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Original Article

Plasma indoxyl sulfate concentration predicts progression of chronic kidney disease in dogs and cats

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ABSTRACT

Indoxyl sulfate is a protein-bound uremic toxin that increases as the severity of impaired renal function increases in humans, laboratory animals, dogs and cats. An elevation of indoxyl sulfate is related to prognosis among people with chronic kidney disease. However, whether indoxyl sulfate is able to predict the progression of chronic kidney disease in dogs and cats has not been previously studied. In the present study, 58 cats and 36 dogs with chronic kidney disease were enrolled. Plasma indoxyl sulfate was measured by high performance liquid chromatography. Renal progression was defined as an increase by one International Renal Interest Society (IRIS) stage and/or a rise in serum creatinine concentration of 0.5 mg/dL during the same stage within a 3-month period.

Compared with the non-progression groups, across different stages of renal failure, the baseline plasma indoxyl sulfate concentration was increased in the renal progression group ($P < 0.05$), especially for IRIS stages 2 and 3 animals. The area under the receiver operator characteristic curves of indoxyl sulfate, when predicting renal progression, was above 0.75 for both dogs and cats. Indoxyl sulfate concentrations were also correlated with the increase of blood urea nitrogen, serum creatinine, and phosphate and the decrease of hematocrit among cats; while in dogs, concentrations were only correlated with the increase of phosphate concentrations. Indoxyl sulfate served as a biomarker of progression risk in dogs and cats with chronic kidney disease.

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Introduction

Numerous organic compounds are retained in uremic patients and some are uremic toxins able to further damage the kidneys and other organs (Lisowska-Myjak, 2014). As renal function declines, the concentrations of uremic toxins increase, inducing a self-perpetuating cycle that creates a progressive impairment of renal function (Niwa et al., 1997). Indoxyl sulfate is one of these uremic toxins (Glassock, 2008). This compound originates from the metabolic breakdown of tryptophan. In the intestine, tryptophan is metabolized into indole by intestinal bacteria and this indole is then taken up and converted to indoxyl sulfate by the liver (Motojima et al., 2003). Indoxyl sulfate is classified as a protein-bound compound. About 90% of the indoxyl sulfate in plasma is bound to albumin (Sudlow et al., 1975; Meijers et al., 2008). The indoxyl sulfate–albumin complex is transported to renal tubular cells where indoxyl sulfate is taken up and excreted via organic anion transporters (OAT1 and OAT3) located on the tubular cell membrane. The decline of renal function causes the accumulation of indoxyl sulfate in proximal tubular cells (Taki et al., 2006) and consequently induces reactive oxidative stress (Dou et al., 2007), inhibits the tubular proliferation (Kawakami et al., 2010) and increases profibrotic cytokines, thereby promotes the progression of chronic kidney disease (CKD) in humans (Niwa and Shimizu, 2012). Serum concentrations of indoxyl sulfate have been reported to increase with the severity of impaired renal function in laboratory animals, humans (Niwa et al., 1997), dogs and cats (Cheng et al., 2015).

Because indoxyl sulfate cannot be eliminated by hemodialysis (Niwa, 2010), indoxyl sulfate toxicity has gained the attention of researchers. Several studies have reported that indoxyl sulfate

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inhibits endothelial proliferation (Dou et al., 2004), increases cell senescence (Yu et al., 2011), increases aortic calcification and stiffness (Adijiang et al., 2008), induces cardiac fibrosis (Lekawanvijit et al., 2010), and increases the epithelial-to-mesenchymal transition in renal tubular cells (Bolati et al., 2011).

Due to the toxicity associated with indoxyl sulfate, an increase in indoxyl sulfate has been found to be related to the prognosis in humans with CKD (Taki and Niwa, 2007), underscoring the importance of indoxyl sulfate. However, the capability of indoxyl sulfate to predict the progression of renal functional decline in cats and dogs with CKD has not yet been studied. The aims of this present study were to evaluate whether indoxyl sulfate can serve as a marker to predict the progression of CKD in cats and dogs and to determine if renal function related laboratory parameters are correlated with indoxyl sulfate concentrations.

Materials and methods

Sample collection

In this study, all plasma and urine samples were collected from outpatient dogs and cats that presented to the National Taiwan University Veterinary Hospital and the study was carried out with Institutional Animal Care and Use Committee approval (Approval number NTU-103-EL-85; Approval date February 2015). Dogs and cats with chronic kidney disease (CKD) that were diagnosed based on the animal's clinical signs, history, serum biochemistry, urinalysis data and intrinsic renal azotemia persisting for at least 3 months, were enrolled and staged using International Renal Interest Society (IRIS) criteria.[2] The inclusion criteria required the animals to be at least IRIS stage 2 CKD (dogs, serum creatinine > 125 μmol/L; cats, serum creatinine > 140 μmol/L). Animals were excluded from the study if they had concurrent hyperthyroidism, a rapid progressive renal disease, urinary tract obstruction/infection, liver disease, system infectious disease, heart failure, or any tumors recorded in the medical records. In addition, animals were excluded if they were being treated with Kremezin (AST-120) prior to the study, as this has been reported to lower indoxyl sulfate (Owada et al., 1997).

Study design

Eligible animals were followed up every month for at least 3 months and classified into a progression group and a non-progression group. Progression was defined by a 0.5 mg/dL increment in serum creatinine during the same IRIS stage or an increase of one IRIS staging, both within 3 months. The medical management of CKD for the enrolled animals followed the IRIS recommendations for each stage of diseases,[3] and the use of concurrently prescribed medications was recorded.

Measurement of indoxyl sulfate concentration

Plasma indoxyl sulfate concentrations were measured by high performance liquid chromatography (HPLC). The sample preparation, reagents and the procedure were performed as described in a previous study (Cheng et al., 2015). Briefly, samples were deproteinized with acetonitrite (J.T. Baker) and then analyzed by reversed-phase HPLC using fluorescence detection, the excitation and emission wavelengths being set at 280 and 375 nm, respectively. The limit of detection and quantification of indoxyl sulfate were 0.25 mg/L and 0.83 mg/L, respectively. Intra-assay and inter-assay variations were determined to be 10 mg/L and 20 mg/L. The coefficients of variation of the intra-assays were 2.05% for 10 mg/L and 5.98% at 20 mg/L. The coefficients of variation of the inter-assays were 7.25% for 10 mg/L and 6.72% at 20 mg/L. The calibration curves were constructed by spiking standard indoxyl sulfate solution (Sigma) into normal plasma collected from a clinically healthy dog (10:90, V/V) that had normal laboratory data. This created spiked plasma indoxyl sulfate concentrations of 10, 20, 50 mg/L. The background indoxyl sulfate concentration of the blank plasma sample was also determined. A linear relationship existed between the known indoxyl sulfate concentration and peak area, with the regression analysis resulting in an $r^2 \geq 0.996$. All the above statistical analyses were performed using analytic software (Peak-ABC, Kingtech Scientific).

Statistical methods

Statistical analysis of the results was performed using SPSS software (v.20). To assess the difference between groups, the Mann–Whitney *U* test was used for non-normally distributed data, which was identified using the Shapiro–Wilk test, and this data is represented as the median with interquartile range (IQR). The Student's *t* test was used for normally distributed data and this data is represented as the mean with standard deviation (SD). The differences between categorical variables, which are represented as percentages, were analyzed by Chi-square test or the Fisher's exact test. The capability of indoxyl sulfate to predict renal progression was assessed by receiver operator characteristic (ROC) curve analysis. Logistic regression was applied to calculate odds ratios (ORs) for the selected variables using 95% confidence intervals. Spearman correlation coefficients and linear regression were used to determine the association between indoxyl sulfate and other biochemical information. A P value <0.05 was considered statistically significant.

Results

Thirty-six dogs and fifty-eight cats were eligible and enrolled. Among the dogs, the progression group consisted of eight dogs with IRIS stage 2 and 12 dogs with IRIS stage 3, whereas there were eight dogs with IRIS stage 2 and eight dogs with IRIS stage 3 in the non-progression group. Among the cats, the progression group contained 12 cats with IRIS stage 2, 12 cats with IRIS stage 3 and five cats with IRIS stage 4, whereas the non-progression group consisted of 16 cats with IRIS stage 2 and 13 cats with IRIS stage 3.

The baseline findings and clinical characteristics of the feline and canine patients are summarized in Table 1. Cats with progressive CKD had higher indoxyl sulfate plasma concentrations than cats with non-progressive CKD (median [IQR] 15.8 [12.1–20.9] mg/L vs. 9.7 [6.7–12.6] mg/L; $P < 0.05$). Cats with progressive CKD had lower hemoglobin concentrations than cats with non-progressive CKD (9.3 [7.1–12.3] g/dL vs. 12.1 [10.6–13.3] g/dL; $P < 0.05$), and lower hematocrit (25.3 [21–33.5] % vs. 33.4 [29.4–37.6] %; $P < 0.01$). Cats with progressive CKD had higher phosphate concentrations than cats with non-progressive CKD (5.3 [4.6–6.3] mmol/L vs. 4.4 [3.8–4.8] mmol/L; $P < 0.05$) and higher calcium phosphate product than cats with non-progressive CKD (64.5 [52.5–78] $mmol^2/L^2$ vs. 44.1 [35.7–54.3] $mmol^2/L^2$; $P < 0.05$). However, serum creatinine concentrations, systolic blood pressure, and the UPC did not differ between the two groups. ($P = 0.239$, $P = 0.494$ and $P = 0.782$, respectively). Additionally, groups did not differ with respect to medical prescriptions, with the exception that cats with progressive CKD were more commonly prescribed phosphate binders (Table 2).

Dogs with progressive CKD had higher indoxyl sulfate plasma concentrations than dogs with non-progressive CKD (17.8 [11.2–34.4] mg/L vs. 7.4 [6.4–11.7] mg/L; $P < 0.05$). However, systolic blood pressure, hemoglobin, hematocrit, phosphate, calcium, calcium phosphate, albumin, baseline serum creatinine concentration, and urine protein–creatinine ratio (UPC) did not differ between groups (data not shown). Categorical variables (gender, breed, IRIS staging) in both dogs and cats did not achieve significance between the progression and non-progression groups (data not shown). The indoxyl sulfate plasma concentrations did not differ between cats (or dogs) receiving phosphate binders or not (in cats, 14.8 [11.1–18.6] mg/L, $n = 20$ vs. 12.1 [8.5–15.7], $n = 18$; $P = 0.06$; in dogs, 10.9 [1.4–21.4] mg/L, $n = 11$ vs. 12 [6.8–17.2] mg/L, $n = 23$; $P = 0.98$).

A previous report has indicated that indoxyl sulfate plasma concentrations increase as the IRIS stage increases (Cheng et al., 2015). Based on this finding, analyses of the progression of IRIS stage 2 CKD and IRIS stage 3 CKD were undertaken separately (Fig. 1). Twenty-eight cats were classified as IRIS stage 2 CKD: 12 with progressive CKD and 16 with non-progressive CKD. In addition, 25 cats were classified as IRIS stage 3 CKD: 12 with progressive CKD and 13 with non-progressive CKD. Cats with progressive IRIS stage 2 CKD had higher indoxyl sulfate concentrations than cats with non-progressive IRIS stage 2 CKD (14.7 [11.6–17.8] mg/L vs. 10.6 [7.2–14] mg/L; $P < 0.05$). Similarly, cats with progressive IRIS stage 3 CKD had higher indoxyl sulfate concentrations than cats with non-progressive IRIS stage 3 CKD (22.4 [13.2–31.6] mg/L vs. 11.07 [8.97–13.17] mg/L; $P < 0.05$).

[2] See: http://www.iris-kidney.com/guidelines/.
[3] http://www.iris-kidney.com/guidelines/recommendations.html.

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