Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure

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Objective—To determine whether urine protein-to-creatinine ratio (UP:C) ≥ 1.0 at initial diagnosis of chronic renal failure (CRF) is associated with greater risk of development of uremic crises, death, and progression of renal failure in dogs.

Design—Prospective cohort study.

Animals—45 dogs with CRF.

Procedure—Dogs were prospectively assigned to 2 groups on the basis of initial UP:C < 1.0 or ≥ 1.0. The association between magnitude of proteinuria and development of uremic crises and death was determined before and after dogs with initial UP:C ≥ 1.0 were assigned to 3 subgroups and compared with dogs with initial UP:C < 1.0. Changes in reciprocal serum creatinine concentration were used to estimate decrease in renal function.

Results—Initially, dogs had similar clinical characteristics with the exception of systolic blood pressure and UP:C. Relative risks of development of uremic crises and death were approximately 3 times higher in dogs with UP:C ≥ 1.0, compared with dogs with UP:C < 1.0. Relative risk of adverse outcome was approximately 1.5 times higher for every 1-unit increment in UP:C. The decrease in renal function was of greater magnitude in dogs with UP:C ≥ 1.0, compared with dogs with UP:C < 1.0.

Conclusions and Clinical Relevance—Initial UP:C ≥ 1.0 in dogs with CRF was associated with greater risk of development of uremic crises and death, compared with dogs with UP:C < 1.0. Initial determinations of UP:C in dogs with naturally occurring CRF may be of value in refining prognoses. (J Am Vet Med Assoc 2005;226:393–400)

Identification of the primary cause of renal dysfunction and secondary factors that contribute to disease progression may help in developing treatments that slow the rate of progression of renal diseases to end-stage renal failure. In recent years, proteinuria has been incriminated as an independent mediator of progression of renal disease.13 This association is supported by the observation that the magnitude of proteinuria correlates with the rate of progression of renal failure in rats with experimentally induced renal failure and in humans with naturally occurring renal failure.3,11 A decrease in the magnitude of proteinuria after treatment with angiotensin-converting enzyme inhibitors reduced the rate of progression of renal failure in humans and rats.6,10 Results of 2 studies12,13 in dogs with naturally occurring protein-losing nephropathies revealed that treatment with enalapril significantly decreased the magnitude of proteinuria, slowed the progression of renal disease, and prolonged survival time. Although results of these studies revealed a beneficial antiproteinuric effect of enalapril on various clinical outcomes, direct evidence that proteinuria is injurious to the kidneys of dogs with chronic renal failure (CRF) was not provided.

The purpose of the study reported here was to determine whether a urine protein-to-creatinine ratio (UP:C) ≥ 1.0 at the time of initial diagnosis of CRF in dogs is associated with greater risk of development of uremic crises, progression renal failure, and death.

Materials and Methods

Dogs—Forty-five dogs met the inclusion and exclusion criteria and were enrolled in the present study. Thirty-eight of these dogs were concurrently participating in a double-masked, randomized, controlled clinical trial designed to evaluate the efficacy of dietary modification in the management of CRF.14 An additional 7 dogs were referred to the University of Minnesota to participate in the diet study. However, they were excluded from that study because their systolic blood pressure (SBP) at the time of initial visit exceeded 180 mm Hg. The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Minnesota. Owners of participating dogs gave their informed consent for all procedures. Because dogs were enrolled from January 1997 through April 1999, the duration of the study for each dog varied. Dogs that did not attain the primary end points of the study (uremic crisis, died of renal disease, or died of any cause) were monitored for a minimum of 225 days. The study was terminated in November 1999.

Medical history and results of physical examination, determination of PCV, serum biochemical analyses (SUN, creatinine, total CO2, inorganic phosphorus, and albumin concentrations), urinalysis (including examination of urine sediment), quantitative aerobic bacterial culture of urine specimens, determination of UP:C, and indirect blood pressure
measurements were considered. Dogs were included in the study if they were > 1 year of age and had stable renal function and serum creatinine concentration of 2.0 to 8.0 mg/dL. Renal function was considered stable if serum creatinine concentration did not increase or decrease by > 20% within 3 to 13 days of initial measurement. Dogs were excluded from the study if they were expected to die as a result of nonrenal illness prior to completion of the study; if they had diabetes mellitus, hyperadrenocorticism, or overt signs of uremia (ie, anorexia, vomiting, and lethargy); and if they were being treated with corticosteroids, H₂-receptor–blocking drugs, antineoplastic drugs, antihypertensive drugs, parenterally administered fluids, vitamin supplements, phosphate binders, alkalinizing agents, potassium supplements, recombinant human erythropoietin, or vitamin D supplements.

Groups and subgroups—A UP:C ≥ 1.0 in dogs with normal urine sediment is considered to be abnormal; therefore, dogs were assigned to 2 groups on the basis of initial UP:C (ie, the first UP:C determined for each dog in this study). Dogs with UP:C < 1.0 (range, 0.01 to 0.90) were included in the UP:C < 1.0 group (n = 20). Dogs with UP:C ≥ 1.0 (range, 1.00 to 15.80) were included in the UP:C ≥ 1.0 group (n = 25).

Dogs with initial UP:C ≥ 1.0 were retrospectively assigned to 3 subgroups (UP:C of 1.00 to 1.99, UP:C of 2.00 to 2.99, and UP:C ≥ 3.00). Eight dogs with UP:C ranging from 1.00 to 1.67 were included in the low UP:C (L-UP:C) group, 8 dogs with UP:C ranging from 2.00 to 2.77 were included in the intermediate UP:C (I-UP:C) group, and 9 dogs with UP:C ranging from 3.00 to 15.80 were included in the high UP:C (H-UP:C) group.

Study protocol—Each dog was evaluated during the initial visit and 2 months after entering the study. Medical history, physical examination, measurement of blood pressure, serum biochemical analyses (SUN, creatinine, total CO₂, inorganic phosphorus, and albumin concentrations), and PCV determination were performed. Beginning at 3 months and continuing for up to 24 months after the initial visit, dogs were reevaluated at 3-month intervals or whenever clinical signs warranted evaluation. Phone interviews were conducted every month when on-site examinations were not scheduled.

Measurement of blood pressure—An oscillometric method was used to measure blood pressure indirectly in 43 dogs. In 2 dogs, reliable results could not be obtained by use of the oscillometric method; therefore, an ultrasonic Doppler method was used to measure blood pressure in these dogs (1 dog in the UP:C < 1.0 group and 1 dog in the H-UP:C group).

Blood sample collection and clinicopathologic analyses—Owners were instructed to withhold food from dogs for 12 hours prior to reevaluation. During each visit, a blood sample was collected from the jugular vein into evacuated tubes. Serum was separated within 30 minutes of collection. If biochemical analyses could not be performed on the day serum was obtained, serum was stored at 4°C overnight and analyzed the following day. Serum biochemical analyses were measured by use of a commercial analyzer: Blood samples for determination of PCV were collected into hemocrit tubes, and PCV was determined by use of a commercial centrifuge.

Collection of urine samples and determination of UP:C—Urine samples were collected via cystocentesis. A complete urinalysis, including sediment examination, was performed during each visit. Urine protein concentration was measured by use of the Coomassie brilliant blue dye precipitation method and spectrophotometry. Urine creatinine concentration was determined by use of a commercial autoanalyzer-based kinetic Jaffe reaction. Urine samples for protein and creatinine concentration determinations were stored at 4°C and analyzed within 24 hours of collection.

Treatment protocols—With the exception of diet and antihypertensive drugs, treatment protocols for management of CRF were standardized as described. In the UP:C < 1.0 group, 6 of 20 dogs were treated for hyperphosphatemia, compared with 7 of 25 dogs in the UP:C ≥ 1.0 group. One of 20 dogs in the UP:C < 1.0 group and 2 of 25 dogs in the UP:C ≥ 1.0 group were treated for gastrointestinal bleeding. Although none of the dogs in the UP:C < 1.0 group were treated for hyperproliferative anemia, 4 of 25 dogs were in the UP:C ≥ 1.0 group.

Thirty-eight dogs were concurrently participating in a controlled study designed to evaluate the efficacy of dietary modification in the management of CRF. These dogs were fed either a diet formulated for dogs with renal failure or an adult maintenance diet. Of the remaining 7 dogs, 3 were fed a manufactured renal failure diet. In 2 dogs, the owner chose to give a manufactured maintenance diet rather than a therapeutic renal failure diet. In the UP:C < 1.0 group, 9 of 20 dogs were fed a diet formulated for dogs with renal failure and 11 of 20 dogs were fed an adult maintenance diet. In the UP:C ≥ 1.0 group, 15 of 25 dogs were fed a diet formulated for dogs with renal failure and 10 of 25 dogs were fed an adult maintenance diet. Seven of 8 dogs in the L-UP:C group were fed a diet formulated for dogs with renal failure, and 1 dog was fed an adult maintenance diet. In the I-UP:C group, 5 of 8 dogs were fed a diet formulated for renal failure and 3 dogs were fed an adult maintenance diet. In the H-UP:C group, 6 of 9 dogs were fed an adult maintenance diet and 3 dogs were fed a diet formulated for dogs with renal failure.

Over the course of the study, 11 dogs with SBP ≥ 180 mm Hg were treated with antihypertensive drugs with the goal of decreasing SBP to < 160 mm Hg. Seven dogs were detected during the examination, and 4 dogs with initial SBP < 180 mm Hg subsequently developed sustained SBP ≥ 180 mm Hg. Enalapril maleate (0.25 to 0.75 mg/kg [0.11 to 0.34 mg/lb], PO, q 12 to 24 h), amloidipine besylate (0.05 to 0.75 mg/kg [0.02 to 0.34 mg/lb], PO, q 12 to 24 h), and diltiazem hydrochloride (0.5 mg/kg [0.23 mg/lb], PO, q 8 h) were used. Initially, the lowest recommended dosage of an antihypertensive drug was used. Within the recommended range, dosage was incrementally increased on the basis of serial measurements of SBP. If SBP remained high (≥ 160 mm Hg) after treatment with the highest recommended dosage, a second antihypertensive drug was added to the treatment protocol. Two dogs in the H-UP:C group were treated with enalapril. Five dogs (1 dog in the UP:C < 1.0 group, 1 dog in the I-UP:C group, 2 dogs in the L-UP:C group, and 1 dog in the H-UP:C group) were treated with amloidipine. Four dogs (1 dog in the UP:C < 1.0 group, 1 dog in the I-UP:C group, 1 dog in the L-UP:C group, and 1 dog in the H-UP:C group) were treated with a combination of enalapril and a calcium channel blocker (amloidipine in 3 dogs and diltiazem in 1 dog). Of 11 dogs treated with antihypertensive drugs, the treatment goal of SBP < 160 mm Hg was achieved in only 1 dog.

Diagnosis of uremic crisis—A diagnosis of uremic crisis was made on the basis of 3 criteria: the owner’s observation of 2 or more clinical signs consistent with uremia that included, but were not limited to, signs of depression, lethargy, anorexia, vomiting, uremic breath odor, and uremic stomatitis; a SUN concentration ≥ 20% greater than the SUN concentration measured during the previous visit when signs of uremia were absent; and no other plausible explanation for clinical signs...
and the increase in SUN concentration that could be identified via the medical history and results of physical examination, limited serum biochemical analyses, PCV determination, urinalysis, aerobic bacterial culture of urine, abdominal radiography, and indirect measurement of blood pressure.

Identification of causes of death—By use of the medical history, physical examination findings, results of clinico-pathologic tests, objective criteria that defined uremic crisis, and necropsy findings (when available), causes of death were categorized as definitely not renal-associated, possibly renal-associated, probably renal-associated, and definitely renal-associated. Dogs placed in either of the first 2 categories were considered to have died as a result of a nonrenal-associated cause. Dogs placed in either of the third or fourth categories were considered to have died as a result of a renal-associated cause. Nonrenal-associated death was defined as death resulting from causes other than uremia.

Statistical analyses—Values for clinical parameters determined at the initial visit in the UP:C < 1.0 group were compared with those in the UP:C ≥ 1.0 group by use of an unpaired t test. Although the clinical outcome of dogs fed the diet formulated for dogs with renal failure differed from that of dogs fed the adult maintenance diet, the association between UP:C and clinical outcome was similar within each diet group in our study; therefore, for analyses of the association between UP:C and clinical outcome, data for the diet groups were combined. A Spearman rank correlation test was used to determine the correlation between initial UP:C and initial SBP measurement. Kaplan-Meier survival analysis with a logrank test was used to evaluate the hypothesis that the reciprocal serum creatinine concentration (1/serum creatinine) was an independent predictor of adverse outcomes in dogs with UP:C ≥ 1.0.

The Cox proportional hazard regression model was used to categorically evaluate the relationship between initial proteinuria and the relative risk (RR) of development of uremic crises and death. The same method was used to evaluate the influence of the cointervention diet on the development of uremic crises and death between groups (because by design, diets varied among groups) as well as the influence of other initial covariates (age; weight; SBP; PCV, and SUN; serum creatinine, inorganic phosphorus, total CO₂, and albumin concentrations) on the aforementioned clinical outcomes. The Cox proportional hazard model was also used to categorically evaluate the association between initial proteinuria in the subgroups and the RR of development of uremic crises and death.

We previously reported that SBP influences the risk of development of uremic crises and death. In that study, dogs with initial SBP in the highest tertile (SBP = 161 to 201 mm Hg) had a significantly greater risk for development of uremic crises and death than dogs with lower SBPs. A direct relationship between higher SBP and greater proteinuria has been reported. To determine whether the effect of proteinuria on development of uremic crisis and death was dependent on SBP, we examined the effect of the magnitude of proteinuria (UP:C ≥ 1.0 vs. UP:C < 1.0) on the risk for these outcomes in dogs with initial SBPs in the low (SBP = 107 to 143 mm Hg), intermediate (144 to 160 mm Hg), and high (SBP = 161 to 201 mm Hg) tertiles.

The relationship between outcome and initial UP:C was also evaluated after entering initial UP:C as a continuous variable in the Cox proportional hazard regression model. The influence of the cointervention SBP was included in this continuous model. The RR was expressed as the risk associated with a 1-unit increment in initial UP:C.

The association between magnitude of initial proteinuria and decline in renal function was determined by comparing the rate of renal failure progression in the UP:C < 1.0 group with the UP:C ≥ 1.0 group. Similarly, the association between initial proteinuria and the rate of renal failure progression was determined by comparing decline in renal function in the UP:C < 1.0 group with each subgroup (L-UP:C, I-UP:C, and H-UP:C). The mean of the reciprocal serum creatinine concentrations for the UP:C < 1.0 group, UP:C ≥ 1.0 group, and the subgroups was calculated for each sampling time (initial visit, 30, 60, 90, 180 days); best-fit lines indicating the pattern of change in renal function were computer-generated by use of the least-square method. For each dog, the reciprocal of serum creatinine concentration (1/serum creatinine concentration) measured at the initial visit (A) and the mean of the reciprocal of serum creatinine concentrations measured at each subsequent sampling time (B) were recorded. Then, in each group of dogs, a paired t test was used to test the hypothesis that the reciprocal serum creatinine concentration would progressively decrease (A compared with B) as a result of progressive decrease in renal function (within-group comparison). Because of the high mortality rate in dogs with a UP:C ≥ 1.0, only data collected to day 180 were used to compare the decrease in renal function over time.

The decrease in renal function in each group was estimated by calculating the difference between B and A (A = B – A). We then compared the association between the magni-
tude of proteinuria at the initial visit with changes in the reciprocal serum creatinine concentration by use of ANOVA. Terminal data (ie, data that could be associated with a uremic crisis) were not included in any of the analyses mentioned in this paragraph.

Statistical analyses were performed by use of computer software packages. Values of $P < 0.05$ were considered significant.

Results

Findings at initial examination—With the exception of initial SBP, there were no significant differences in age, weight, serum biochemical analytes (SUN, creatinine, phosphorus, total carbon dioxide, and albumin concentrations), and PCV between dogs in the UP:C < 1.0 and UP:C $\geq$ 1.0 groups (Table 1). Quantitative aerobic bacterial cultures of urine yielded no growth at the time of initial UP:C determinations, and no abnormalities of urine sediment were detected.

A significant correlation ($r = 0.57; P < 0.001$) was found between initial UP:C and initial SBP. Dogs with...
initial UP:C ≥ 1.0 had significantly higher initial SBP than dogs with initial UP:C < 1.0 (Table 1).

**Relationship between proteinuria and SBP**—The RRs for uremic crises and death were similar between SBP tertiles (Table 2). A UP:C ≥ 1.0 (compared with a UP:C < 1.0) was associated with a greater RR for these clinical outcomes for each SBP tertile, although differences were not significant. On the basis of these results, it did not appear that the relationship between proteinuria and clinical outcomes could be explained by blood pressure alone.

**Association between proteinuria and uremic crises**—Kaplan-Meier analysis revealed that the median time to uremic crisis was significantly (P = 0.014) shorter in the UP:C ≥ 1.0 group, compared with the UP:C < 1.0 group (Figure 1; Table 3). When the Cox proportional hazard regression model was used to categorically determine the association between proteinuria and outcome, the RR of uremic crises was significantly greater in the UP:C ≥ 1.0 group, compared with the UP:C < 1.0 group. When adjustment for the effect of the covariate initial SBP was performed, the RR of uremic crises associated with a UP:C ≥ 1.0 decreased (P > 0.05), but the relationship remained positive.

When UP:C subgroups were evaluated, Cox proportional hazard regression analysis revealed that the RR of the development of uremic crises was significantly greater in the H-UP:C subgroup, compared with the UP:C < 1.0 group. Although not significantly different, the RRs for the development of uremic crises were greater in the I-UP:C and L-UP:C subgroups, compared with the UP:C < 1.0 group. When adjustment for the effect of the covariate initial SBP was performed, the association between initial UP:C and development of uremic crises continued to be positive in the L-UP:C and I-UP:C subgroups and the RR remained significantly different in the H-UP:C subgroup, compared with the UP:C < 1.0 group (Table 4).

When initial UP:C was examined as a continuous variable in the Cox proportional hazard regression model, a significant relationship was found between the magnitude of proteinuria and the RR of development of uremic crises. For every 1-unit increment in initial UP:C, the RR of development of uremic crises increased by 60%. When the effect of initial UP:C was adjusted for the effect of covariate initial SBP on development of uremic crises, the relationship remained significantly positive (Table 5).

**Association between proteinuria and renal-associated death**—Kaplan-Meier analysis revealed that the

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**Table 5—Relative risk of adverse outcomes in dogs with CRF associated with a 1-unit increment in initial UP:C.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uremic crisis</th>
<th>Renal-associated deaths</th>
<th>All causes of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted* UP:C</td>
<td>1.6</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.2–2.2</td>
<td>1.2–2.2</td>
<td>1.5–2.8</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adjusted* UP:C</td>
<td>1.6</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.2–2.1</td>
<td>1.1–2.2</td>
<td>1.2–2.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.005</td>
<td>0.006</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Effect of initial UP:C used as a continuous variable in the Cox proportional hazard regression model. See Table 3 for remainder of key.
median time to renal-associated death was significantly shorter in the UP:C ≥ 1.0 group, compared with the UP:C < 1.0 group (Figure 3; Table 3). When the association between initial UP:C and renal-associated death was categorized by use of the Cox proportional hazard regression model, the RR of renal-associated death was significantly greater in the UP:C ≥ 1.0 group, compared with the UP:C < 1.0 group. After adjusting for the effect of the covariate initial SBP in this model, the relationship between initial SBP and the RR of renal-associated death associated with a UP:C ≥ 1.0 decreased (P > 0.05), but the relationship remained positive.

Cox proportional hazard regression analysis revealed that the RR for renal-associated death was significantly greater in the H-UP:C subgroup, compared with the UP:C < 1.0 group (Table 4). Although not significantly different, the RRs of renal-associated death were greater in the I-UP:C and L-UP:C subgroups, compared with the UP:C < 1.0 group. When adjustment for the effect of covariate initial SBP was performed, the RR of renal-associated death continued to be positive in the L-UP:C and I-UP:C subgroups and remained significantly different in the H-UP:C subgroup, compared with the UP:C < 1.0 group.

When initial UP:C was examined as a continuous variable in the Cox proportional hazards regression model, a significant relationship was found between the magnitude of proteinuria and the RR of renal-associated death. For every 1-unit increment in initial UP:C, the RR of renal-associated death increased by 60% (Table 5). After adjusting for the effect of covariate initial SBP, the RR of renal-associated death continued to be positive in the L-UP:C and I-UP:C subgroups and remained significantly different in the H-UP:C subgroup, compared with the UP:C < 1.0 group.

When initial UP:C was examined as a continuous variable in the Cox proportional hazards regression model, the RR of death was significantly greater in the H-UP:C and I-UP:C subgroups, compared with the UP:C < 1.0 group. Although not significantly different, the RR of all causes of death was greater in the L-UP:C subgroup, compared with the UP:C < 1.0 group. When adjustment for the effect of covariate initial SBP was performed, the RR of all causes of death continued to be positive in the L-UP:C and I-UP:C subgroups and remained significantly different in the H-UP:C subgroup, compared with the UP:C < 1.0 group (Table 4).

When initial UP:C was examined in the Cox proportional hazards regression model as a continuous variable, for every 1-unit increment in initial UP:C, the RR of all causes of death significantly increased by 80% (Table 5). When the effect of covariate initial SBP was adjusted for in this model, the relationship between all causes of death and initial UP:C remained significantly positive.

Association between proteinuria and progression of renal failure—The reciprocal serum creatinine concentration decreased significantly from the value for the initial visit in the UP:C ≥ 1.0 group but not in the UP:C < 1.0 group (Figure 4; Table 6). The reciprocal serum creatinine concentration decreased significantly from the value for the initial visit in the H-UP:C and I-UP:C subgroups; however, no significant decrease in the reciprocal serum creatinine concentration from the value for the initial visit was found in the L-UP:C subgroup and the UP:C ≥ 1.0 group.

Analysis of variance indicated that the change in renal function was significantly higher for dogs in the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>P value</th>
<th>Mean ± SD</th>
<th>P value</th>
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</thead>
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<td></td>
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<td>UP:C &lt; 1.0</td>
<td>0.331 ± 0.100</td>
<td>0.322 ± 0.119</td>
<td>0.62</td>
<td>0.009 ± 0.009</td>
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<td>UP:C ≥ 1.0</td>
<td>0.342 ± 0.112</td>
<td>0.269 ± 0.109</td>
<td>&lt; 0.001</td>
<td>-0.071 ± 0.006</td>
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</tr>
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<td>Subgroups</td>
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<tr>
<td>UP:C &lt; 1.0</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>L-UP:C</td>
<td>0.322 ± 0.111</td>
<td>0.283 ± 0.111</td>
<td>0.12</td>
<td>-0.019 ± 0.057</td>
<td>0.006</td>
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<tr>
<td>I-UP:C</td>
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<td>0.252 ± 0.096</td>
<td>0.008</td>
<td>-0.096 ± 0.058</td>
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</tr>
<tr>
<td>H-UP:C</td>
<td>0.367 ± 0.110</td>
<td>0.272 ± 0.127</td>
<td>0.01</td>
<td>-0.095 ± 0.091</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SD values for the reciprocal of serum creatinine concentrations measured at the time of initial diagnosis of chronic renal failure. †Mean ± SD values for the reciprocal of serum creatinine concentrations measured throughout the study period. ‡Mean ± SD values of the difference between the reciprocals of initial serum creatinine concentrations and the serum creatinine concentrations measured throughout the study period. §P value associated with a paired t test comparing reciprocals of initial value and overall serum creatinine concentrations in each group or subgroup. ‡P value associated with an ANOVA of the difference in reciprocals of serum creatinine concentrations between groups or subgroups. Dogs were assigned to UP:C < 1.0 and UP:C ≥ 1.0 on the basis of initial UP:C measurements at the time of diagnosis of CRF. Dogs included in the UP:C ≥ 1.0 group were further divided into 3 subgroups: L-UP:C, I-UP:C, and H-UP:C subgroups.

See Table 4 for remainder of key.
UP:C ≥ 1.0 group, compared with dogs in the UP:C < 1.0 group. When the decrease in renal function in the UP:C < 1.0 group was compared with the decrease in the UP:C subgroups via ANOVA, a significant decrease in renal function was found in the UP:C ≥ 1.0 group but not compared with the UP:C < 1.0 group. No significant difference in the decrease in renal function was found between the UP:C < 1.0 group. When the decrease in renal function in the UP:C ≥ 1.0 in dogs with naturally occurring CRF was also associated with faster progression of renal failure as reflected by serial reciprocal serum creatinine concentrations. The association between the magnitude of proteinuria and the development of uremic crises and death is likely related to the association between magnitude of proteinuria and rate of progression of renal failure. Our results parallel those reported in studies in humans and rodents in which a significant relationship between the magnitude of proteinuria and rate of progression of renal disease to end-stage renal failure and death was found.

Proteinuria may promote progression of renal injury in several ways. At this time, the most widely proposed cause of renal tubular injury in protein-losing diseases of the kidney is excessive tubular uptake of filtered proteins or protein-bound substances. Excess protein in the urine may injure renal tubules via toxic or receptor-mediated pathways or via overload of lysosomal degradative mechanisms. Abnormal amounts of filtered protein accumulate in the lumen of the proximal tubule and, after endocytosis, into proximal tubular epithelial cells and contribute to renal tubulointerstitial injury via a complex cascade of intracellular events. Small molecular-weight lipids bound to filtered proteins may be liberated during resorption; inflammatory or chemotactic properties of these lipids may promote tubulointerstitial disease. Complement components that are filtered through the glomerular capillary wall may initiate interstitial injury. Insippation of filtered proteins as a result of tubular reabsorption of water in the distal nephron may lead to formation of casts that obstruct nephrons.

Proteinuria may have been associated with causes of renal injury in protein-losing diseases of the kidney. Although mild proteinuria may occur with any type of renal disease, proteinuria is generally considered a hallmark of glomerular disease. It is likely that glomerular disease was more prevalent among dogs with proteinuria in our study. Glomerulopathies are reportedly associated with poor long-term outcomes in dogs. In humans, most forms of progressive noncystic renal diseases involve the glomerulus.27

Discussion
The results of our study support the hypothesis that an initial UP:C ≥ 1.0 in dogs with naturally occurring CRF is a risk factor for development of uremic crises, renal-associated deaths, and death as a result of all causes. We detected a graded association between the risk of these outcomes and the magnitude of proteinuria. A UP:C ≥ 1.0 in dogs with CRF was also associated with faster progression of renal failure as reflected by serial reciprocal serum creatinine concentrations. The association between the magnitude of proteinuria and the development of uremic crises and death is likely related to the association between magnitude of proteinuria and rate of progression of renal failure. Our results parallel those reported in studies in humans and rodents in which a significant relationship between the magnitude of proteinuria and rate of progression of renal disease to end-stage renal failure and death was found.

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Proteinuria may have been associated with causes of renal injury in protein-losing diseases of the kidney. Although mild proteinuria may occur with any type of renal disease, proteinuria is generally considered a hallmark of glomerular disease. It is likely that glomerular disease was more prevalent among dogs with proteinuria in our study. Glomerulopathies are reportedly associated with poor long-term outcomes in dogs. In humans, most forms of progressive noncystic renal diseases involve the glomerulus.27

In humans with renal disease, hypertension can lead to development of proteinuria. Results of our study revealed that increased SBP was associated with high UP:C 57% of the time, compared with dogs with low SBP. Further evidence that supported an association between high SBP and proteinuria was found when the relationship between initial proteinuria and outcomes was adjusted for the effect of the initial SBP covariate. The finding that the effect of proteinuria on the RR of outcomes was decreased by adjusting for the effect of the covariate initial SBP is consistent with an association between proteinuria and SBP. Hypertension may contribute to nephron loss by promoting loss of protein through the glomerular barrier.

Our study was not designed to evaluate the effect of antihypertensive drugs on the development of uremic crises, progression of renal failure, and death. However, it is likely that in dogs, treatment with enalapril resulted in a decrease in the magnitude of proteinuria and therefore in an underestimation of the association between magnitude of proteinuria and clinical outcomes. Results of previous studies revealed that treatment with angiotensin-converting enzyme inhibitors significantly decreased the magnitude of proteinuria and slowed the progression of renal disease in humans and dogs with CRF. Although still controversial, results of experimental studies in rats and dogs have raised questions regarding the renoprotective value of calcium channel blockers. These drugs may promote proteinuria; therefore, we cannot rule out the possibility that the calcium channel blockers used in 9 dogs in our study may have resulted in an increase in the magnitude of proteinuria via a preferential vasodilatation of the afferent glomerular arteriole that led to higher glomerular capillary pressure. However, the distribution of dogs treated with amlodipine or diltiazem was balanced among dogs in the UP:C ≥ 1.0, L-UP:C, I-UP:C, and H-UP:C groups. Likewise, the distribution of dogs treated with a combination of a calcium channel blocker and enalapril was balanced among groups. In addition, the impact of other therapeutic interventions on outcomes was likely to be minimal because all dogs were treated in a similar fashion according to a predetermined protocol and the distribution of dogs treated for hyperphosphatemia, gastrointestinal bleeding, hypoproliferative anaemia, and metabolic acidosis was similar between groups.

Results of our study indicate that an initial UP:C ≥ 1.0 is associated with a greater risk of development of uremic crises, progression of CRF, and death. We suggest that UP:C determinations be considered when evaluating dogs with CRF with the goal of refining prognosis. Our findings emphasize the need to design studies to confirm that treatments used to decrease the magnitude of proteinuria slow the progression of renal failure and prolong survival in dogs with naturally occurring CRF.

References
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