4 Jahre alt) über 21 Tage und 6 kastrierte Katzen (14 Jahre alt) mit einem erhöhten Harnstoff- und Phosphorgehalt im Plasma 35 Tage mit einem entsprechenden Futterzusatz gefüttert. Dieser wurde einem kommerziellen Dosenfutter zugesetzt. Die scheinbare Verdaulichkeit des Phosphors war in der Supplementierungsphase gegenüber der Kontrollperiode reduziert ( $p < 0.05$ ). Die mittlere Harnstoffkonzentration und ebenso der anorganische Phosphorgehalt im Plasma wurde nach 35 Tagen mit dem Zusatz signifikant ( $p < 0.05$ ) abgesenkt. Es wurde ein signifikanter Einfluss dieses Supplements auf die Verdaulichkeit der Bruttoenergie, der Trockensubstanz, der Rohasche, der Rohfaser, des Rohproteins und des Phosphats bei gesunden Katzen nachgewiesen. Diese Supplementierung könnte für Katzen, die eine Nierendiät benötigen würden, eine weitere diätetische Alternative sein.

**Schlüsselwörter:** chronische Niereninsuffizienz, Chitosan, Katze, Plasmaharnstoff, Plasmaphosphat, Phosphorbinder, Nährstoffverdaulichkeit

(\*)

## Introduction

Chronic renal failure (CRF) is the most common renal disease in dogs and cats. It is characterized by progressive and irreversible renal structural lesions and nephron losses. Patients with CRF show clinical and biochemical signs, depending on the progression of the disease. Laboratory findings are azotemia or uremia, including metabolic acidosis and hyperphosphatemia. Serum creatinine and blood urea nitrogen (BUN) concentrations are commonly used screening tests. Serum creatinine and urea levels are negatively correlated with the glomerular filtration rate.

Phosphorus is absorbed from the gastrointestinal tract and primarily excreted by the kidneys. Renal excretion reflects the net effect of glomerular filtration and tubular reabsorption. If dietary phosphorus intake remains constant, a decline in the glomerular filtration rate will lead to phosphorus retention and hyperphosphatemia and consequently to renal hyperparathyroidism. Hyperphosphatemia can be managed by restricted dietary phosphorus intake. If this is not sufficient to reduce increased serum inorganic phosphate levels, oral administration of intestinal phosphorus binding agents is recommended (Polzin et al. 1995). Traditionally, phosphate binders containing aluminium have been used effectively to control serum phosphorus levels in patients with chronic renal failure. Barber et al. (1999) and Elliott et al. (2000) combined a veterinary diet restricted in phosphorus and protein with or without an intestinal phosphate binding agent (aluminium hydroxide) and investigated plasma phosphate and parathyroid hormone (PTH) concentrations in cats. Phosphate binders reduced serum phosphorus and PTH levels. Several studies evaluated the phosphate binding capacity of calcium carbonate (Slatopolsky et al., 1986), aluminium hydroxide (Takamoto et al., 1985) and calcium acetate (Janssen et al., 1996; Lau et al., 1998) in humans with renal failure. Addition of ferrihydrite, calcium acetate (Weaver et al., 1999) and zirconyl chloride octahydrate (Graff and Burnel, 1995) was found to be effective in rats. High phosphate concentrations are also reduced by iron (III) hydroxide complex (Yamaguchi et al., 1999). Rats (15 male Wistar rats) were fed for 7 days with a rodent chow containing 0, 1, 4 and 8 % of the iron (III) hydroxide complex. The urinary phosphorus levels dropped significantly ( $p < 0.01$ ) in a dose dependant manner.

The effects of chitosan-coated dialdehyde cellulose as an oral adsorbant of urea and ammonia were examined in rats with adriamycin induced progressive chronic renal failure (CRF) (Nagano et al., 1995). Chitosan (5 %) or a charcoal adsorbent (5 %) were fed over four months. CRF rats fed the normal diet and the charcoal adsorbent developed progressive azotemia, hyperphosphatemia, proteinuria and anaemia. After 9 weeks increased number of losses occurred. In contrast, chitosan treated rats had decreased blood urea nitrogen, serum creatinine and serum phosphate and longer survival periods.

Furthermore Jing et al. (1997) investigated the effects of chitosan on eight haemodialysis patients from 30 to 72 years of age. After a pre period of 1 week the patients received 30 chitosan tablets (45 mg chitosan/tablet) three times a day. Significant reductions in urea and creatinine levels in serum were observed after 4 weeks of chitosan ingestion. After 12 weeks physical strength, appetite and sleep had been improved.

The effect of chitosan on Calcium ( $Ca^{47}$ ) metabolism was investigated in male Wistar rats by Wada et al. (1997). Rats were fed a 5 % chitosan diet for 40 days and whole body retention of  $Ca^{47}$  was significantly decreased compared with rats fed a cellulose diet, but showed no significant difference to rats fed a fibre-free diet. The urinary excretion of  $Ca^{47}$  was significantly increased in the chitosan group when compared with the cellulose group.

In rats fed an iron (III) chitosan complex serum phosphorus levels were significantly reduced after 15 days. The faecal phosphorus levels were higher ( $p < 0.01$ ), while urinary phosphorus was not significantly reduced (Baxter et al. 2000).

Studies in dogs and cats on the effects of calcium carbonate in combination with chitosan have not been published to our knowledge. In cats, practical problems occur frequently due to low palatability of veterinary diets in patients with chronic renal failure. Alternatives to the standard dietary treatment would be useful especially in cases with mild signs of renal failure.

The aim of the present study in cats was to investigate the potential effects of calcium carbonate and chitosan on blood parameters in aged cats with biochemical signs of chronic renal failure and on the calcium and phosphorus balance in adult healthy cats.

## Material and Methods

### Balance Trial

Animals: Ten cats (8 female and 2 male neutered) were allocated into single cages (1 × 1 m, 3 m height). The age of the cats ranged from two to four years. The cats did not show clinical signs of renal dysfunctions. Vaccinations and deworming procedures were performed according to established protocols.

Diet: A commercial canned diet (Whiskas senior; Masterfoods Austria OHGA-2460 Bruck/Leitha) was fed. Crude nutrients, gross energy, calcium and phosphorus content of the diet are summarized in table 1. The amount of food was adjusted to meet maintenance requirements of the cats.

In the treatment period chitosan and calcium carbonate (Paketine® Vetoguinol, Lure Cedex, France; composition: 8 % crab shell extract; 10 % calcium carbonate and 82 % lactose; ingredients: crude ash 9.9 %, crude protein 4 %, ether extract 0.55 %, crude fiber <0.1 %, potassium 0.015 %, calcium 3.7 % and phosphorus <0.01 %) was added to the canned diet. The applied dosage was 1 g/5 kg body mass/twice daily. The control and the treatment period lasted 21 days.

Procedures: Urine was collected from day 7 to 14. The urine pH, volume and the calcium and phosphorus concentrations were measured. The 24 hour urine collection was done under a thin layer of thymol/mineral oil solution to prevent losses by microbial activities and evaporation.

A digestibility trial was performed from days 14 to 21. Analytical methods: Proximate analysis in feed and faeces was performed according to the procedures of Naumann and Bassler (1993). Minerals were measured in faeces and urine after wet ashing of the samples in a mixture of a 40 %  $HNO_3$  (65 %), 10 %  $HCl$  (35 %), 20 %  $H_2O_2$  (30 %) and 30 % water in a microwave oven (MLS GmbH.; MLS-Ethos plus, Leutkirch im Allgäu, Ger-

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**TABLE 1: Crude nutrients, gross energy and minerals of the canned diet fed to the cats.**

		fresh matter	dry matter
dry matter	%	17.2	100
crude ash	%	1.25	7.24
crude protein	%	8.27	48.0
ether extract	%	3.77	21.9
crude fiber	%	0.66	3.80
nitrogen free extract	%	3.28	19.0
gross-energy	MJ/kg	4.05	23.50
calcium	g/kg	2.97	17.2
phosphorus	g/kg	1.54	8.92

**TABLE 2: Dry matter intake and weight of the faeces (g DM/d) of the experimental cats in the balance trial.**

period		feed	faeces
control	mean	45.7	8.8
	SD	7.4	0.5
treatment	mean	43.8	11.5
	SD	7.7	0.5

**TABLE 3: Apparent digestibility of crude nutrients during the treatment period (supplementation with calcium carbonate/chitosan) and the control period in the experimental cats in the balance trial.**

period		dry matter	crude ash	crude protein	ether extract	crude fiber	nitrogen free extract	gross energy
		%	%	%	%	%	%	%
control	mean	8.1	50.1	83.8	93.6	58.5	76.2	85.1
	SD	5.6	21.4	5.0	3.2	17.0	7.4	7.0
treatment	mean	74.7*	27.9*	79.2*	91.6	30.6*	70.5	78.1*
	SD	5.0	14.9	4.8	1.6	19.6	8.1	4.4

\* (p < 0.05)

**TABLE 4: Apparent digestibilities of phosphorus and calcium in the experimental cats in the balance trial**

period		phosphorus		calcium	
		calcium	phosphorus	calcium	phosphorus
control	mean	38.1	21.9	21.9	21.9
	SD	17.8	22.1	22.1	22.1
treatment	mean	17.2*	-4.5*	-4.5*	-4.5*
	SD	19.6	22.0	22.0	22.0

\* (p < 0.05)

**TABLE 5: Intake and urinary excretion of calcium and phosphorus in the experimental cats in the balance trial.**

period		intake		excretion	
		calcium	phosphorus	calcium	phosphorus
		mg/kg BW/day		mg/kg BW/day	
control	mean	187.9	97.4	0.9	103.8
	SD	39.5	20.5	0.7	22.1
treatment	mean	197.8	93.4	0.8	87.6
	SD	39.9	19.9	0.6	15.3

many). Calcium was measured by atomic absorption spectrometry (Perkin Elmer 3030B, Wellesley, USA), phosphorus by the vanadate molybdate method using a spectrophotometer (Hitachi U 3000, Tokyo, Japan).

#### *Effects of chitosan with calcium carbonate in older cats with increased plasma urea and phosphorus*

**Animals:** Six cats, average age 14 years (2 male and 4 female neutered), with an increased urea and phosphorus concentration in the plasma. Vaccinations and deworming procedures were done regularly, the 6 cats were allocated in a common kennel in the Institute of Nutrition (12.3 m<sup>2</sup>, 3 m height).

**Diet:** Cats were fed with the diet as described in table 1 for at least 5 weeks before blood sampling. All cats were subsequently fed the identical diet supplemented with chitosan and calcium carbonate for 35 days before blood samples were taken (1 g/5 kg body mass/twice daily).

**Sampling:** Blood was taken from the Vena cephalica antebrachii into lithium-heparin vials (Greiner Bio one GmbH, Kremsmünster, Austria). Differential blood counts and biochemistry (urea, creatinin, total protein, calcium, phosphorus, aspartate aminotransferase, alanine amino-transferase) were done by the central laboratory of the University of Veterinary Medicine, Vienna.

**Analytical methods:** All biochemical tests were run on an automated Hitachi 911 analyzer (Hitachi, Tokyo, Japan): Urea (Urease, Roche Diagnostics 1 489 364),

creatinin (Jaffé compensated kinetic, Roche Diagnostics 1 489 291), total protein (Biuret, Roche Diagnostics 1 553 836), calcium (Kresolphthalein-Komplexon, Roche Diagnostics 1 489 216), phosphorus (Molybdat, Roche Diagnostics 1 489 348), aspartate aminotransferase (AST, opt. Standardmethode DGKC, Roche Diagnostics 816 337), alanine aminotransferase (ALT, opt. Standardmethode DGKC, Roche Diagnostics 816 442).

Differential blood counts were performed by laser flow cytometry (Advia 120™, Bayer Diagnostics, Wien) and, if necessary, by microscopic control.

#### *Statistics*

Data are expressed as means and standard deviations (SD). Group differences were evaluated by Student t-test (WinSTAT® Microsoft Excel® 1999) and in the old cats by a paired Student t-test (p < 0.05).

## **Results**

#### *Balance trial*

The calcium intake of the cats during the experimental period was 830 mg/day (SD = 132.3) and in the control period 787 mg/day (SD = 128.3). The mean phosphorus intake of the cats was 392 mg/day (SD = 68.6) and in the control period 408 mg/day (SD = 66.5). The mean dry matter intake, faeces weight are presented in table 2 and the apparent digestibilities of crude nutrients are presented in table 3. Dry matter, crude protein, crude fiber, crude ash and gross-energy digestibility decreased significantly (p < 0.05), but the variation between the individuals was high.

The apparent digestibility of phosphorus was significantly ( $p < 0.05$ ) reduced in the experimental period compared to the control period (table 4). The apparent digestibility of calcium was slightly negative in the treatment period and reached 21.9 % in the control period.

The urine volume during the treatment period was 130,2 ml/day (SD= 26,0) compared to 134,0 ml/day (SD = 27,5) in the control period. The pH was in both feeding periods around 7.8 (SD = 0.3). The urinary excretion of phosphorus and calcium was not significantly influenced by the dietary treatment (table 5).

*Effects of chitosan with calcium carbonate in older cats with increased plasma urea and phosphorus*

The mean urea concentration in the plasma of the old cats was 85.6 mg/dl (SD = 18.1) at day 1 (reference 20–65 mg/dl) and was ( $p < 0.05$ ) reduced to 61.2 mg/dl (SD = 11.4) after 35 days of treatment. Figure 1 demonstrates the urea concentrations for each cat at the beginning and after 35 days of the treatment. Plasma inorganic phosphate (figure 2) decreased significantly ( $p < 0.05$ ) after 35 days of treatment from 1.7 mmol/l (SD = 0.2) at day 1 to 1.1 mmol/l (SD = 0.3) at day 35 (normal range 0.8–1.6 mmol/l). Practically no change was observed in the plasma calcium content after 35 days of treatment. The mean calcium concentration was 2.8 mmol/l (SD = 0.2) at days 1 and 35. At the beginning and at the end of the treatment the plasma creatinine levels were comparable with a mean of 1.2 mg/dl (SD = 0.1). Total protein and packed cell volume were in the normal ranges. The experimental cats had an increased activity of alanineamino-transferase at the beginning (105.8 U/l, SD = 58.6). The results of the haematology and blood chemistry are summarized in tables 6 and 7.

**Discussion**

The aim of the study was to investigate the potential effects of a dietary supplement containing calcium carbonate and chitosan on blood parameters in aged cats with biochemical signs of moderate chronic renal failure and on the mineral balance in adult healthy cats. Cats are highly susceptible to develop chronic renal failure with increasing age. Dietetic treatment is mainly based on moderate protein restriction in combination with decreased phosphorus intake (Barber et al., 1999; Elliot et al., 2000; Polzin et al., 2000). Unfortunately, palatability problems

**TABLE 6:** Blood chemistry of the 6 older cats before (day 1) and after 35 days of treatment.

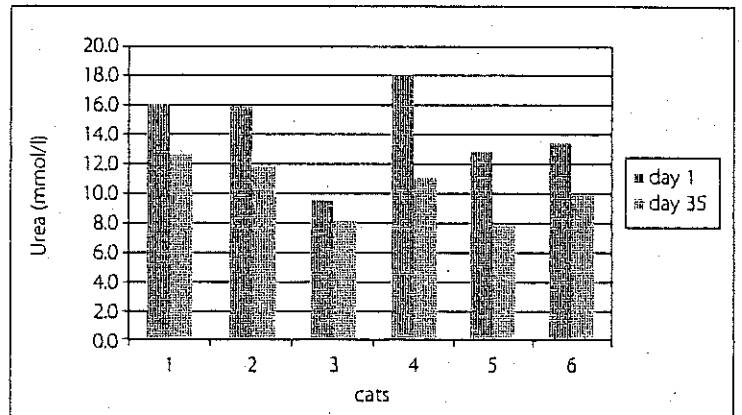
period		urea (mmol/l)	creatinine (mmol/l)	total proem (g/l)	AST (U/l)	ALT (U/l)	calcium (mmol/l)	phosphorus (mmol/l)
control	mean	14.3	106.1	84.6	38.8	105.8	2.8	1.7
	SD	3.0	11.2	7.85	43.5	58.6	0.16	0.17
treatment	mean	10.2*	112.0	87.7	18.7	103.5	2.8	1.1*
	SD	1.9	27.2	6.49	12.2	92.5	0.08	0.28

\* $p < 0.05$ ; AST = aspartate aminotransferase; ALT = alanine aminotransferase

**TABLE 7:** Haematology of the 6 older cats before (day 1) and after 35 days of treatment.

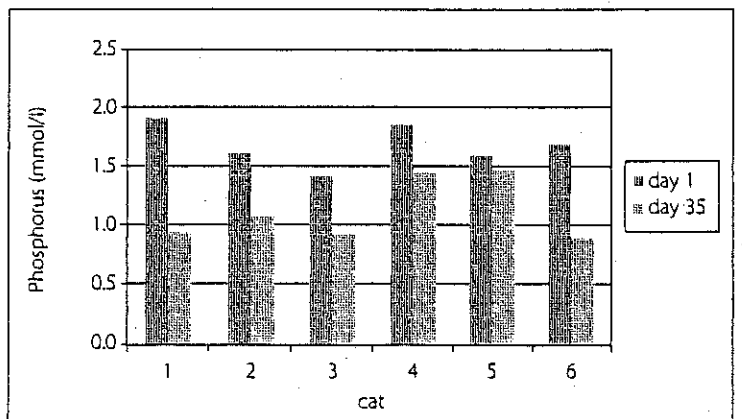
period		Hb (mmol/l)	PCV (l/l)	RBC (10 <sup>12</sup> /l)	MCV (fl)	MCH (fmol)	MCHC (mmol/l)	WBC (10 <sup>9</sup> /l)
control	mean	7.3	0.35	8.3	42.5	0.88	20.7	21.1
	SD	1.01	0.05	1.04	1.35	0.02	0.19	6.8
treatment	mean	7.1	0.35	8.4	41.2	0.83	20.6	24.3
	SD	0.77	0.03	0.67	1.42	0.04	0.06	10.7

Hb = haemoglobin, PCV = packed cell volume, RBC = red blood cell, MCV = mean corpuscular volume, MVH = mean corpuscular haemoglobin, MCHC = mean corpuscular haemoglobin concentration, WBC = white blood cell



**FIGURE 1:** Plasma urea concentration before (day 1) and after 35 days of treatment with the chitosan/calcium supplement in the older cats (mean concentrations differed significantly between day 1 and 35,  $p < 0.05$ ).

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**FIGURE 2:** Plasma phosphorus concentration before (day 1) and after 35 days of treatment with the chitosan/calcium supplement in the older cats (mean concentrations differed significantly between day 1 and 35,  $p < 0.05$ ).

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are frequent with such diets and may lead to a low compliance of owners. Therefore, alternative treatments are warranted that can decrease the levels of urea and phosphorus. The study shows, that feeding a dietary supplement based on chitosan and calcium carbonate was efficient in both aspects. Plasma inorganic phosphorus levels were reduced significantly. A similar result was found in rats by Baxter et al. (2000). The results of this trial showed no influence on the urine parameters. Due to the low calcium carbonate intake by the supplement the urine pH value was not changed during the treatment.

The flexible structure of the polymer chain of chitosan could be another reason for the fixation of phosphorus in the gut. This structure enables the molecule to take suitable configurations for the complexation with metal ions and also with calcium and phosphorus. This might explain the negative digestibility of calcium in the balance trial (Bernkop-Schnürch, 2000).

The underlying mechanism that is responsible for the observed shifts in phosphorus metabolism is not clear but might be related to several factors.

In a study of Zhang and Neau (2002) the degradative activities of extracellular and cell-associated portions of rat cecal and colonic enzymes, whose activities are comparable to that in the human colon, against five chitosan qualities were characterized. The effects of the molecular weight (MW) and degree of deacetylation (DD) of chitosan on its susceptibility to degradation were investigated. In addition, the degradation function of rat bacterial enzymes was compared to that of a commercially available beta-glucosidase that contains a chitinase. The results show that rat bacterial enzymes had the ability to degrade chitosan with extracellular enzymes exhibiting a more profound effect than did cell-associated enzymes. The reaction to bacterial enzymatic degradation was dependent on both the MW and DD of the chitosan sample. Those samples with a lower MW and lower DD were more susceptible substrates.

Chitosan can act as an absorption enhancer in the intestine by increasing the residence time of drugs at mucosal sites, inhibiting proteolytic enzymes, and increasing the permeability for protein and peptide drugs across mucosal membranes. Recently, it was found that chitosan is degraded by the microflora that are present in the colon. As a result, this polymer could have promising application in colon-specific drug delivery. In consequence of the physical, chemical, and biological properties, chitosan has been used in many different formulations for drug and gene delivery in the gastrointestinal tract (Hejazi and Amiji, 2003).

The apparent protein digestibility was decreased in the treated cats. Yoshimoto et al. (1995) and Razdan and Petersson (1996) observed a decreased apparent protein digestion in a dose-dependent manner by chitosan in rats and chickens, respectively. The authors explained this effect by a lower ammonium absorption due to high bacterial growth activities, which are able to use ammonia as a nitrogen source. The significant decrease of blood urea levels in our cats might have been caused by a reduction in protein digestibility and ammonia absorption of the treated cats.

In conclusion, the treatment had a significant effect on the phosphorus- and protein digestibility in adult healthy cats. The practical implication could be an alternative treatment option for cats refusing to ingest veterinary renal diets: Reduction of hyperphosphatemia and the resulting risk for renal hyperparathyroidism is considered as one of the most important aspects of the treatment of patients with renal insufficiency. The efficacy of chitosan and calcium supplementations as additional supplement to veterinary diets in cases with severe renal failure needs further evaluation.

Additionally, investigations on the mode of action of chitosan and the consequences for the development of secondary hyperparathyroidism and for the calcium- and protein metabolism are of clinical interest.

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