The Veterinary Journal 220 (2017) 43–47

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Utility of urinary alkaline phosphatase and γ-glutamyl transpeptidase in diagnosing acute kidney injury in dogs

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ARTICLE INFO

Article history:
Accepted 15 December 2016

Keywords:
Canine
Renal failure
Acute kidney injury
Urinary alkaline phosphatase
γ-Glutamyl transpeptidase

ABSTRACT

The diagnostic utility of urinary alkaline phosphatase (uALP) and γ-glutamyl transpeptidase (uGGT) activities in naturally occurring acute kidney injury (AKI) was investigated in a heterogeneous group of dogs. The study included client-owned dogs with AKI ($n = 32$), chronic kidney disease (CKD, $n = 13$), lower urinary tract infection (LUTI, $n = 15$) and healthy controls ($n = 24$). uGGT and uALP activities were normalised to urinary creatinine (uCr) concentrations (uGGT/uCr and uALP/uCr, respectively). uALP/uCr and uGGT/uCr were positively and significantly correlated ($r = 0.619$, $P < 0.001$), and differed significantly ($P \leq 0.001$) among groups, as well as between AKI and LUTI or CKD groups ($P < 0.05$), but not between the AKI and control groups. Areas under the receiver operator characteristics (ROC) curve for uALP/uCr and uGGT/uCr as predictors of AKI were 0.75 and 0.65, respectively, with optimal cut-off points showing poor to moderate sensitivity (59% for uALP/uCr and 79% for uGGT/uCr) and specificity (59% for uALP/uCr and 75% for uGGT/uCr). Higher cut-off points, with 90% specificity, showed low sensitivity (41% for both uALP/uCr and uGGT/uCr). In conclusion, uALP/uCr is superior to uGGT/uCr as a marker of AKI, but both uGGT/uCr and uALP/uCr have unsatisfactory discriminatory power for diagnosing naturally occurring AKI in dogs and therefore cannot be recommended as sole screening tests for canine AKI. However, both may serve as ancillary, confirmatory, biomarkers for detecting AKI in dogs if appropriate cut-off points with high specificities are used.

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Introduction

Acute kidney injury (AKI) in dogs is associated with high morbidity and mortality (Ross, 2011). Early recognition of AKI is pivotal for slowing and potentially reversing progression to overt renal failure (Cowgill and Langston, 2011; Ross, 2011; Kellum et al, 2013). Glomerular filtration rate (GFR) is considered to be the reference standard for assessing global kidney function (Von Hendy-Willson and Pressler, 2011). Due to technical aspects and limited availability of various methods for measuring GFR, serum creatinine concentration (sCr) commonly serves as a surrogate GFR marker (Braun et al., 2003; Von Hendy-Willson and Pressler, 2011). However, sCr has several shortcomings (Braun et al., 2003; Hokamp and Nabity, 2016): (1) sCr is affected by muscle mass and thus varies among healthy dogs of different breeds; (2) sCr is not expected to increase above the reference interval (RI) until 75% of kidney function is lost; (3) sCr does not represent the severity of renal damage until a steady state is reached; and (4) sCr reflects GFR changes, rather than tubular damage per se.

Readily available kidney function and tubular injury markers, including urine specific gravity, glycosuria and cylinduria, lack sensitivity or specificity (Cowgill and Langston, 2011). Other urinary biomarkers may serve as early indicators of tubular injury, even before GFR changes or azotaemia occur (Cobrin et al., 2013; De Loor et al., 2013; Hokamp and Nabity, 2016). Amongst these, urinary enzyme activities are specific indicators of renal tubular injury, since their molecular size precludes glomerular filtration and their urinary excretion increases following tubular injury (Clemo, 1998; D'Amico and Bazzi, 2003; Cobrin et al., 2013; De Loor et al., 2013). The diagnostic and prognostic value of urinary enzyme activities has been demonstrated in dogs and human beings with AKI (D'Amico and Bazzi, 2003; Cobrin et al., 2013; De Loor et al., 2013).

Measurement of urinary alkaline phosphatase (uALP) and γ-glutamyl transpeptidase (uGGT) activities is simple, widely available and cost-efficient. Both are brush border enzymes located primarily in the metabolically active proximal renal tubule (Guder and Ross, 1984; Clemo, 1998). With their high molecular weight, the urinary activity of these enzymes is primarily considered to be of tubular origin rather than derived from the glomerular filtrate (Heiene et al., 1991; Clemo, 1998). Most studies of uGGT and uALP in dogs are limited to small cohorts of single aetiologies of AKI (Ellis et al., 1973; Adelman et al., 1979; Greco et al., 1985; De Schepper et al., 1989; Rao et al., 1990; Uechi et al., 1994a; Grauer et al., 1995;

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http://dx.doi.org/10.1016/j.tvjl.2016.12.010
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Rivers et al., 1996; Palacio et al., 1997; Clemo, 1998; Lobetti and Lambrechts, 2000; Lobetti and Joubert, 2000; Heiene et al., 2001; Raekallio et al., 2006; Palviainen et al., 2013; Ibba et al., 2016). Only the study by Heiene et al. (1991) evaluated their use in naturally-occurring canine AKI.

We investigated the clinical utility of uALP and uGGT in the diagnosis of naturally occurring AKI in a larger, more diverse, cohort of dogs. This study had two main aims: (1) to assess the utility of these biomarkers in differentiating AKI from other urinary tract diseases, specifically CKD, because of the prognostic implications of such a distinction; and (2) to serve as a preliminary study for further research regarding the use of these biomarkers in the recognition of early AKI, prior to the development of clinical signs and biochemical perturbations.

Materials and methods

Animals and study design

The study was conducted at the Hebrew University Veterinary Teaching Hospital, Koret School of Veterinary Medicine, Israel, and approved by the Institutional Animal Care and Ethics Committee (approval number KSVM-VTH/20-2015; date of approval 2 November 2015). Client-owned dogs were prospectively enrolled, and divided into three groups: (1) AKI; (2) chronic kidney disease (CKD); and (3) lower urinary tract infection (LUTI). Controls included staff-owned dogs and dogs presented for elective neutering, which were deemed to be healthy on the basis of their history, physical examination and complete blood count findings. Azotaemia was an exclusion criterion.

Diagnosis of LUTI was based on compatible clinical signs, and confirmed by urinalysis and a positive urine culture. Dogs were excluded from this group if they presented with azotaemia or ultrasonographic findings indicative of ascending urinary tract infection (Choi et al., 2010). CKD and AKI were diagnosed based on the International Renal Interest Society (IRIS) guidelines and grading system. The aetiology of AKI was recorded when identified.

Collection of samples and laboratory methods

Blood specimens for serum chemistry were collected as part of the basic clinical diagnostic work-up, in tubes containing no anticoagulant, with gel-separators. The blood was allowed to clot, then centrifuged, and the serum was separated and analysed within 60 min of collection. Urine samples were obtained as part of the basic clinical diagnostic work-up by cystocentesis and analysed within 30 min of collection. Biochemistry was determined using a wet chemistry analyser (Cobas Integra 400 Plus, Roche; 37 °C). uALP and uGGT activities were normalised to urinary creatinine concentration (uCr), i.e. uALP/uCr and uGGT/uCr, respectively.

Statistical analysis

The distribution of continuous variables was assessed using the Shapiro–Wilk test. The non-parametric Kruskal–Wallis test was subsequently used to compare continuous variables among groups, with pair-wise Mann–Whitney *U* test post-hoc comparisons and Bonferroni's correction. Spearman's correlation test was used to investigate the association between uALP/uCr and uGGT/uCr. The reference interval was calculated based on the 2.5th to 97.5th inter-percentile ranges of the control group results. The uALP/uCr and uGGT/uCr results of each dog were later classified as above or within/below this proposed reference interval. The receiver operator characteristic (ROC) analysis, with its area under the curve (AUC) and 95% confidence interval (CI), was used to assess uALP/uCr and uGGT/uCr as predictors of AKI. The Youden index (J) was used to locate the optimal cut-off point (Perkins and Schisterman, 2006). All tests were two-tailed and a P value < 0.05 was considered to be significant. Statistical analyses were performed using SPSS 22.0.

Results

The study included client-owned dogs with naturally-occurring AKI (n = 32 dogs), CKD (n = 13) or LUTI (n = 15), and healthy control dogs (n = 24), with median ages of 96 (range 7–168), 42 (range, 12–162), 108 (range 24–180) and 10 (range 3–216) months, respectively. The median age of the control group was lower than for other groups (P < 0.05). Intact males and females constituted the majority of dogs in the AKI, CKD, LUTI and control groups (65% and 19%, 53% and 38%, 57% and 42%, and 8% and 79%, respectively). Median sCr concentrations and the IRIS classification of dogs in the AKI and CKD groups are shown in Table 1. Specific aetiologies were identified in 11/32 AKI cases and included pancreatitis, previous anaesthesia and snakebite (two cases of each), and pyometra, trauma, carprofen intoxication, cycad intoxication and leptospirosis (one each).

uALP/uCr and uGGT/uCr varied considerably within groups (Fig. 1). Dogs with AKI had higher uALP/uCr, with a median of 0.01 and range of 0–6.39, expressed in (U/L)/(mg/dL), than dogs with CKD (median 0.01, range 0–0.31) or LUTI (median 0, range 0–0.07), but not control dogs (median 0.058, range 0.005–0.48). Dogs with AKI had higher uGGT/uCr, with a median of 0.40 and range of 0–31.4, expressed in (U/L)/(mg/dL), than dogs with CKD (median 0.025, range 0–2.2) or LUTI (median 0, range 0–2.1), but not control dogs (median 0.30, range 0.12–0.76). uALP/uCr and uGGT/uCr were significantly and positively correlated (r = 0.62, P < 0.001). The agreement between uALP/uCr and uGGT/uCr for each dog (when classified either as above or within/below reference interval) was 83%. Only dogs with AKI had uALP/uCr values above the reference interval, whilst increased uGGT/uCr was also noted in dogs with CKD (1/13 dogs) and LUTI (3/15 dogs), albeit not as commonly as in the AKI group (11/32 dogs).

The ROC curve AUCs (95% CI) for uALP/uCr and uGGT/uCr as predictors of AKI were 0.75 (0.64–0.86) and 0.65 (0.53–0.78), respectively, with sensitivity and specificity for optimal cut-offs of 59% and 79%, and 59% and 75%, respectively. Cut-offs with 90% specificity had low sensitivities (41% for both; Table 2). ROC analyses for uALP and uGGT activities, not normalised to uCr, had inferior diagnostic performance as predictors of AKI (AUC 0.60 and 0.49, respectively).

Discussion

This study investigated uGGT and uALP in a relatively large heterogeneous group of dogs with naturally acquired AKI. In contrast with a previous study (Heiene et al., 1991), uGGT/uCr and, to a lesser extent, uALP/uCr demonstrated unsatisfactory discrimination between dogs with AKI and dogs with other urinary tract conditions and healthy controls.

Kidney damage is a continuum, with the initial injury progressing to kidney dysfunction and potentially culminating in kidney failure and overt azotaemia (Basile et al., 2012). Early diagnosis of AKI might allow timely intervention and improved prognosis (Basile et al., 2012). Since sCr is inadequate for detecting early AKI, urinary

Table 1
Median (range) serum creatinine concentrations among the study groups and the distribution of cases in the acute kidney injury and chronic kidney disease groups, based on International Renal Interest Society (IRIS) grading and staging guidelines.

	Acute kidney injury					Chronic kidney disease				Lower urinary tract infection	Control
Median sCr[a] (range)	6.9 (1.5–22.0)					4.4 (1.3–11.7)				0.66 (0.46–1.35)	0.7 (0.3–1.2)
IRIS grade/stage[b]	I	II	III	IV	V	1	2	3	4	NA	NA
%	3	6	25	38	28	8	23	31	38		

NA, not applicable.
[a] Serum creatinine (mg/dL).
[b] IRIS staging of chronic kidney disease (http://iris-kidney.com/guidelines/staging.html; accessed 21 August 2016) and grading of acute kidney injury (http://www.iris-kidney.com/pdf/grading-of-acute-kidney-injury.pdf; accessed 21 August 2016).

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