Comparison of ultrasonographic findings in cats with and without azotaemia

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Abstract

Objective. To identify the renal ultrasonographic (US) findings most strongly associated with azotaemia in cats.

Methods. Ultrasonographic findings in 238 cats with (serum creatinine >180μmol/L) and 270 cats without azotaemia were compared in a retrospective case-control study. Cats with pre-renal azotaemia or urethral obstruction were excluded. Data extracted from the medical records included age, body weight and body condition score (BCS). Quantitative and subjective US findings were extracted from archived ultrasound images and contemporaneous reports.

Results. In non-azotaemic cats, mean renal length was 40.1mm (SD 5.5mm). Male cats had larger kidneys than female cats (mean difference 5.2mm, p=0.001) and on average the right kidney was slightly larger than the left (mean difference 1.6mm, p=0.01). Azotaemic cats had significantly lower mean body weight and BCS, and greater mean age and renal pelvic diameter. Renal pelvic diameter was negatively correlated with urine specific gravity (ρ -0.44, p<0.001). Compared to non-azotaemic cats, there was no difference in mean renal length of azotaemic cats because the numbers with enlarged kidneys and small kidneys were similar. Radiologists' subjective assessments of renal size differed markedly between azotaemic and non-azotaemic cats, with azotaemic cats more likely to be recorded falsely as having abnormally small or enlarged kidneys. US findings significantly associated with azotaemia were perinephric fluid (OR 26.4, CI 3.4-207.7), small kidneys (OR 8.4, CI 4.0-17.4), hyperechoic renal cortex (OR 4.1, CI 2.2-7.6), loss of corticomedullary differentiation (OR 4.1, CI 1.8-9.6), renal calculi (OR 2.7, CI 1.4-4.9), enlarged kidneys (OR 2.5, CI 1.2-5.5) and dilated renal pelvis (OR 1.6, CI 1.3-1.9).

Conclusion and relevance. Perinephric fluid was the US finding most strongly associated with azotaemia in this study and may merit more emphasis than it has received to date. Bias in radiologists' subjective assessments of renal size suggests that other subjective findings will also be biased.

Introduction

Renal azotaemia can occur because of an acute kidney injury (AKI) or the cumulative effects of chronic kidney disease (CKD).[1, 2] In cats, causes of AKI include ureteral obstruction[3, 4], ethylene glycol or lily toxicity[3], and pyelonephritis[3], and causes of CKD include polycystic kidney disease[5-8], interstitial inflammation and fibrosis[9], and nephrolithiasis.[10] AKI and CKD can be present together, for example when ureteral obstruction occurs as a sequel to nephrolithiasis.[4, 11] In patients with azotaemia, ultrasonography (US) is indicated to examine the kidneys in order to distinguish AKI from CKD[12], particularly to look for signs of urinary obstruction[13], which requires specific treatment. Given that unilateral renal abnormalities will not result in azotaemia if the contralateral kidney is functioning well, it is essential to examine both kidneys.

US abnormalities can be divided into subjective findings, including abnormal renal shape and echogenicity, and quantitative findings, including abnormal renal length and pelvic dilatation.[14] Both subjective and quantitative abnormal findings can occur in cats with or without azotaemia because of overlap between the normal and abnormal ranges, because of the occurrence of subclinical renal disease that does not cause azotaemia, and because the kidneys may be affected secondarily in cats with various non-renal diseases, such as cardiomyopathy[15] or acromegaly.[16] It is unclear what subjective or quantitative US findings are most strongly associated with azotaemia and, therefore, are most likely to represent accurate signs of clinically significant renal disease. For example, renal length is routinely measured during abdominal US examinations and there have been multiple studies of normal renal size in cats[17-22]; however, the diagnostic accuracy of renal length measurements has not been assessed.

The aim of the present study was to compare US findings in cats presenting with and without azotaemia in order to identify the ultrasonographic findings most strongly associated with azotaemia.

Methods

For this retrospective case-control study, electronic medical records of the Queen Mother Hospital for Animals (QMHA) between June 2009 and May 2015 were reviewed. The criteria for inclusion were cats presented for the first time during this period that had ultrasonography of the urinary tract, ultrasound report and images available for review, and had serum creatinine determination. Azotaemia was defined as serum creatinine at presentation >180µmol/L as determined by the clinical pathology laboratory or plasma creatinine >140µmol/L as determined by bench-top biochemistry analyser (Bioprofile 300, Nova Biomedical, USA). Cats with pre-renal azotaemia or urethral obstruction were excluded. Determination of pre-renal azotaemia was based on serum creatinine on admission above the reference range, a urine specific gravity (USG) >1.040, and no ultrasonographic evidence of urinary obstruction.[3]

Cases were collected in two stages: all azotaemic cats that satisfied the inclusion criteria were collected first for use in a study of ureteral obstruction[23], followed by collection of a similar number of non-azotaemic cats presented during the same time period, regardless of their clinical diagnosis. Data extracted from the medical records included signalment, body weight, body condition score (BCS), serum creatinine, and urine specific gravity. US findings were extracted from contemporaneous reports written by 6 different Board-certified ultrasonographers employed at the QMHA during the period covered by the study. Archived ultrasound images were reviewed in order to add renal measurements absent from the report. US findings included objective renal length in sagittal or dorsal images, objective transverse pelvic diameter, subjective renal size, subjective pelvic and ureteral dilatation, renal shape (irregular, asymmetrical, nodule or mass lesion), presence of renal scars (focal depressions in the cortical surface with adjacent hyperechoic cortical segment), echogenicity of the cortex and medulla, presence of renal cysts, calcification of the renal parenchyma, presence of perinephric fluid, and presence of renal, ureteral or bladder calculi (Table 1). Clinical and ultrasonographic data for each cat were derived from the first period of hospitalization only.

Non-azotaemic cats

In non-azotaemic cats, renal length was tested for Normality. The effect of gender, body weight and laterality (left or right) on renal length was tested using a linear mixed effects model that accounted for repeated measures from each cat. Correlation between USG and renal pelvic diameter (neither of which were Normally distributed) was tested using Spearman's coefficient (ρ). Associations between age of non-azotemic cats and likelihood of abnormal US findings affecting either kidney were tested using binary logistic regression.

Comparisons between azotaemic and non-azotaemic cats

Continuous variables were tested for Normality and differences in continuous variables between azotaemic and non-azotaemic cats tested using an independent samples *t*-test. The differences in body condition score and renal pelvic diameter between azotaemic and non-azotaemic cats were tested using Mann-Whitney tests. Subjective US findings for the left and right kidney in each cat were aggregated for statistical analysis. Pairwise testing of differences in prevalence of US findings between azotemic and non-azotemic cats were tested using chi-square methodology. Associations between US findings and azotaemia were tested using binary logistic regression with step-wise removal of non-significant variables. Results were expressed as odds ratio (OR) and 95% confidence intervals (CI). Statistical tests were done using a proprietary application (SPSS Statistics, version 22, IBM Corporation). Differences with $p<0.05$ were considered significant.

Results

Records were found of 238 azotemic cats and 270 non-azotemic cats. There were 286 males (275 neutered) and 222 females (210 neutered). Their median age was 7y (range 2w-22y). There were 286 (56%) Domestic shorthair cats, 23 (5%) Persians, 30 (6%) Domestic longhairs, 21 (4%) British shorthair cats, 18 (4%) Ragdolls, 16 (3%) Bengals, 16 (3%) Siamese, 15 (3%) mixed breed cats, 14 (3%) Burmese, 10 (2%) Maine Coons, 8 (2%) Birmans, 8 (2%) British Blues, 6 (1%) Tonkinese and 15 other feline breeds with less than 5 affected individuals. Median body condition score was 4/9 (range 1-8) and mean body weight was 4.1kg (range 0.9-8.5kg).

Median serum creatinine in azotemic cats was 417µmol/L (range 184-2100µmol/L) as determined by the clinical pathology laboratory (n=199) and median USG was 1.018 (range 1.006-1.050). Ureteral obstruction was the most frequent tentative diagnosis, recorded in 92/238 (39%) azotemic cats, and of these 38 (41%) were proved to have ureteral obstruction by pyelography.[23]

Non-azotemic cats

Renal length had a Normal distribution with mean 40.1mm (SD 5.5mm). Five (2%) juvenile (<9 months old) non-azotaemic cats were excluded from this calculation. There were significant effects on renal length for gender ($p<0.001$) and laterality ($p<0.01$), but not body weight ($p=0.85$). Males had larger kidneys than females (mean 42.1mm versus 36.9mm) and the right kidney was larger than the left (mean 40.9mm versus 39.3mm).

In non-azotaemic cats, there was a significant association between likelihood of abnormal US findings and increasing age ($p=0.001$). Specifically, the prevalence of dilated renal pelvis (OR 1.2, 95% CI 1.07-1.32), hyperechoic renal cortex (OR 1.1, 95% CI 1.02-1.21) and calcification of renal parenchyma (OR 1.3, 95% CI 1.02-1.58) increased with age.

Comparisons between azotaemic and non-azotaemic cats

Azotemic cats had significantly lower mean body weight and BCS, and greater mean age and renal pelvic diameter than non-azotemic cats (Table 2). No significant difference in median renal length was observed because the numbers of azotaemic cats with enlarged kidneys and small kidneys were similar (see below).

Subjective renal length was reported to be abnormal in 182 (76%) azotemic cats, with 101 (42%) having subjectively small kidneys and 81 (34%) having subjectively enlarged kidneys; however, based on using renal size in the non-azotaemic cats in this study as a reference range, small kidneys

(<29mm) and enlarged kidneys (>51mm) were present in only 16% and 6% cats with azotaemia, respectively. Plots of the probability that renal length was recorded as subjectively normal versus actual renal length demonstrate markedly different distributions in non-azotaemic and azotaemic cats (figure 1). In non-azotaemic cats, the kidneys were more likely to be recorded as subjectively normal in size in the range 29-51mm, which corresponds closely with the reference range observed in these cats. In contrast, the kidneys of azotaemic cats were more likely to be recorded as subjectively normal in the narrower range 35-45mm.

Renal pelvic diameter was negatively correlated with USG (ρ -0.44, $p<0.001$) (figure 2). If the 38 cats with proven ureteral obstruction were excluded, the correlation between renal pelvic diameter and USG was not changed significantly.

Abnormalities affecting the kidneys, ureters and/or bladder were observed in 226 (95%) cats with azotaemia and 126 (47%) cats without azotaemia (Table 3). On the basis of pairwise testing, all recorded US findings were significantly more prevalent in azotaemic cats, except renal nodule or mass, polycystic disease, the medullary rim sign, halo sign and perinephric pseudocyst, which occurred with similar frequency in azotaemic and non-azotaemic cats. In the final regression model, US findings significantly associated with azotaemia were perinephric fluid (OR 26.4, 95% CI 3.4-207.7), small kidneys (OR 8.4, 95% CI 4.0-17.4), hyperechoic renal cortex (OR 4.1, 95% CI 2.2-7.6), loss of corticomedullary differentiation (OR 4.1, 95% CI 1.8-9.6), renal calculi (OR 2.7, 95% CI 1.4-4.9), enlarged kidneys (OR 2.5, 95% CI 1.2-5.5), and dilated renal pelvis (OR 1.6, 95% CI 1.3-1.9).

Discussion

The cats in this series represent heterogeneous samples of azotemic and non-azotemic cats. In the majority of azotemic cats, a specific final diagnosis was not determined[23] and diagnosis in non-azotemic cats was not recorded for the purposes of the present study. Under these circumstances, only relatively general conclusions are possible about the meaning of the US findings. For example, perinephric fluid was the US finding most strongly associated with azotaemia, the majority of possible US signs of renal disease had low sensitivity for azotaemia and low specificity, with abnormalities affecting the kidneys reported frequently in cats without azotaemia. Although US is recommended for investigation of individual cats with CKD[24], it is not recommended as a screening test for CKD in cats[21] because of the poor correlation between US findings and renal function and the prevalence of US abnormalities in non-azotaemic cats, the significance of which is difficult to assess.

Abnormalities affecting the kidneys were reported in 47% non-azotaemic cats in the present study. The increasing prevalence with age of dilated renal pelvis, hyperechoic renal cortex and calcification of the renal parenchyma may reflect subclinical renal disease that gradually becomes more marked over time.[1, 9] Other studies have also found a high prevalence of US abnormalities in cats without azotaemia. For example, US changes including segmental cortical lesions and abnormal renal capsule were detected in 66/133 (50%) healthy Ragdoll cats and 25/62 (40%) healthy cats of other breeds.[25] The occurrence of abnormalities affecting the kidneys in cats without azotaemia is not surprising because azotaemia is an insensitive indicator of renal function[26] that becomes elevated only when a large proportion of functional nephrons have been lost and may be low despite clinically significant renal disease in cats with low body weight.[27, 28] Insensitivity of serum creatinine means that the group of non-azotaemic cats in the present study will include individuals with renal disease. More accurate quantitative assessment of renal function requires measurement of glomerular filtration rate[28]; however, serum creatinine remains the test most widely used for assessment of renal function in cats (and dogs) because it is widely available and inexpensive compared to measurement of glomerular filtration rate.

Polycystic renal disease and medullary rim sign occurred with similar frequency in azotemic and non-azotemic cats. Polycystic renal disease encompasses a wide spectrum of severity, including subclinical.[29, 30] That polycystic renal disease was found just as frequently in cats without signs of renal dysfunction as in cats with azotaemia emphasizes that its significance in an individual feline patient must be interpreted in combination with other clinical findings. As previously reported in dogs[31], there appears to be no association between the medullary rim sign and clinical renal disease in cats.

Occurrence of perinephric fluid has been reported previously in cats with azotaemia[23, 32] and has been associated with hyperkalaemia in cats with urinary obstruction.[33] Although perinephric fluid was not significantly associated with ureteral obstruction or severity of renal dysfunction in some previous studies[23, 32], it was the US finding most strongly associated with azotaemia in the present study and, therefore, may merit more emphasis than it has received to date. Perinephric fluid may be distinguished from subcapsular collections or perinephric pseudocyst when it has a pointed shape on its non-renal border and/or is confluent with hypo- or anechoic fluid dissecting between fat in the retroperitoneum. By analogy to cardiac failure, in which pulmonary oedema is a more accurate indicator of cardiac dysfunction than the radiographic appearance of the cardiac silhouette[34], perinephric fluid appears to be a more accurate sign of renal dysfunction than the US appearance of the kidneys. Perinephric fluid is liable to accumulate in cats with renal disease when renal ultrafiltrate leaks into the renal interstitium in sufficient quantity to overwhelm the drainage capacity of capsular lymphatics.[32] Perinephric fluid in cats with renal dysfunction is more likely to be observed after administration of intravenous fluids than at presentation when cats are liable to have hypovolaemia.

Renal length in healthy cats has been studied in some detail. Using US measurements, the normal reference range has been reported as 30.4-42.9mm in 10 cats[17] and 29.8-50.9mm in 56 Ragdoll cats.[35] Minor, non-significant inter-breed differences were observed in renal length of sphynx cats, British Shorthair and Ragdoll cats.[36] Multiple studies have found that the right kidney in cats is slightly longer than the left.[20, 22, 36] Renal length in cats has also been positively correlated with bodyweight[20, 35], fat accumulation in the kidney[37], age[35] and male gender.[35] In a radiographic study, neutered cats had smaller kidneys than sexually intact cats.[18] The present study provides additional evidence that the reference range for feline kidneys should be approximately 29-51mm, that male cats have larger kidneys than female cats (mean difference 5.2mm), and on average the right kidney is normally slightly larger than the left (mean difference 1.6mm).

The diagnostic accuracy of renal length measurements is low because relatively few cats with azotaemia have either small or large kidneys. In the present study, small kidneys (<29mm) and enlarged kidneys (>51mm) were present in only 16% and 6% cats with azotaemia, respectively, hence the sensitivity of this measurement for azotaemia is low; however, the kidneys of azotaemic cats in the present study were more likely to be recorded as subjectively abnormal than kidneys of the same size in non-azotaemic cats. This finding indicates that ultrasonographers' judgements about renal size were biased by the knowledge that patients had azotaemia. This observation raises questions about the validity of subjective renal size assessment in azotaemic cats specifically, and questions about the validity of subjective organ size assessment in clinical patients generally. Interpretation of diagnostic images (and other test results) tends to be more accurate if the clinical history is known[38]; however, one argument against providing clinical information is that readers may perceive abnormalities that are not present (false positives). It appears that the ultrasonographers whose data were used for the present study employed different thresholds for abnormally small and abnormally large depending on the clinical history of azotaemia and, therefore, were recording abnormalities that may not have been present. It is important not to over-emphasize organ size as a diagnostic criterion because the normal size ranges for many anatomical structures are very wide (particularly in dogs), hence there is marked overlap between normal and pathologic ranges, which limits the sensitivity and specificity of tests based on measurements.[39]

If subjective assessment of renal size is prone to bias, the same may be true of other subjective US findings significantly associated with azotaemia in the present study, such as hyperechoic renal cortex or loss of corticomedullary differentiation. Hyperechoic renal cortex is a finding based on subjective comparison of renal echogenicity with adjacent structures, such as the liver. The renal cortex in cats normally has similar echogenicity as the adjacent liver[19], although this relationship may be affected by normal variations in fat deposition in the kidney[37] and/or liver[40, 41] or the type of ultrasound transducer used.[42] In cats, interstitial nephritis, interstitial necrosis and fibrosis are associated with increased renal cortical echogenicity.[43] Particularly in a cat with CKD, in which these conditions are suspected, renal echogenicity is liable to be over-interpreted. The low specificity of this US finding is also emphasized by the finding that it was the abnormality reported most frequently in cats without azotaemia in the present study.

Median renal pelvic diameter was significantly greater in azotaemic cats compared to non-azotaemic cats. This difference likely reflects both the occurrence of urinary obstruction in the group of azotemic cats, which was proven in 38/238 (16%) instances, and their lower median USG, which will frequently be associated with polyuria. Based on all cats for which USG data were available, renal pelvic diameter was negatively correlated with USG. The tendency for pyelectasia in animals producing dilute urine represents a physiologic variation in pelvic diameter occurring in response to different rates of urine output. This effect has been demonstrated experimentally in dogs.[44]

Conclusion

On the basis of the present study, it appears that perinephric fluid is strongly associated with azotaemia and may be less prone to bias than subjective assessments of renal size or echogenicity. Therefore, it may prove to be one of the most accurate US signs of renal dysfunction.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Ultrasonographic criteria

Criterion	Value recorded
Renal length	mm
Pelvic transverse diameter	mm
Subjective renal size	Normal; small; enlarged
Subjectively dilated pelvis	No; slight; marked
Subjectively dilated ureter	No; slight; marked
Renal shape	Normal; irregular; asymmetrical; rounded; nodule; mass
Cortical scars	None; slight; marked
Echogenicity of cortex	Normal; increased; heterogeneous
Echogenicity of medulla	Normal; increased; heterogeneous; medullary rim sign; halo signs; loss of corticomedullary differentiation
Calcification of renal parenchyma	None; present
Renal cyst	Single cyst; polycystic renal disease
Perinephric fluid	None; slight; marked; perinephric pseudocyst
Renal calculi	None; single; multiple
Calculi in ureter	None; single; multiple
Calculi in bladder	None; single; multiple

Table 2. Comparison of continuous variables cats with and without azotaemia

Variable	Azotaemic (n=238)	Non-azotaemic (n=270)	p-value
Age (y)	8.1 (4.7)	6.0 (4.0)	<0.001
Body weight (kg)	3.9 (1.1)	4.3 (1.3)	0.02
Body condition score (/9)	4 (1-8)	4 (2-8)	0.02
Urine specific gravity	1.018 (1.006-1.050)	1.041 (1.011-1.070)	<0.0001
Renal length (mm)	39.3 (8.5)	40.1 (5.5)	0.11
Renal pelvic diameter (mm)	2.0 (0-50)	0 (0-12)	<0.001

Values are mean (SD) for age, body weight and renal length; values are median (range) for body condition score, urine specific gravity and renal pelvic diameter.

Table 3. Comparison of ultrasonographic signs in cats with and without azotaemia

Ultrasonographic signs	Azotemic (n=238)	Non-azotemic (n=270)	p-value
Subjectively small kidney	101 (42%)	15 (6%)	<0.001
Subjectively enlarged kidney	81 (34%)	21 (8%)	<0.001
Subjectively dilated pelvis	152 (64%)	17 (6%)	<0.001
Subjectively dilated ureter	86 (36%)	3 (1%)	<0.001
Irregular renal shape	69 (29%)	14 (5%)	<0.001
Rounded kidney	9 (4%)	0	0.001
Renal nodule or mass	1 (0.4%)	1 (0.4%)	1
Cortical scars	41 (17%)	18 (7%)	<0.001
Hyperechoic renal cortex	105 (44%)	31 (12%)	<0.001
Hyperechoic renal medulla	74 (31%)	20 (7%)	<0.001
Medullary rim sign	22 (9%)	27 (10%)	0.88
Halo sign	0	0	1
Loss of corticomedullary differentiation	61 (26%)	14 (5%)	<0.001
Calcification of renal parenchyma	12 (5%)	3 (1%)	0.01
Polycystic disease	12 (5%)	16 (6%)	0.70
Perinephric fluid	54 (23%)	1 (0.4%)	<0.001
Perinephric pseudocyst	1 (0.4%)	0	0.47
Renal calculi	92 (39%)	13 (5%)	<0.001
Calculi in ureter	77 (32%)	1 (0.4%)	<0.001
Calculi in bladder	49 (21%)	12 (4%)	<0.001

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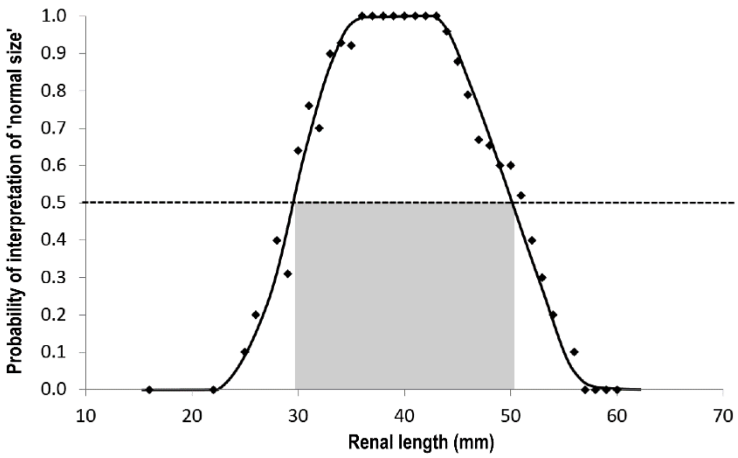
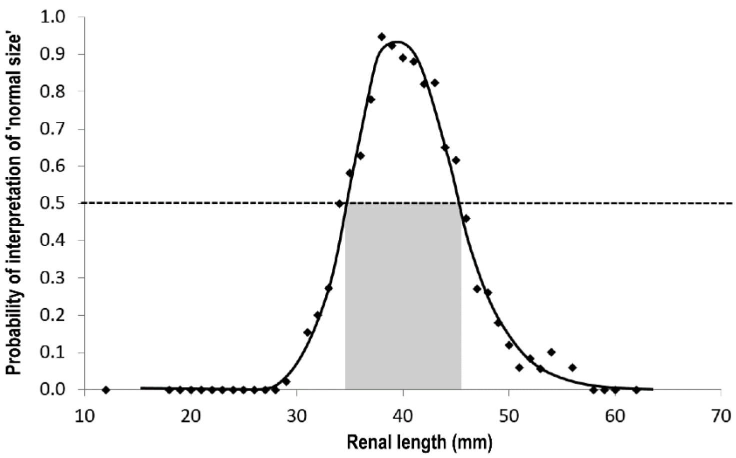
Figure legends

Figure 1. Plots of the probability that renal length was recorded as subjectively normal versus actual renal length in (A) non-azotaemic cats and (B) azotaemic cats. Probability of a kidney being reported as normal size exceeds 50% in the range 29-51mm (grey zone) for non-azotaemic cats and the narrower range 35-45mm for azotaemic cats. Trend lines were drawn manually for illustration purposes only.



A



B

Figure 2. Scatter plot of renal pelvic diameter against USG in 368 cats. There is a moderate negative correlation (ρ = -0.44, $p<0.001$).