Effects of Sodium Chloride on Selected Parameters in Cats*

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*Supported by a grant from the Science and Technology Center, Hill’s Pet Nutrition, Inc., Topeka, Kansas. Address correspondence to Dr. Jewell: telephone, 785-286-8089; email, dennis_jewell@hillspet.com.
increase the risk of hypertension in humans and animals.\textsuperscript{7,8} Hypertension is a well-established cause of increased morbidity and mortality related to end-organ damage. Pet populations with increased risk of hypertension include those with advanced age, renal disease, cardiac disease, or obesity. The association between high NaCl intake and hypertension is widely recognized. However, high NaCl intake may be detrimental to health without any measurable increase in blood pressure.\textsuperscript{9–11} NaCl restriction has, therefore, been advocated in human and veterinary medicine to reduce the risk of hypertension, heart disease, stroke, osteoporosis, and calcium oxalate urolithiasis. Recently, the validity of these widespread recommendations as public health policy has been challenged critically.\textsuperscript{12} Data supporting the correlation between high dietary NaCl intake and health disorders are predominantly from epidemiologic studies, animal models, and poorly designed human trials.

In veterinary medicine, limited evidence exists supporting NaCl restriction in the general dog and cat population. Studies are available that show some benefit of NaCl restriction in disease states associated with NaCl retention or hypertension.\textsuperscript{12–14} Because most pets are not critically evaluated for hypertension, controlling NaCl excess has been recommended in foods designed for pets.\textsuperscript{15,16} Additionally, high NaCl intake promotes excess urine calcium excretion and calcium oxalate urolith formation in humans.\textsuperscript{17} Studies in cats have found that, unlike in people and rats, healthy cats probably do not excrete increased amounts of urinary calcium in response to higher dietary NaCl intake.\textsuperscript{4} Increased dietary NaCl intake stimulates water intake, increases the volume of urine output, decreases urine calcium concentration, and decreases the risk of urolithiasis.\textsuperscript{4,5} Furthermore, in these short-term (2 weeks or less) feeding trials, increased NaCl intake did not alter blood pressure or measures of general health.

Despite the evidence from short-term studies that increased NaCl intake in cats appears safe and efficacious for increasing water intake and decreasing urine mineral concentration, long-term feeding trials are needed. As in humans, rats, and dogs, a subset of cats may be classified as “salt sensitive” (i.e., readily develop adverse effects in response to NaCl feeding).\textsuperscript{16} Animal models may not respond to dietary salt in a fashion similar to cats with naturally occurring renal function loss; furthermore, epidemiologic relationships cannot be used to show causality. Therefore, to fully evaluate the impact of supplemental NaCl feeding on cat health, it is important to test cats at risk for adverse effects in response to high dietary NaCl intake.

The primary objective of this study was to determine the effect of high NaCl intake on general health, renal function, hypertension, calcium balance, and cardiac function in healthy, obese, geriatric, and renal function–impaired cats. The secondary objectives were to compare the impact of high and low dietary NaCl intake on water intake and urine volume
and to evaluate the long-term improvement in LUTD risk reduction associated with NaCl-induced diuresis.

\section*{MATERIALS AND METHODS}

\subsection*{Foods}

The foods used in this study were complete and balanced expanded dry foods suitable for long-term maintenance of adult cats. The ingredient composition of the foods was identical except for the levels of sodium and chloride (Table 1). The low NaCl (LSC) control food contained 0.35% sodium and 0.7% chloride (as fed); the high NaCl (HSC) test food contained 1.1% sodium and 2.06% chloride (as fed).

\subsection*{Study Design}

The study used 36 cats, which were blocked by physiologic status into four groups:

- Healthy ($n = 10$): 2 to 6 years of age with a body condition score of 3/5
- Obese ($n = 10$): Greater than 30% body fat
- Aged ($n = 10$): Older than 10 years
- Renal insufficiency ($n = 6$): Serum urea nitrogen above 35 mg/dl and creatinine above 1.5 mg/dl

Cats from each block were randomly assigned to one of two dietary treatments. Cats were fed their initial assigned food (LSC or HSC) for 12 weeks and then switched to the opposite food for an additional 12 weeks. This design allowed each animal to be present in both dietary groups and allowed 12 weeks for each cat to respond to each dietary treatment. If the assumption that a cat did not reach equilibrium after 12 weeks is not valid, then type II error (i.e., the chance of saying there is no difference when a difference exists) increases; however, type I error (i.e., the chance of saying a difference exists when there is no difference) does not increase. The study plan was approved by the Institutional Animal Care and Use Committee at Hill’s Science and Technology Center. Animals were housed and cared for in accordance with the principles outlined in the National Institutes of Health \textit{Guide for the Care and Use of Laboratory Animals}.\textsuperscript{18}

\begin{table}
\caption{Experimental Cat Food Chemical Composition (\% as fed)\textsuperscript{a}}
\begin{tabular}{|l|c|c|}
\hline
\textbf{Nutrient} & \textbf{LSC Control Diet} & \textbf{HSC Test Diet} \\
\hline
Dry matter & 93.5 & 92.7 \\
Protein & 31.9 & 31.7 \\
Fat & 16.2 & 15.6 \\
Crude fiber & 1.0 & 0.9 \\
Ash & 5.1 & 7.2 \\
Calcium & 0.76 & 0.79 \\
Phosphorus & 0.69 & 0.69 \\
Potassium & 0.87 & 0.87 \\
Sodium & 0.35 & 1.10 \\
Chloride & 0.7 & 2.06 \\
Magnesium & 0.07 & 0.07 \\
Calculated ME & 387 & 374 \\
\hline
\end{tabular}
\textsuperscript{a}Food analysis performed by Woodson-Tenet Laboratories, Des Moines, IA.

HSC = high sodium chloride; LSC = low sodium chloride; ME = metabolizable energy (kcal/100 g), calculated as \([8.5 \times \text{fat concentration} + (3.5 \times \text{protein concentration}) + (3.5 \times \text{nitrogen free extract concentration})]\).
\end{table}

\subsection*{Data Collection}

Baseline body weight and food and water intake were measured the week immediately preceding day 0 of the study. Thereafter, body weights were measured weekly. Water was provided free choice in water bottles with sipper tubes; intake was adjusted for spillage and recorded daily. Average intake was calculated
during weeks 1, 12, and 24. Cats were offered food free choice unless weight gain exceeded 10% of initial body weight. Cats with excessive weight gain were offered sufficient food to maintain stable body weight for the remainder of the study.

Blood samples were collected for complete blood count (Dell-Dyn, Abbott, Santa Clara, CA) and serum biochemistry (Hitachi 912 Autoanalyser, Boehringer Mannheim, Indianapolis, IN) analyses at weeks 0, 12, and 24 of the study. Serum total thyroxine (T\textsubscript{4}) was evaluated at baseline (week 0) in all cats to screen for hyperthyroidism (Antech Diagnostics, Memphis, TN).

Forty-eight-hour urine samples were collected through individual urine collection systems on days 6 and 7 of the collection week. Collections were obtained on weeks 0, 12, and 24. Urine samples were preserved by thymol (Sigma, St. Louis, MO), which was added to the collection system. Urine from day 6 was refrigerated and combined with the day 7 collection. Urine volume, pH, and specific gravity (SG) of the 48-hour urine samples were determined after thorough mixing. Urine calcium was measured by inductively coupled electrophoresis (Perkin Elmer P400, Norwalk, CT), whereas urine creatinine was determined using an autoanalyser (Hitachi 912).

Urinary fractional excretion (FE) of calcium was also determined. FE, expressed as a percentage, was calculated using the formula in the box to the left.

Systolic, diastolic, and mean arterial pressure were measured in cats at rest by indirect oscillometry (Dinamap 8300, Critikon, Tampa, FL, and Cardell 930IV, CAS Medical Systems, Branford, CT) using the ventral tail artery (most cases) or cranial metacarpal artery. Cats were evaluated at the same time each day, in a quiet room, following a 10-minute adaptation period and before any other testing or restraint. At least 48 hours were allowed after sedation or anesthesia before measuring blood pressure. Values were assessed at baseline and weeks 6, 12, 18, and 24. Measurements were taken on two separate days for each time assessment. Five consecutive pressure readings were recorded on each day of measurement. A single investigator (C. A. K.) evaluated all pressures at the end of the study in a masked fashion. Values were discarded if the heart rate was below 100 bpm, systolic values were less than 60 mm Hg, or there was clear discordance between a single measure and the remaining values. The final blood pressure value represented the mean of all remaining values for the two collection days within the week.

Body composition and bone mineral density were assessed using dual x-ray absorptiometry (DXA Hologic QDR 4500 Elite, Hologic, Waltham, MA) in cats at time 0 and weeks 12 and 24. Short-term immobilization for scans was induced with a combination of 100 mg/ml ketamine HCl (Phoenix Scientific, St. Joseph, MO) and 5 mg/ml diazepam (Abbott Laboratories, North Chicago, Il) mixed 1:1 and given IV at 1 ml/10 kg.

A board-certified radiologist provided cardiac ultrasonographic examination at weeks 0, 12, and 24. Echocardiography was conducted using a 7.5-MHz convex scanner (Ausonics Im-
pact VFI, Ausonic, New Berlin, WI, or Apogee CX 200, Interspec ATL, Ambler, PA). Scans included measures of intraventricular septum end-systole, intraventricular septum end-diastole, left ventricular end diameter at diastole (LVEDD), left ventricular end diameter at systole (LVESD), heart rate, fractional shortening (FS), left atrium (LA), aortic outflow (AO), and LA:AO ratio. Seven cats required sedation (1:1 ketamine:valium at 1 ml/10 kg IV at each ultrasonographic procedure).

A fundic examination for signs of hypertension (retinal hemorrhage, edema, detachment, and vessel tortuosity) was performed by indirect ophthalmoscopy at weeks 0, 12, and 24. Examinations were performed by one of two observers. Suspected retinal detachments were evaluated by a board-certified ophthalmologist.

Blood was collected for plasma antidiuretic hormone, renin activity, and aldosterone (Michigan State University Endocrinology Laboratory, Ann Arbor, MI) at weeks 0, 12, and 24. Whole blood (5 ml) was collected using a heparin-flushed syringe. Samples were immediately transferred to collection tubes containing aprotinin (Sigma; 0.2 trypsin inhibitor unit/ml of blood); within 30 minutes, plasma or serum was separated by centrifugation (2,060 ×g for 10 minutes) and stored at −70°C until analysis.

Statistical Analysis

All variables were analyzed using the general linear model system of SAS (SAS/STAT 2000 User’s Guide Release 6.12, Cary, NC). Food intake, water intake, body weight, body composition, cardiographic variables, urine response, and hormonal response were tested for an effect of treatment, time, group, and all interactions. Data were evaluated as a crossover design, with time 0 and after 12 weeks used as the baseline data for periods 1 and 2, respectively. To evaluate the effect of dietary NaCl on cats with preexisting high blood pressure, cats with systolic blood pressure consistent with hypertension were identified and evaluated by chi-square analysis. The effect of the HSC diet on renal function was evaluated through an analysis of the change in the relationships between the original concentration of serum creatinine (time 0) and the response variables that were measured at the end of each food consumption (i.e., FE of calcium and the concentrations of serum urea nitrogen, serum creatinine, and serum phosphorus). This evaluation assessed the effect of food on renal function. If a cat was negatively influenced by a food, the circulating concentrations would be expected to increase; conversely, a decreased concentration of these parameters would indicate a positive effect on renal function. This analysis allows an estimate of the change in these parameters after the variation associated with initial creatinine concentration is removed, as well as an estimate of the effect of the initial concentration of creatinine on the subsequent effect of the food. FE of calcium is not a direct indicator of renal function; however, this analysis is similar to that of the circulating parameters in that it quantifies the effect of the HSC food versus that of the LSC food after removal of the variation associated with the initial concentration of creatinine. It also provides an estimate of the effect of the initial concentration of creatinine on the subsequent effect of either the HSC or LSC food on FE of calcium.

This analysis used food, period, group, and the interactions of food with group, food with period, and food with initial creatinine concentration as factors. The interaction term of food with initial creatinine concentration was used to evaluate the effect of food on the relationship between initial creatinine concentration and the listed response variables after 12 weeks of consuming either the HSC or LSC food.
RESULTS

Thirty-four cats completed the study. Two cats from the impaired renal function group were removed during the course of the study because of reduced food intake. Data for these cats were included in the statistical evaluation to the point of removal: One cat was removed after completing the LSC feeding period and

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### TABLE 2. Effect of Dietary Sodium and Physiologic Group on Food and Water Intake, Body Composition, Heart Function, and Circulating and Urinary Parameters in Cats

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>LSC</th>
<th>HSC</th>
<th>SD</th>
<th>Food</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intake</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily water intake (ml)</td>
<td>88</td>
<td>102</td>
<td>17.6</td>
<td>P &lt; .01</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Daily food intake (g)</td>
<td>55.6</td>
<td>53.4</td>
<td>8.8</td>
<td>NSD</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final body weight (kg)</td>
<td>5.1</td>
<td>5</td>
<td>1.4</td>
<td>NSD</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Bone mineral content (g)</td>
<td>111</td>
<td>117</td>
<td>20.5</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Bone mineral density (g/cm²)</td>
<td>0.28</td>
<td>0.28</td>
<td>0.03</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td><strong>Cardiographic variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>117</td>
<td>112</td>
<td>10.8</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>145</td>
<td>138</td>
<td>13.7</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>98</td>
<td>93</td>
<td>11.2</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>1.4</td>
<td>1.4</td>
<td>0.19</td>
<td>NSD</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>LVEDS (cm)</td>
<td>0.74</td>
<td>0.70</td>
<td>0.17</td>
<td>NSD</td>
<td>P = .05</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>47</td>
<td>50</td>
<td>6.1</td>
<td>P &lt; .05</td>
<td>NSD</td>
</tr>
<tr>
<td><strong>Urine response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine volume (ml/48 hr)</td>
<td>124</td>
<td>165</td>
<td>66.1</td>
<td>P &lt; .05</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>1.049</td>
<td>1.039</td>
<td>0.007</td>
<td>P &lt; .05</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.7</td>
<td>6.9</td>
<td>0.37</td>
<td>NSD</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td><strong>Hormonal response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>360</td>
<td>264</td>
<td>190</td>
<td>NSD</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>Plasma antidiuretic hormone (pmol/L)</td>
<td>9.5</td>
<td>17.7</td>
<td>15.5</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.7</td>
<td>6.9</td>
<td>0.37</td>
<td>NSD</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td><strong>Circulating analyte response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea nitrogen (mg/dl)</td>
<td>25.2</td>
<td>28.1</td>
<td>4.8</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>4.80</td>
<td>5.39</td>
<td>0.93</td>
<td>P &lt; .05</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.23</td>
<td>1.41</td>
<td>0.23</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Fractional excretion of calcium (%)</td>
<td>0.0030</td>
<td>0.0058</td>
<td>.0030</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
</tr>
</tbody>
</table>

*Group means at week 12.

*Combined physiologic groups.

*Square root of pooled estimate of inherent variation.

*Effect of low vs. high sodium.

*Effect of physiologic group of cats (healthy, obese, aged, renal-impaired).

HSC = high sodium chloride; LSC = low sodium chloride; LVEDD = left ventricular end diameter at diastole; LVEDS = left ventricular end diameter at systole; NSD = no significant difference (P > .05).
starting on the HSC food, whereas the other cat was removed after initially starting on the HSC food. Overall conclusions would not have been changed if only the cats completing all sections of the study had been used for analysis.

**Food Intake, Water Intake, and Body Weight**

Food intake and body weights were not affected by dietary treatment but were influenced by physiologic group (Table 2). The obese cats were significantly (group effect \( P < .05 \)) heavier and ate more than the healthy, aged, and renal function–impaired cats. Food intake was not different between healthy cats and cats with impaired renal function. Water intake was significantly affected by dietary treatment \( (P < .01) \) and time \( (P < .05) \). Water intake was increased in cats eating the HSC food compared with those eating the LSC food (102 ml/d vs. 88 ml/d, respectively). Cats with renal insufficiency had increased water consumption compared with all other groups \( (P < .05) \) but did not increase water intake further in response to the HSC food.

**Urine Volume and Specific Gravity**

HSC intake significantly \( (P < .05) \) increased urine volume compared with LSC intake. Urine production in the final week of feeding the different foods was 124 ml/48 hr in the cats fed the LSC food and 165 ml/48 hr in cats fed the HSC food. Although there was an overall increase in urine volume in healthy, obese, and aged cats in response to the HCS food, urine volume did not increase in cats with impaired renal function. Cats classified as having impaired renal function initially had elevated urine volumes and maintained a high level of urine output throughout the study (Table 3). There was a significant reduction in urine SG in response to HSC intake. HSC intake resulted in average urine SG of 1.039 versus 1.049 in the LSC group \( (P < .05; \) Table 2). This finding is consistent with previous observations of increased water intake and urine volume in

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**TABLE 3. Effect of Dietary Sodium Chloride and Renal Insufficiency on Changes in Urinary Parameters in Healthy Control (Normal) and Impaired Renal Function (Renal) Cats**

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>LSC Food</th>
<th>HSC Food</th>
<th>Initial vs. Final</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
</tr>
<tr>
<td>Urine volume (ml/48 hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>133</td>
<td>108</td>
<td>93</td>
</tr>
<tr>
<td>Renal</td>
<td>199</td>
<td>229</td>
<td>218</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.049</td>
<td>1.054</td>
<td>1.058</td>
</tr>
<tr>
<td>Renal</td>
<td>1.030</td>
<td>1.026</td>
<td>1.032</td>
</tr>
<tr>
<td>Total urine calcium (mg/48 hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4.6</td>
<td>6.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Renal</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

\(\text{a}\)Square root of pooled estimate of inherent variation. 
HSC = high sodium chloride; LSC = low sodium chloride; NSD = no significant difference \( (P > .05) \).
cats fed high levels of NaCl. Dietary NaCl did not affect urine SG in cats previously defined as having renal dysfunction (Table 3). The average urine SG in cats with renal dysfunction (1.026) was lower than that of all other groups throughout the study regardless of the food fed ($P < .001$).

### Blood Pressure
Neither dietary treatment nor group affected mean arterial, systolic, or diastolic blood pressure (Table 2). Across all measurements, there was a significant time effect ($P < .01$); values increased across time for all measures. Despite the modest increase in blood pressures over time, all group means remained within the normal range for cats. Systolic hypertension was identified in five of 33 (15%) cats when eating the HSC food and seven of 32 (22%) cats when eating the LSC food. There was no significant difference associated with dietary NaCl consumption.

### Fundic Examination
There was no statistically significant effect of diet on retinal vessels, retinal hemorrhage, retinal detachment, or edema. One normal adult cat, with observed vessel tortuosity at baseline, developed retinal edema at 12 weeks following HSC feeding. The retinal changes did not resolve following an immediate switch to the LSC food.

### Echocardiography
Echocardiography identified significant differences between groups in LVEDD and LVEDS ($P < .05$; Table 2). Overall, obese cats and those with renal dysfunction tended to have increased thickness of the intraventricular septum and left ventricular end diameter at both systole and diastole, indicating a possible increase in afterload and mild cardiac hypertrophy. There was no effect of dietary NaCl on these parameters. Percent FS was significantly ($P < .01$) increased over time in all cats fed the HSC food compared with cats fed the LSC food (Table 2). The percent change was largely due to a reduction in LVEDS, which was not significant. Values remained within the normal ranges for awake cats and cats under ketamine:diazepam sedation.$^{19}$

### Bone Minerals
There was no effect of dietary NaCl or physiologic group on bone mineral content or bone density (Table 2).

### Urine Biochemistry
There was no effect of dietary treatment on urine pH, total urine creatinine, magnesium, potassium, or phosphorus excretion (mg/48 hr; Table 2). Surprisingly, renal and aged cats had urine pH values that were higher than those in healthy and obese cats. Initial urine calcium excretion was more than twofold higher in cats with impaired renal function compared with other groups ($P < .05$; Table 3). Total urine calcium excretion increased significantly in renal function–impaired and healthy cats fed the HSC food compared with baseline ($P < .05$; Table 3). Cats with renal dysfunction had a significant increase in urine calcium excretion compared with all other groups ($P < .01$; Table 3). Feeding an HSC food significantly increased the excretion of calcium in cats with initial hypercalciuria, whereas the LSC food had no effect on the relationship between initial and final calcium excretion (Table 3).

As expected, total urine sodium and chloride excretions were strongly influenced by NaCl intake. Increased sodium intake resulted in a nearly fourfold increase in urine sodium content ($P < .01$; Table 2); increased chloride intake resulted in a twofold increase in chloride excretion ($P < .01$; Table 2).
Urine calcium FE (%) was significantly influenced by initial creatinine concentration \((P < .01)\), and the relationship of calcium FE to initial serum creatinine concentration was influenced by dietary NaCl intake. The HSC food increased urine calcium loss, and its effect was greater in cats with higher initial circulating creatinine concentrations.

Hormonal Assays

Serum \(T_4\) concentrations at baseline were within the normal range for all cats (data not shown). Plasma aldosterone concentration decreased with exposure to HSC levels in healthy, obese, and aged cats \((P < .05; \text{Table 2})\). Conversely, aldosterone levels increased from weeks 0 to 12 \((406 \text{ pmol/L} \text{ to } 678 \text{ pmol/L}, \text{respectively})\) in cats with impaired renal function. The increase in aldosterone secretion in cats with renal impairment was not significantly different from baseline following consumption of the HSC food. The pattern of change between renal dysfunction cats and all other groups was significant \((P < .05)\). A dietary effect was apparent in both the time by diet and group by diet interactions \((P < .05)\). Plasma antidiuretic hormone concentration did not differ by group but increased numerically during feeding of the HSC food, although the increase was not significant (Table 2). Plasma renin activity was not influenced by dietary treatment (data not presented).

Serum Factors

Concentrations of serum urea nitrogen, creatinine, and phosphorus after 12 weeks of eating either the LSC or HSC food was significantly influenced by initial creatinine concentration \((P < .01)\). Average initial creatinine concentration was 1.23 mg/dl for all cats and 1.56 mg/dl for the renal group. Average initial serum urea nitrogen was 25.2 mg/dl for all cats and 32.8 mg/dl for the renal group.

All cats had a different response to the HSC food compared with that observed after eating the LSC food. This change was seen in the relationship between initial creatinine and the following circulating parameters after 12 weeks of either the HSC or LSC food: serum urea nitrogen \((P < .001)\), serum creatinine \((P < .05)\), and serum phosphorus \((P < .05)\). An incremental change in initial serum creatinine resulted in a 2.4 greater increase in subsequent urea nitrogen, a 1.6 greater increase in serum creatinine, and a 5.9 greater increase in serum phosphorus when the response of cats consuming the HSC food was compared with that of the cats eating the LSC food (Table 4).

| TABLE 4. Effect of Dietary Sodium Chloride on the Relationship between Initial Creatinine Concentration and Final Fractional Calcium Excretion, Serum Creatinine, Urea Nitrogen, and Phosphorus |
|--------------------------------------------------|-------------------|-------------------|-------------------|-------------------|
| Response criteria                               | Slope on HSC Food | Slope on LSC Food | Effect of Initial Creatinine | Difference Between Slopes |
| Final urea nitrogen                             | 25.3              | 10.4              | \(P < .001\)              | \(P < .001\)              |
| Final creatinine                                | 1.27              | 0.79              | \(P < .001\)              | \(P < .05\)               |
| Final phosphorus                                | 2.44              | 0.41              | \(P < .01\)               | \(P < .01\)               |
| Final FE of calcium                             | 0.0156            | 0.0050            | \(P < .001\)              | \(P < .001\)              |

FE = fractional excretion; HSC = high sodium chloride; LSC = low sodium chloride.
DISCUSSION

It is widely accepted that increasing water intake and urine dilution are beneficial in preventing the major causes of feline LUTD (urolithiasis and interstitial cystitis). Practitioners have devised numerous strategies to help increase water intake in cats prone to urinary tract disease. Most strategies are cumbersome for clients and of unproven efficacy in cats. Dietary NaCl supplementation has long been known as an effective means of increasing water intake and urine output in cats. Recent short-term high-NaCl feeding trials (2 weeks or less) in cats have demonstrated enhanced urine dilution and reduced risk of urolithiasis without evidence of hypertension. However, the impact of long-term feeding of high-NaCl diets has not been previously addressed.

In this study, feeding a food with high dietary NaCl effectively increased water intake and urine output in the majority of cats. The increased urine output was correlated with a significant reduction in urine SG, which has been suggested to impart benefits in the management of feline LUTD. Similar to results in previously reported short-term studies, high NaCl intake was not associated with increased blood pressure or hypertension in healthy cats or those at increased physiologic risk (obese, aged, or with impaired renal function). One cat developed retinal edema while consuming the HSC food; however, these changes were not associated with measurable increases in blood pressure nor did they resolve when the LSC food was fed. It is therefore difficult to ascribe this observation to HSC feeding.

Overall, echocardiographic variables were highly stable over time and between treatments. This presumably highlights the ability of cats to regulate intravascular volumes and pressure via a variety of mechanisms. One such mechanism appeared to be an increase in systolic work, as noted by a significant increase in percent FS in cats fed the HSC food. Increases in systolic function are ascribable primarily to an increase in preload or afterload, a positive inotropic effect, or a compensatory change in heart rate to a more favorable force–frequency relationship. Despite the lack of echocardiographic evidence for increased preload (no increase in LA or LA:AO ratio), the changes in hormonal profile and animal behavior are more indicative of intravascular volume expansion in response to NaCl supplementation. In response to HSC, serum aldosterone concentrations were decreased and urine volumes were increased in cats without renal dysfunction. Although we cannot rule out a change in afterload, there was no difference in blood pressure that would support a change in systemic vascular resistance due to HSC. Thus, it appears most probable that mild vascular volume expansion contributed to an increased ventricular contraction force (i.e., decreased LVEDD) and increased systolic work via Starling’s law. The biologic significance of this change over time is unknown; however, studies in cats demonstrate myocardial hypertrophy in response to hemodynamic overload regardless of the renin–angiotensin response.

Dietary NaCl intake has been shown to influence ventricular hypertrophy. DuCailar et
al\textsuperscript{22} demonstrated that left ventricular hypertrophy in normotensive and hypertensive people was positively correlated with urinary sodium excretion. In a similar study, Daniels et al\textsuperscript{23} reported that salt intake was an influential determinant of left ventricular hypertrophy, which was independent of changes in blood pressure. In animal models in which investigators provided different NaCl intake to rats over 7 months, high NaCl intake resulted in an increase in heart mass, which was independent of changes in blood pressure.\textsuperscript{24} Furthermore, investigators using a two kidney–one clip model of renal insufficiency reported that increasing NaCl intake significantly increased left ventricular mass.\textsuperscript{25} There was no difference in measurements of ventricular hypertrophy in this study. Therefore, the observed reduction in FS was independent of any measurable effect on blood pressure.

It has been reported that dietary NaCl causes functional renal injury without affecting arterial hypertension.\textsuperscript{26} These authors concluded that in a model of renal insufficiency (uninephrectomized spontaneously hypertensive rats), dietary NaCl exacerbated compensatory renal growth. In addition, this NaCl effect occurred without activation of the renin–angiotensin system. They concluded that the beneficial effects of NaCl restriction on renal function were independent of hypertension or the action of renin. This model may not reflect the data observed in this study, as the cats were not subjected to surgery. However, it is interesting to note that both studies observed renal changes in the presence of different high NaCl concentrations without inducing arterial hypertension. In a study investigating the relationship between NaCl intake and hypertension, Limas et al\textsuperscript{27} showed that vascular changes were aggravated by sodium intake within 5 weeks and that this aggravation was independent of changes in blood pressure. In another study investigating the effect of high NaCl intake, Tobian and Hanlon\textsuperscript{28} reported a significant increase in mortality associated with high NaCl intake in a uninephrectomized model of renal damage. In this model, high NaCl intake resulted in increased mortality after 8 weeks. Increased mortality occurred in the absence of any effect on blood pressure.

In addition to the progressive deterioration of renal function and increased fractional excre-tion, cats lost the ability to excrete creatinine. The normal adaptive mechanisms were overcome by the increased NaCl load on the kidney. This negative effect of NaCl intake either was not at a point where it affected muscle accretion or the 12-week study did not allow for the ongoing muscle accretion to become measurable.

Although it appears that high NaCl intake may benefit cats with LUTD, this study indicates that there is a population of cats that are deleteriously affected by high dietary NaCl. The most striking effects were increased concentrations of serum urea nitrogen, creatinine, and phosphorus in all cats, with these increases becoming larger in cats with higher initial creatinine concentrations. The progressive increase in these circulating metabolites indicates that as cats lost the ability to excrete creatinine, the normal adaptive mechanisms were overcome by the increased NaCl load on the kidney. This negative effect of NaCl intake...
tion, our study shows that dietary NaCl was associated with an increase in total urinary calcium excretion in cats with an equal incremental change in initial serum creatinine concentration. This increased calcium excretion is reflected in the total increase in urinary calcium over 48 hours and the increased percent calcium FE. Cats with a higher initial creatinine concentration and subsequent higher change in calcium FE have a response similar to that in humans, in which urinary calcium excretion has frequently been shown to respond to dietary NaCl intake. In their review of the relationship between dietary NaCl, urinary calcium, and kidney stone risk, Massey and Whiting reported that there was a linear relationship between sodium and calcium excretion. These authors pointed out that NaCl intake had a greater influence on calcium excretion in patients with hypercalciuria than it did with normocalciuric patients. In this way, cats are similar to people in that the group with higher calcium excretion at the beginning of the study (i.e., those with impaired renal function) was also the group that had the largest increase in urinary calcium excretion in response to increased dietary NaCl. Increased calcium excretion despite urine dilution in cats with impaired renal function might explain the common occurrence of calcium oxalate nephroliths in cats with renal disease. This observation suggests that urine dilution has less of an effect within the kidney at the point of oxalate excretion than might be expected. The biologic relevance of this finding is significant for cats with renal disease and those with hypercalciuria.

The significant effect of food on the slopes of initial creatinine concentration versus subsequent creatinine, urea nitrogen, or phosphorus shows that dietary NaCl changes the response of these factors to initial creatinine concentration. The increased slope in this relationship seen in the cats eating the HSC food shows that a small change in initial creatinine concentration while eating the HSC food resulted in a much greater change in these responses when compared with the LSC food. Because all of the slopes showed a greater increase in response criteria when the cats were consuming the HSC foods, it can be seen that decreasing renal function (as measured by initial creatinine concentration) resulted in a more detrimental effect on final renal function (as measured by serum creatinine, urea nitrogen, and phosphorus) when the cats eating the HSC food were compared with those consuming the LSC food.

The time associated with the feeding period in this study bears consideration. Despite 6 months of feeding (3 months/treatment), this period may not accurately reflect the health effects of lifelong NaCl exposure. This study showed that 12 weeks of feeding resulted in significant effects on renal function as shown by changing concentrations of circulating analytes. If these changes continued over time, longer term NaCl feeding may have a more deleterious impact on overall health. Thus, the consequence of feeding high NaCl foods for long-term maintenance must be considered carefully, especially because apparently healthy cats can have a significant degree of renal dysfunction that is undetected on routine biochemical screening. Similar to our findings, a recent study found sodium was not a risk for the develop-

**High NaCL food was associated with a progressive decline in renal function.**
ment of hypertension in cats with renal dysfunction (remnant kidney model and renal wrapping model). These authors concluded that sodium was not protective against secondary hypertension, increased glomerular filtration rate, and suppressed the renin–angiotensin system, whereas sodium restriction increased the risk for hypokalemia. The result of mineral excretion in cats in our study differed from that of the renal model. Aldosterone concentrations were suppressed with HSC in healthy cats but increased in cats with naturally occurring renal disease. The difference between these two studies may be explained by the differences in sampling time between the studies or due to differences in renal function in cats with naturally acquired versus surgically induced renal disease. The naturally occurring reduction in renal function in the cats used in this study compared with the more severe reduction in the experimental model may be the cause of this difference in response to high NaCl feeding.

In the evaluation of foods, the cornerstone of dietary recommendations should be to “first do no harm.” This has relevance in that this study indicates that although salt supplementation increased water intake and urine dilution, high NaCl intake increases calcium excretion and percent of fractional shortening in cats. Furthermore, HSC food was associated with a progressive decline in renal function as shown by changes in serum creatinine, serum urea nitrogen, and serum phosphorus.

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