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Effects of Dietary Salt Intake on Renal Function: A 2-Year Study in Healthy Aged Cats

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Background: Increasing salt intake to promote diuresis has been suggested in the management of feline lower urinary tract disease. However, high dietary salt intake might adversely affect blood pressure and renal function.

Objectives: The objective of this study was to assess the long-term effects of increased salt intake on renal function in healthy aged cats.

Methods: This study was controlled, randomized, and blinded. Twenty healthy neutered cats (10.1 ± 2.4 years) were randomly allocated into 2 matched groups. One group was fed a high salt diet (3.1 g/Mcal sodium, 5.5 g/Mcal chloride) and the other a control diet of same composition except for salt content (1.0 g/Mcal sodium, 2.2 g/Mcal chloride). Clinical examination, glomerular filtration rate, blood pressure measurement, cardiac and kidney ultrasonography, and urinary and blood tests were performed before and over 24 months after diet implementation. Statistics were performed using a general linear model.

Results: Sixteen cats completed the 2 year study. The only variables affected by dietary salt intake were plasma aldosterone and urinary sodium/creatinine ratio, respectively, higher and lower in the control group all over the study period and urinary specific gravity, lower in the high salt diet group at 3 months.

Conclusions and Clinical Importance: Glomerular filtration rate (GFR), blood pressure, and other routine clinical pathological variables in healthy aged cats were not affected by dietary salt content. The results of this 2 year study do not support the suggestion that chronic increases in dietary salt intake are harmful to renal function in older cats.

Key words: Aldosterone; Blood pressure; Glomerular filtration rate; Kidney; Salt.

Increasing urine volume, dilution, or both can be reliably achieved in healthy cats by feeding a dry diet with an increased content of salt.[1-4,a,b] Appropriately designed dry diets with an increased salt content are able to dissolve naturally occuring struvite stones with a decrease or at least no change in the risk of calcium oxalate crystals formation.[5,6,a,b] High levels of dietary sodium are thought to play a role in the development of hypertension and cardiovascular and renal diseases in humans.[7–9] However, such potential detrimental effects are still controversial.[10] Several studies have specifically addressed this issue in cats. To date, all have found no effect of increased salt intake on blood pressure.[3,4,11,12,c] One study reported that serum creatinine, urea nitrogen, and phosphorus concentrations increased when cats were fed a high salt diet[4] whereas in all others the markers of kidney function were unaffected by a high dietary salt intake.[11,12,c] These studies ran from 1 week to 6 months and most used healthy young cats. However, testing cats at risk for adverse effects has been recommended to fully evaluate the impact of a high dietary salt intake.[4] Aged cats could be at risk for both systemic hypertension[13] and chronic kidney disease (CKD),[14] two of the major concerns that might result from excessive salt intake in

Abbreviations:

ALT	alanine aminotransferase
CD	control diet
CKD	chronic kidney disease
DM	dry matter
GFR	glomerular filtration rate
HSD	high salt diet
PTH	parathyroid hormone
RAAS	renine angiotensin aldosterone system
RI	resistive index
TDI	tissue Doppler imaging
U-Na/C	urinary sodium/creatinine ratio
UPC	urine protein/creatinine ratio
U-pH	urinary pH
USG	urine specific gravity

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other species. Moreover, many homeostatic mechanisms, including those involved in sodium regulation, might decline with increasing age. It is therefore likely that aged cats could be especially sensitive to deleterious effects of dietary salt as observed in elderly people.[15–17]

The objective of the present study was to assess, in healthy aged cats, the long-term effects of dietary salt intake on renal function and blood pressure in a prospective, randomized, blinded, and controlled study.

Materials and Methods

Cats

Twenty-six Domestic Shorthair neutered cats (10.4 ± 2.4 [5.3–14.5] years; 4.8 ± 0.7 [3.6–6.5] kg) housed in an indoor research facility with a 12 hour light/dark cycle, controlled temperature (18–21°C), and ventilation (250 m^3/h, 12 h/d) were used. For practical purposes, cats were identified with a number (1 through 26). After baseline evaluations, cats were included in the study if they were healthy and cooperative enough during all the procedures performed. Cats were declared healthy according to clinical examination, blood pressure measurement, routine urine and blood analyses (including urine protein/creatinine ratio [UPC] and total thyroxine), kidney ultrasonography, and conventional echocardiography/Doppler at baseline.

To control for the potential confounding factor of cardiac functional alteration on renal function, stratified randomization was performed. Cats meeting the inclusion criteria were first stratified in 3 subsets according to cardiac Tissue Doppler Imaging (TDI) examination results at baseline. The following randomization procedure was then performed separately within each subset: cats were ranked according to their glomerular filtration rate (GFR) and paired. In each pair of cats, the first was randomly (coin flip) assigned to one diet group and the second was assigned to the other diet group. This ensured that the cats in each diet group were well matched with regard to renal function and cardiac structure/function. Cats were allowed to acclimate with the other cats of their group for a period of 2 weeks. Then, cats were fed either the high salt diet (HSD) or the control diet (CD) according to the group and monitored over 2 years. Housing and environmental conditions remained similar for both groups throughout the study. Any condition (occurrence of disease, need for treatment) that could interfere with the study objective or for which continuation of the study raised ethical concerns led to exclusion of affected cats.

Diets, Feeding and Watering

During screening, inclusion, group allocation, and acclimation, cats were fed a maintenance dry expanded diet[d] with a sodium content of 2.3 g/Mcal as fed. During the study, cats were fed either the HSD[e] or CD of exactly the same composition except for the level of sodium and chloride that was replaced with corn flour. Analysis of the diets confirmed that differences between the 2 diets were negligible and could not interfere with the study objective (Table 1). Cats had free access to water and were individually offered 70 g/d of either HSD or CD according to their group. This amount was arbitrarily selected to be greater than the usual consumption of these cats. Food leftovers were weighed and each cat's exact food intake recorded daily.

Table 1. Nutrient composition of the diets.

Nutrient (g/Mcal ME)	HSD[a]	CD
Proteins	87.0 ± 3.8	84.0 ± 2.8
Fat	39.2 ± 1.8	39.5 ± 1.5
Moisture	13.6 ± 0.8	16.0 ± 1.5
Minerals	21.1 ± 1.3	15.3 ± 0.3
Total dietary fiber	16.1 ± 2.0	18.0 ± 2.3
Sodium	3.1 ± 0.1	1.0 ± 0.1
Chloride	5.5 ± 0.3	2.2 ± 0.3
ME (kcal/kg, NRC 2006)	3976 ± 55	4000 ± 32

HSD, high salt diet; CD, control diet; DM; dry matter; ME, metabolizable energy; NRC, National Research Council.

[a]Veterinary Diet Urinary High Dilution, Royal Canin, Aimargues, France.

Study Design

The protocol was reviewed and approved by the suitable ethics committee. This study was conducted according to conditions approved by the French Ministry of Agriculture and to the guidelines of the Guide for Care and Use of Laboratory Animals.[f]

Clinical evaluation, blood pressure measurement, urinalysis (specific gravity [USG], dipstick, microscopic sediment examination, UPC, albumin and aldosterone concentrations, sodium/creatinine ratio [U-Na/C] and pH), complete blood count and smear examination, routine and specific biochemistry (total thyroxine, plasma renin activity, aldosterone and parathyroid hormone [PTH]), GFR measurement, kidney ultrasonography including renal resistive index (RI) assessment, conventional cardiac ultrasonography/Doppler and TDI examinations were performed at baseline. After diet implementation, procedures and testing used for follow-up in this study were repeatedly performed over 24 months, according to a predetermined schedule (Table 2). All measurements were performed in all cats at each time point. Blood sampling for hematology and hormone assays (jugular venipuncture, total volume of blood collected = 10 mL/cat) and blood sampling for routine biochemistry and GFR testing (cephalic veins microsampling, total volume of blood collected = 5 mL/cat) were performed on separate weeks. For delayed analyses, plasma, serum and urine were stored at −80°C until assayed in batches after each time point of the follow-up. Body weight was assessed weekly throughout the study.

Investigators were blinded to the treatment groups and cats were randomly ranked for iterative measurements (ie, physical examination, blood pressure measurements, and kidney ultrasound) at each follow-up point.

Biochemistry

Routine plasma biochemical assays were performed by a dry-slide technology analyzer.[g] Serum total thyroxine was measured with a validated chemiluminescent immunoassay.[h] Plasma renin activity was measured with a radioimmunoassay.[i] Urine and plasma aldosterone were measured by a radioimmunoassay.[j] Plasma PTH concentration was measured with an immunoradiometric assay.[k] All plasma and urine hormone assays have been validated in the cat.[18–20] Urine albumin concentration was evaluated by a quantitative albumin ELISA previously validated for use with feline urine.[21]

GFR Measurement

Exogenous plasma creatinine clearance test was performed.[22,23] Plasma creatinine concentration was measured as described

Table 2. Timing of repeated procedures and tests performed during the follow-up period.

	Time				
Test/Procedure	0 (Baseline)	3 months	6 months	12 months	24 months
Physical examination	X	X	X	X	X
Blood pressure	X	X	X	X	X
Urinalysis[a]	X	X	X	X	X
GFR	X	X	X	X	X
Plasma biochemistry (renal panel)[b]	X	X	X	X	X
Plasma aldosterone	X	X	X	X	X
Plasma renin activity	X	X	X	X	X
Plasma parathormone	X	X	X	X	X
Kidney ultrasound	X	–	X	X	X
Plasma biochemistry (general)[c]	X	–	–	X	X
CBC	X	–	–	X	X
Serum total thyroxine	X	–	–	X	X
U-Na/C	X	–	–	X	X
U-pH	X	–	–	X	X

GFR, glomerular filtration rate; CBC, complete blood count; U-Na/C, urinary sodium/creatinine ratio; U-pH, urinary pH.

[a]Specific gravity, dipstick, sediment, protein/creatinine ratio, albumin.

[b]Concentrations of sodium, potassium, chloride, total carbon dioxide, calcium, phosphate, total protein, urea, creatinine.

[c]Concentrations of albumin, bilirubin, glucose, cholesterol, triglycerides and activities of alanine aminotransferase and alkaline phosphatase.

above in fasted cats before and 5, 30 minutes, 1, 2, 3, 5, and 8 hours after administration of an intravenous bolus of a sterile solution of exogenous creatinine at a nominal dose of 20 mg/kg. Creatinine solution (80 mg/mL) was prepared the day before testing by dissolving anhydrous creatinine[l] in distilled water. The solution was sterilized by filtration through a 0.2-μm filter. Exact individual dose was determined from syringe weight. Plasma data for creatinine concentration were subjected to noncompartmental analysis by a software program.[m] The area under the curve was determined using the trapezoidal rule with extrapolation to infinity. Clearance (ie, GFR) was calculated by dividing the amount of exogenous creatinine administered by the area under the curve.

Blood Pressure Measurement

Systemic arterial blood pressure was measured indirectly in awake cats by the same trained observers (CCS, ET) by use of a Doppler system,[n] as previously described[24] and according to current guidelines.[25] A period of acclimatization was allowed for each cat before measuring blood pressure. Several measurements were performed over 5–10 minutes to obtain an average of 5 values from a stable set of measurements. Cats were considered hypertensive if the average of these 5 arterial blood pressure values was greater than 160 (systolic) and/or 100 (diastolic) mmHg in unstressed animals.[25]

Renal Ultrasonography

Ultrasonography of both kidneys and Doppler measurements of renal RI were obtained in awake cats in dorsal recumbency by the same trained observer (IT). Ultrasonographic aspect, length, width, and height of both kidneys were assessed. Doppler measurements of RI were obtained on a longitudinal section of each kidney for the renal and interlobar artery by use of an ultrasonographic unit[o] with a microconvex 8 MHz probe. For renal artery, the sample gate was placed close to its origin from the abdominal aorta. The image was frozen when Doppler flow pattern was considered adequate. The measurement cursor was then placed on peak systolic velocity and end-diastolic velocity points of each chosen flow pattern. Five successive measurements were performed. An interlobar artery was identified by use of color Doppler. The sample gate was placed on this interlobar artery and the same measurements as for the renal artery performed. Resistive index of the renal and an interlobar artery of the left and right kidney was calculated according to the following formula: RI = (peak systolic velocity − end-diastolic velocity) / peak systolic velocity. When vasoconstriction or kidney damage occurs, vascular resistance and RI increase.[26]

Conventional Echocardiography/Doppler and TDI

Standard transthoracic echocardiography and two-dimensional (2D) color TDI were performed by a single trained operator (VC) in awake standing cats with continuous electrocardiogram monitoring by use of an ultrasonographic unit,[p] equipped with 2 phased-array transducers (4–8 MHz and 4.5–11.5 MHz), as previously described and validated.[27–29]

Statistical Analysis

Time course of body weight was analyzed with a statistical software program[30] by use of the following linear mixed effects model:

$$BW_{i,j,k} = \mu + \alpha day_{i,j,k} + diet_i + cat(diet)_{j,i} + \alpha cat(diet)_{j,i} \times day_{i,j,k} + \alpha diet_i \times day_{i,j,k} + \epsilon_{i,j,k}$$

where $BW_{i,j,k}$ is the weight at $day_{i,j,k}$ of cat j fed with diet i; α is the slope (fixed effect of day); $diet_i$ is the (fixed) differential effect of diet i (i = HSD or CD); $cat(diet)_{j,i}$ is the random effect of cat j fed with diet i; $\alpha\ cat(diet)_{j,i}$ is the random effect of cat j fed with diet i on slope; $\alpha\ diet_i$ is the fixed effect of diet on slope; $\varepsilon_{i,j,k}$ is a residual term of the model.

For other variables, standard repeated measures analyses were performed with another statistical software program[q] by use of the following generalized linear model:

$$Y_{i,j,k} = \mu + diet_i + period_j + diet \times period_{i,j} + cat(diet)_{j,k} + \epsilon_{i,j,k}$$

where $Y_{i,j,k}$ is the value of variable Y for Cat k with diet i in Period j; μ is the general mean effect; $diet_i$ being the effect of diet (i = HSD or CD); $period_j$ is the effect of period (j = 0, 3, 6, 12 or 24 months); diet × $period_{i,j}$ is the diet by period interaction term of the model; $cat(diet)_{j,k}$ is the effect of cat nested in its diet group; $\varepsilon_{i,j,k}$ is the error of the model.

Homogeneity of variance was checked for all variables by visual inspection of residual plots. When heteroscedasticity was

evidenced, statistical analysis was performed on log transformed data and results are expressed as geometric mean and 95% confidence interval. Otherwise, results obtained from native data were used and are expressed as mean ± standard deviation. Compound symmetry, ie, conditional independence in repeated measures analysis, was assumed. A statistical power analysis was performed for 2 primary variables of interest: GFR and systolic blood pressure. Based on 10 cats by group, the statistical analysis was found to be powerful enough to reliably detect a 20% change in these variables. Indeed, using standard deviations of 0.3 mL/min/kg and 15 mmHg and an effect size of 0.4 mL/min/kg and 20 mmHg for GFR and SBP, respectively, statistical power was found to be 85% for both variables. Effect of dietary salt intake on tested variables was primarily assessed through the diet by period interaction term of the model. Whenever a significant diet by period interaction was detected, results of cats from the HSD group were compared with those from the CD group at each period by use of the Student's *t*-test. A value of $P < .05$ was considered significant.

Results

Cats Included

Among the 26 cats initially screened, disease was detected in 5 animals (hyperthyroidism and CKD n = 1, CKD n = 1, hypertrophic cardiomyopathy n = 1, CKD, myocardial hypocontractibility and paroxysmal sinus tachycardia n = 1, chronic liver disease n = 1). One cat was not included because of marked uncooperative behavior. The remaining 20 healthy cats (10 males and 10 females; 10.1 ± 2.4 [5.3–11.7] years; 4.8 ± 0.7 [3.6–6.5] kg) were included in the study.

Color TDI examination was classified as normal for 8 cats, subnormal (presence of regional postsystolic contraction waves for the left ventricular free wall and/or the interventricular septum longitudinal motion wall without any other alteration) for 6 cats and abnormal (mild to moderate regional diastolic alterations with or without postsystolic contraction waves) for 6 cats. Results of randomization process according to GFR value in each of these 3 blocks of cats are shown in Table 3. Sex ratio, age, body weight and all the variables assessed at baseline were similar between groups.

Table 3. Final group allocation for the 20 cats included in the study.

Cat ID Code	TDI Results	Sex	Age (years)	GFR (mL/min/kg)	Group
16	Normal	M	7.0	1.2	C
18	Normal	M	11.6	1.8	HS
7	Normal	M	11.5	1.8	C
13	Normal	F	7.1	1.8	HS
25	Normal	M	11.5	2.1	HS
23	Normal	F	10.9	2.1	C
14	Normal	F	11.5	2.5	HS
5	Normal	F	5.3	2.5	C
9	Subnormal	F	11.6	1.7	HS
21	Subnormal	F	11.6	1.9	C
4	Subnormal	M	6.3	1.9	C
6	Subnormal	F	5.3	2.0	HS
19	Subnormal	M	11.7	2.2	C
10	Subnormal	F	11.5	2.3	HS
8	Abnormal	M	10.9	1.6	C
17	Abnormal	M	11.6	1.6	HS
12	Abnormal	M	11.6	1.7	HS
24	Abnormal	F	11.0	1.8	C
11	Abnormal	M	11.6	1.9	HS
22	Abnormal	F	11.6	2.1	C

GFR, glomerular filtration rate; M, male; F, female; C, control group; HS, high salt group; TDI, tissue Doppler imaging; subnormal, presence of regional postsystolic contraction waves for the left ventricular free wall and/or the interventricular septum longitudinal motion wall without any other alteration; abnormal, mild to moderate regional diastolic alterations with or without postsystolic contraction waves.

Follow-up

All cats completed the first 12 month period and 16/20 the 24 month follow-up. Four cats (2 from each group) were removed from the study between 12 and 24 months after initiation of the diet test period. Cats 11 and 18 died suddenly at 13 and 21 months, respectively. Full necropsy revealed no obvious cause and intracranial meningioma, respectively. Cat 24 was euthanized at 13 months because of development of an aggressive fibrosarcoma and cat 16 was removed from the study at 17 months because of occurrence of diabetes mellitus. All data obtained from these 4 cats were included in the statistical analysis. All 16 other cats remained healthy throughout the 24 months period of follow-up. No cat developed clinical hypertension or had a blood pressure measure >160 (systolic) or >100 (diastolic) mmHg at any time point during the follow-up.

Mean caloric intake over the study period was 46 ± 11 kcal ME/kg/d for HSD group and 48 ± 6 kcal ME/kg/d for CD group. This represents an average dietary sodium intake of 144 ± 36 and 45 ± 5 mg/kg in HSD and CD group, respectively. A mild but significant ($P = .043$) decrease in body weight of approximately 120 g/y was similarly observed in both diet groups during the study period (from 4.8 ± 0.7 kg on the 1st day of the diet test period to 4.5 ± 0.8 kg after 2 years in the whole group).

Time Course of Variables

A significant diet by period interaction over the study period was observed for USG ($P = .014$) and UPC ($P = .022$), plasma aldosterone ($P = .006$), U-Na/C ($P < .001$), plasma albumin ($P = .005$), and alanine aminotransferase ($P = .028$). When compared at each period, only plasma albumin (Table 6) and USG (Table 4) were significantly different between groups at individual time points (baseline and 3 months, respectively) whereas plasma aldosterone (Table 4) and U-Na/C (Table 6) were persistently altered by dietary salt intake. Other variables were not affected by the diet (Table 4–6).

Table 4. Effects of dietary salt content on selected renal variables and blood pressure over 24 months.

Variable (unit)	0		3 months		6 months		12 months		24 months	
	C	HS	C	HS	C	HS	C	HS	C	HS
USG	1.041 ± 0.008	1.047 ± 0.011	**1.043 ± 0.010**	**1.034 ± 0.006**	1.041 ± 0.011	1.037 ± 0.008	1.044 ± 0.012	1.038 ± 0.011	1.033 ± 0.013	1.034 ± 0.008
UPC	0.27 ± 0.10	0.22 ± 0.08	0.22 ± 0.06	0.22 ± 0.08	0.13 ± 0.05	0.17 ± 0.07	0.20 ± 0.07	0.25 ± 0.09	0.19 ± 0.06	0.16 ± 0.07
U-aldosterone (pg/mL)[a]	991 [546–1800]	846 [521–1373]	1106 [554–2210]	818 [465–1439]	1092 [582–2050]	809 [527–1243]	1427 [497–4099]	839 [184–3818]	934 [190–4592]	487 [171–1383]
U-albumine (μg/mL)[a]	15.8 [2.1–119.4]	16.4 [4.0–67.9]	17.1 [2.9–102.7]	9.4 [2.0–43.8]	9.4 [4.3–20.4]	8.1 [2.4–26.9]	20.7 [5.2–81.9]	18.6 [6.7–52.0]	33.4 [6.3–178.0]	35.5 [6.3–199.8]
SABP (mmHg)	149.1 ± 6.4	153.0 ± 3.3	144.5 ± 8.8	142.3 ± 15.1	153.0 ± 5.0	152.0 ± 3.9	141.9 ± 14.8	147.7 ± 6.8	142.6 ± 8.9	143.3 ± 8.8
DABP (mmHg)	78.2 ± 8.2	78.1 ± 10.8	68.5 ± 11.2	66.8 ± 10.9	68.1 ± 10.4	67.5 ± 7.2	67.2 ± 11.2	73.3 ± 11.4	69.5 ± 12.5	71.0 ± 8.3
GFR (mL/min/kg)	1.9 ± 0.3	2.0 ± 0.3	1.9 ± 0.2	1.9 ± 0.3	1.7 ± 0.2	1.5 ± 0.3	2.0 ± 0.3	1.7 ± 0.4	1.7 ± 0.3	1.6 ± 0.3
P-urea (mg/dL)	49 ± 7	51 ± 9	49 ± 4	45 ± 8	47 ± 8	48 ± 7	41 ± 7	41 ± 7	50 ± 9	44 ± 9
P-creatinine (mg/dL)	1.4 ± 0.1	1.5 ± 0.3	1.4 ± 0.1	1.6 ± 0.3	1.5 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.3	1.3 ± 0.1	1.5 ± 0.3
P-sodium (mEq/L)	153 ± 2	153 ± 4	152 ± 2	153 ± 2	150 ± 2	150 ± 2	154 ± 1	155 ± 1	152 ± 2	152 ± 1
P-potassium (mEq/L)	4.2 ± 0.6	4.3 ± 0.4	4.2 ± 0.7	4.5 ± 0.5	4.3 ± 0.6	4.4 ± 0.3	3.9 ± 0.6	3.8 ± 0.2	4.1 ± 0.6	4.3 ± 0.3
P-chloride (mEq/L)	118 ± 2	119 ± 2	119 ± 2	119 ± 2	119 ± 2	118 ± 2	116 ± 2	117 ± 1	118 ± 2	117 ± 2
P-total CO_2 (mEq/L)	20 ± 2	19 ± 2	19 ± 1	19 ± 1	21 ± 1	21 ± 1	21 ± 2	20 ± 1	19 ± 1	19 ± 1
P-calcium (mg/dL)	9.9 ± 0.3	9.8 ± 0.5	10.2 ± 0.4	10.1 ± 0.4	10.3 ± 0.3	10.3 ± 0.4	10.0 ± 0.4	10.0 ± 0.3	10.3 ± 0.4	10.5 ± 0.4
P-phosphate (mg/dL)	4.1 ± 0.6	4.0 ± 0.8	4.4 ± 0.7	4.5 ± 0.7	4.3 ± 0.6	4.2 ± 0.6	4.2 ± 0.4	4.4 ± 0.5	4.2 ± 0.5	4.5 ± 0.5
P-proteins (g/dL)	7.4 ± 0.5	7.1 ± 0.3	7.9 ± 0.6	7.7 ± 0.4	8.0 ± 0.7	8.0 ± 0.5	7.0 ± 0.5	6.9 ± 0.4	7.8 ± 0.7	7.5 ± 0.4
P-aldosterone (pg/mL)[b]	70.3 ± 39.9	64.7 ± 50.0	**133.4 ± 93.2**	**55.3 ± 49.6**	**90.0 ± 48.6**	**28.6 ± 22.7**	**153.0 ± 73.2**	**78.9 ± 44.5**	**62.1 ± 34.3**	**19.6 ± 15.3**
P-RA (ng/mL/h)[ab]	15.9 [1.6–155.7]	15.2 [4.3–52.9]	11.4 [1.7–75.1]	8.1 [1.9–34.1]	10.4 [2.0–55.0]	5.9 [2.2–15.6]	13.2 [3.0–57.5]	7.9 [1.6–39.8]	1.2 [0.2–7.0]	0.8 [0.2–4.0]
P-PTH (pg/mL)[c]	7.8 ± 3.1	12.4 ± 11.9	7.7 ± 2.6	13.6 ± 11.1	7.3 ± 2.1	9.0 ± 6.5	6.6 ± 2.2	9.0 ± 5.8	8.5 ± 2.2	10.4 ± 8.6

USG, urinary specific gravity; UPC, urine protein/creatinine ratio; U-, urine; SABP, systolic arterial blood pressure; DABP, diastolic arterial blood pressure; GFR, glomerular filtration rate; P-, plasma; CO_2, carbon dioxide; RA, renin activity, PTH, parathyroid hormone; C, control group; HS, high salt group. For variables in bold, a statistically significant diet by period interaction was found. For these variables, values in bold were statistically different between groups at corresponding period(s).

Samples with P-PTH<5.2 pg/mL were arbitrarily attributed a value of 5.2 for statistical analysis.

[a]Data were log transformed for statistical analysis and are thus presented in the table as geometric mean [95% confidence interval] instead of arithmetic mean ± standard deviation.

[b]Reference intervals (RI) could not be provided as they are highly dependent on sodium intake, which was controlled in this study.

[c]RI: <5.2–17.3 pg/mL, 5.2 pg/mL is the limit of detection of the assay, some normal cats are below this limit.[20]

Table 5. Effects of dietary salt content on renal resistive indices over 24 months.

Resistive Index	0		6 months		12 months		24 months	
	C	HS	C	HS	C	HS	C	HS
LRA	0.69 ± 0.02	0.68 ± 0.02	0.71 ± 0.04	0.71 ± 0.05	0.68 ± 0.07	0.70 ± 0.07	0.64 ± 0.03	0.64 ± 0.04
LIA	0.68 ± 0.04	0.67 ± 0.04	0.68 ± 0.04	0.66 ± 0.06	0.66 ± 0.04	0.64 ± 0.03	0.64 ± 0.03	0.65 ± 0.05
RRA	0.68 ± 0.02	0.67 ± 0.04	0.72 ± 0.04	0.70 ± 0.06	0.70 ± 0.05	0.67 ± 0.06	0.65 ± 0.03	0.63 ± 0.02
RIA	0.68 ± 0.03	0.68 ± 0.03	0.67 ± 0.04	0.67 ± 0.05	0.66 ± 0.04	0.65 ± 0.05	0.65 ± 0.02	0.64 ± 0.04

LRA, left renal artery; LIA, left interlobar artery; RRA, right renal artery; RIA, right interlobar artery; C, control group; HS, high salt group.

Discussion

The main findings of this study were that high dietary salt intake over 24 months had no effects on renal function, blood pressure, and other health parameters in older cats presumed to be at risk for salt-associated morbidity. A mild decrease in body weight was similarly observed in both diet groups. Underfeeding from inappropriate energy requirement determination cannot be responsible for the weight loss observed over the study period as all cats consistently ate less than the amount of food offered. For the same reason, this amount was not individually adjusted during the study period in spite of the mild decrease in body weight observed. This weight loss might have been due to a reduction in muscle mass with increasing age.[31] However, this issue was not specifically addressed and no conclusion can be drawn on weight loss determinism over the study period. Two cats were removed from the study and 2 died during the follow-up period. Full necropsy and post mortem examination were performed and no evidence of renal damage or systemic hypertension was found in any of these cats. The results presented here are consistent with those of other studies performed to date[3,11,12,c] and with current nutritional guidelines.[32] Indeed, cats appear to tolerate reasonably high levels of dietary salt as long as unlimited amounts of water are available.[32] Accordingly, a safe upper limit of dietary sodium in adult cats has not been determined to date and is reported to be >3.8 g/Mcal.[32]

Age-related cardiac functional alterations occur in cats.[33] Adverse effects of such abnormalities on renal function could have been a confounding factor. Azotemia, for example, is a common finding in cats with hypertrophic cardiomyopathy.[34] This was the reason for randomly allocating the cats to diet groups according to baseline TDI and GFR results. The cats in each diet group were indeed well matched with regard to renal function, cardiac structure/function, sex, age, body weight, and all variables assessed at baseline except plasma albumin. However, the difference in plasma albumin observed was negligible and could not have biased the results of the study.

Spot USG was found to be lower in the HSD group at 3 months only. No difference according to salt content of the diet was observed in a similar study that also used clinical urinalysis.[12]In contrast, whenever urine collection was performed over 24 hours or more, USG proved to be consistently altered by dietary salt content.[2–4] Spot urine samples may therefore be inappropriate specimens for reliable assessment of urine dilution in response to an increase in dietary salt load. Higher salt intake was expectedly associated with significantly higher sodium excretion. U-Na/C was actually about 3 times higher in cats fed the HSD. Interestingly, no difference in urinary pH (U-pH) was observed between HSD and CD groups in our study. This result is in accordance with those of previous studies in cats, suggesting that U-pH is unaffected by increased dietary salt intake up to the level used in our study.[4,a,b] In contrast, an effect of dietary salt intake on the renin angiotensin aldosterone system (RAAS) was expected. This hormonal system is pivotal for sodium homeostasis by adjusting renal handling of sodium to sodium input. No effect of salt intake on urinary aldosterone and plasma renin activity could be evidenced yet. However, urinary aldosterone proved to be a less accurate marker of long-term aldosterone secretion in the cat than in other species[19] and plasma renin activity is reportedly less sensitive to salt intake than plasma aldosterone.[11] Actually, plasma aldosterone proved to be 1.4–3 times higher in the control than in the high salt group (Table 4).

Both systolic and diastolic blood pressure were unaffected by salt intake over 2 years in the present study. These results are consistent with all the other studies of shorter duration performed in cats.[3,4,11,12] Actually, current evidence suggests that neither blood pressure nor hypertension is salt sensitive in cats. It is rather likely that, in this species, increased vascular tone may be of particular importance and relative hyperaldosteronism could be one contributor in the determinism of systemic arterial hypertension.[35] Accordingly, salt restriction is currently not recommended in hypertensive cats.[25]

To date, only one study in cats concluded that high salt intake was associated with a progressive decline in renal function.[4] This statement was based on the observation of significantly higher slopes of initial versus final serum creatinine, urea, or phosphate concentrations during higher salt intake period, in a 12-week randomized cross-over design. The biological significance of these results and the reasons why the conclusions of this study differed from all others

Table 6. Effects of dietary salt content on other variables over 24 months.

	0		12 months		24 months	
Variable (unit)	C	HS	C	HS	C	HS
U-Na/C[a]	14.9 [12.1–18.2]	14.1 [11.5–17.3]	**6.4 [4.8–8.5]**	**23.9 [20.4–27.9]**	**7.0 [4.4–11.1]**	**24.1 [18.8–30.9]**
U-pH	6.58 ± 0.22	6.53 ± 0.14	6.47 ± 0.24	6.37 ± 0.29	6.10 ± 0.17	6.19 ± 0.30
Ht (%)	42.5 ± 3.0	38.8 ± 4.6	33.0 ± 4.1	30.7 ± 6.4	33.3 ± 4.4	34.5 ± 3.0
Hb (g/dL)	13.3 ± 0.8	12.3 ± 1.4	10.1 ± 1.3	9.4 ± 1.3	10.4 ± 1.4	10.8 ± 1.0
WBC (10^9/L)[a]	10.2 [6.1–17.2]	10.0 [7.1–14.1]	11.8 [5.6–24.9]	10.9 [7.2–16.3]	12.8 [5.8–28.1]	12.7 [7.4–21.9]
PLT (10^9/L)	473 ± 159	508 ± 176	309 ± 211	402 ± 206	487 ± 162	440 ± 188
GNN (/μL)[a]	5401 [2090–13960]	6568 [4082–10567]	6490 [2139–19697]	5552 [3071–10036]	7517 [2649–21332]	7906 [3980–15706]
GNE (/μL)[a]	290 [45–1863]	345 [102–1165]	618 [155–2467]	507 [78–3308]	611 [132–2835]	531 [152–1860]
L (/μL)[a]	3498 [1633–7491]	2508 [1036–6072]	3687 [1659–8195]	4076 [1851–8976]	3311 [1383–7929]	3510 [1617–7617]
M (/μL)[a]	325 [66–1592]	307 [61–1538]	243 [41–1427]	206 [60–708]	631 [153–2601]	380 [190–760]
P-Glucose (mg/dL)	101 ± 18	86 ± 11	85 ± 7	95 ± 40	70 ± 11	77 ± 7
P-Cholesterol (mg/dL)	186 ± 47	186 ± 35	213 ± 43	213 ± 58	225 ± 58	256 ± 81
P-Triglycérides (mg/dL)	35 ± 14	26 ± 18	50 ± 11	44 ± 7	48 ± 12	48 ± 16
P-Albumin (g/dL)	**3.4 ± 0.2**	**3.3 ± 0.2**	3.1 ± 0.1	3.0 ± 0.2	3.2 ± 0.2	3.3 ± 0.3
P-ALT (U/L)	63 ± 13	75 ± 29	60 ± 22	56 ± 32	54 ± 16	78 ± 34
P-ALP (U/L)	51 ± 11	55 ± 7	54 ± 12	60 ± 13	60 ± 26	69 ± 14
P-Bilirubin (mg/dL)	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.0	0.5 ± 0.1	0.5 ± 0.1
S-total T4 (μg/dL)	2.7 ± 0.3	2.7 ± 0.6	2.1 ± 0.3	2.1 ± 0.4	2.1 ± 0.4	2.1 ± 0.3

U-Na/C, urinary sodium/creatinine ratio; U-pH, urinary pH; Ht, hematocrit; Hb, hemoglobin; WBC, white blood cells; PLT, platelets; GNN, neutrophils; GNE, eosinophils; L, lymphocytes; M, monocytes; P-, plasma; ALT, alanine aminotranferase; ALP, alkaline phosphatase; S-, serum; T4, thyroxin; C, control group; HS, high salt group. For variables in bold, a statistically significant diet by period interaction was found. For these variables, values in bold were statistically different between groups at corresponding period(s).

[a]Data were log transformed for statistical analysis and are thus presented in the table as geometric mean [95% confidence interval] instead of arithmetic mean ± standard deviation.

remain unclear. Indeed, no increase in creatinine, urea and phosphate concentrations associated with high salt intake over similar or longer durations was observed in our study and all others performed in healthy cats.[3,4,11,12,c] One distinct advantage of the study presented here is that renal function was directly assessed through GFR measurement, which is considered the best indicator of overall renal function.[36] GFR was unaffected by dietary salt intake over 24 months in our study as well as in other studies of shorter duration.[11,c] Moreover, a difference in UPC according to salt intake was never evidenced in the study reported here. Similar results over 6 months have been previously published.[12] This is of particular significance as proteinuria is considered to be an early marker of CKD[37,38] and has been shown to be a predictor of the development of azotemia in geriatric cats[39] and a predictor of progressive deterioration of renal function in azotemic cats.[40]

It has also been shown that PTH could be elevated in cats with CKD before the development of azotemia.[41] Plasma PTH concentration was repeatedly measured in the cats of our study and was not affected by salt intake. Lastly, intrarenal blood flow impedance, assessed by Doppler ultrasonography and expressed as RI, has been used to assist in the diagnosis of kidney disease in several species including cats.[26] Renal RI were found to be higher in cats with renal disease than in normal cats.[26,42] No difference according to dietary salt intake in renal and interlobar arteries RI repeatedly measured over 24 months was found in the cats of the present study. Taken together, these results strongly suggest that increasing dietary salt content of a dry expanded diet up to 3.1 g/Mcal did not induce any kidney damage or dysfunction over 2 years in healthy aged cats.

Others have assessed the effects of dietary salt intake in cats with reduced renal mass. Effects of various amounts of dietary salt given for 1 week in cats with experimentally induced CKD were examined in 1 study.[11] Blood pressure and GFR were not altered by high salt feeding. Moreover, inappropriate kaliuresis and stimulation of RAAS occurred on the lowest salt intake and were suppressed by salt supplementation. A similar trend was observed in our healthy aged cats over the 2-year study although level of RASS activity in cats in the CD group would not be considered inappropriate and this was not associated with hypokalemia. Hypokalemia and RAAS activation could contribute to the progression of CKD.[43,44] Moreover, it has been established that elevation of systemic blood pressure, proteinuria and RAAS activation may be responsible for ongoing kidney damage in cats with experimentally induced CKD.[45] The present study and other published reports failed to find an association between increased dietary salt and those pathologic processes.

In conclusion, this study confirms, over a longer period and in older cats likely to be at higher renal risk than younger healthy cats, previous reports indicating that increased salt intake does not appear to induce deleterious effects on feline renal function. These results cannot be extrapolated to cats with spontaneous CKD.

Footnotes

[a] Biourge V, Devois C, Morice G, et al. Increased dietary NaCl significantly increase urine volume but does not increase urinary calcium oxalate relative supersaturation in healthy cats. J Vet Intern Med 2001;15:301 (abstract)

[b] Xu H, Laflamme DP, Bartges JW, et al. Effect of dietary sodium on urine characteristics in healthy adult cats. J Vet Intern Med 2006;20:738 (abstract)

[c] Cowgill LD, Segev G, Bandt C, et al. Effects of dietary salt intake on body fluid volume and renal function in healthy cats. J Vet Intern Med 2007;21:600 (abstract)

[d] Vet Cat Neutered, Young Male, Royal Canin SAS, Aimargues, France

[e] Veterinary Diet, Feline Urinary High Dilution, Royal Canin SAS

[f] Guide for Care and Use of Laboratory Animals, Institute of Laboratory Animals Resources, Commission on Life Sciences, National Research Council. Washington, D.C.: The National Academy Press; 1996

[g] Vitros 250 chemistry system, Ortho-Clinical Diagnostics, Raritan, NJ

[h] Chemiluminescent Immulite 2000, DPC, Los Angeles, CA

[i] Gammacoat plasma renin activity, Diasorin, Stillwater, MN

[j] Coat-a-count aldosterone, Siemens Medical Solutions diagnostics, Los Angeles, CA

[k] Duo PTH kit, Scantibodies Laboratory, Inc, Santee, CA

[l] Anhydrous creatinine, Sigma Chemical Co, St Louis, MO

[m] WinNonlin version 5.2 Pharsight, Mountain View, CA

[n] 811-BL Parks Medical Electronics Inc, Aloha, OR

[o] Biosound MyLab30 Universal Medical Systems Inc, Bedford Hills, NY

[p] Vivid 7 dimension, General Electric medical system, Waukesha, WI

[q] Systat version 8.0, SPSS Inc, Chicago, IL

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