Assessments of Factors that Affect Glomerular Filtration Rate and Indirect Markers of Renal Function in Dogs and Cats

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ABSTRACT. Chronic kidney disease is one of the most common disorders in dogs and cats. The plasma urea nitrogen (P-UN) and creatinine (P-Cre) concentrations are not sufficiently sensitive for early diagnosis of renal dysfunction. Although urine and plasma clearance methods allow earlier detection of reductions in the GFR, it is difficult to estimate a mildly reduced GFR from the values obtained by these methods, as they are also affected by physiological factors, such as body weight (BW) and age. The present study is a retrospective survey designed to assess the factors that affect markers of kidney function and to revaluate the clinical utility of the markers, including P-UN, P-Cre and GFR determined by plasma iothexol clearance (PCio) in dogs and cats. The P-UN, P-Cre and PCio values in dogs and the P-Cre and PCio values in cats were significantly correlated with BW (P<0.001). PCio in smaller dogs (≤ 15.0 kg) was significantly and inversely correlated with age. In smaller dogs, increase of P-UN alone might warrant a suspicion of a decreased GFR, but in contrast, P-Cre may be inefficient for detecting renal dysfunction or determining the severity of CKD compared with that in larger dogs (≥ 15.1 kg). P-Cre in larger dogs correlated better with PCio than in smaller dogs, suggesting that P-Cre in larger dogs was a more sensitive marker of reduced GFR.

KEY WORDS: body weight, plasma creatinine, plasma iothexol clearance, plasma urea nitrogen.

Chronic kidney disease (CKD) is one of the most common disorders and is a common cause of death in dogs and cats. The prevalence of renal diseases has been reported to range from 0.5 to 7% in dogs and from 1.6 to 20% in cats [29, 43]. Although CKD occurs in dogs and cats of all ages, the mortality of CKD commonly increases with age. In human and veterinary medicine, CKD is diagnosed by detecting chronic decreases in the glomerular filtration rate (GFR) or the presence of chronic renal damage [4, 36]. GFR can be evaluated indirectly from the concentrations of plasma and urine markers, which are dependent on the amount eliminated by the kidneys. The plasma urea nitrogen (P-UN) and creatinine (P-Cre) concentrations are widely used as endogenous markers to evaluate renal function in dogs and cats because they can be easily, rapidly and cheaply measured.

GFR is measured directly by urine or plasma clearance methods using inulin, creatinine or iothexol [7, 14, 15, 20, 21, 33, 34]. Although the urinary clearances of inulin and creatinine are considered to be the gold standards for measuring GFR in humans and animals, these methods are impractical in clinical settings because they require insertion of a bladder catheter, which is associated with a risk of developing a urinary tract infection or urethral injury; complete collection of a timed urine sample; and continuous infusion of the marker. The single injection technique can be used to determine plasma clearance from the elimination curve of a marker in plasma after a bolus injection. Plasma clearance can be determined by dividing the dosage of the administered marker by the area under the plasma concentration versus time curve (AUC). This method is easier to perform than the urinary clearance method because it does not involve collection of urine samples or continuous infusion of a marker. However, these tests cannot be used as screening tests. Therefore, any abnormalities, such as azotemia or a low urine specific gravity, should be determined by other screening tests in order to select and perform this plasma clearance method.

CKD can be diagnosed by measuring the P-UN and P-Cre concentrations or by clearance methods for evaluation of GFR. However, P-Cre has poor sensitivity because it usually does not increase until 75% of GFR has been lost [17, 22]. In addition, these measures are known to be affected by various extrarenal factors. The P-UN concentration is increased by high protein intake or large amounts of food intake, decreased circulating blood volume that including due to dehydration or hemorrhaging and intestinal hemorrhaging, fasting or sepsis, which increase protein catabolism [9, 12, 37]. P-UN is decreased by liver insufficiency, portosystemic shunts and malnutrition [10]. Although age also affects P-UN, the variations are irregular [40, 44]. The P-Cre concentration is affected by body weight (BW) and breed in dogs [13, 30]. Enzymatic methods give slightly lower creatinine concentration results than HPLC or the Jaffe reaction in canine plasma [12]. Less information is available about the interindividual factors of variation for the P-Cre concentration in cats. In humans, an equation is available to calculate estimated GFR (eGFR) from P-Cre,
sex and age, and reference values for P-Cre and eGFR have been established according to age and sex [26]. In veterinary practice, no reference range for P-Cre based on body weight or age has been calculated. In dogs and cats, the clinical utility of these GFR markers might also be improved, considering the effects of body weight, age and sex on P-UN and P-Cre. The present study is a retrospective survey designed to assess the factors affecting markers of kidney function and to revaluate the clinically utility of these markers, including P-UN, P-Cre and GFR determined by plasma iohexol clearance in dogs and cats.

MATERIALS AND METHODS

Animals: Six hundred and ninety-nine dogs and 321 cats were included in this study. One hundred and eleven of the 699 dogs and 82 of the 321 cats were raised as laboratory animals in the Department of Veterinary Internal Medicine at Nippon Veterinary and Life Science University (NVLU), and 582 dogs and 239 cats were client-owned animals that were presented to the Nephrology Service of the Animal Medical Center at NVLU or one of 115 other veterinary hospitals in Japan for the measurement of plasma iohexol clearance (PCio). Of all the animals, 460 dogs and 239 cats were diagnosed with CKD based on the presence of azotemia, chronic decreasing urine-specific gravity, renal proteinuria (urinary protein-creatinine ratio > 0.5 for dogs and > 0.4 for cats), abnormal renal morphology and/or decreased PCio (mentioned below) in conformity with the common definition of CKD [36]. Thirty-five of the 460 CKD dogs and 10 of the 239 CKD cats had renal proteinuria or abnormal renal morphology without decreased PCio. In the remaining 239 dogs and 82 cats, no abnormalities were detected by CBC, plasma biochemistry, urinalysis or ultrasonography. These animals were assigned to the control group. Beagle (n=117), cross breeds (n=65), Shih Tzu (n=55), Golden Retriever (n=52), Labrador Retriever (n=43) and the Miniature Dachshund (n=41) were the most common canine breeds, and cross breeds (n=254), American Shorthair (n=117), cross breeds (n=65), Shih Tzu (n=55), Golden Retriever (n=52), Labrador Retriever (n=43) and the Miniature Dachshund (n=41) were the most common feline breeds.

In the healthy group, the mean body weight and age were 13.9 ± 9.6 (range: 0.7 to 57.9) kg and 5.1 ± 3.7 (range: 0.6 to 16.6) years for dogs and 4.0 ± 0.9 (range: 2.2 to 7.2) kg and 7.3 ± 3.6 (range: 0.4 to 15.0) years for cats, respectively. These 239 dogs and 82 cats included 90 male, 93 female, 24 neutered and 32 spayed dogs and 29 male, 31 female, 15 neutered and 7 spayed cats. In the CKD group, the mean body weight and age were 12.6 ± 12.0 (range: 0.9 to 69.3) kg and 8.3 ± 4.2 (range: 0.3 to 17.0) years for dogs and 4.2 ± 1.2 (range: 2.2 to 10.5) kg and 8.2 ± 4.6 (range: 0.5 to 21.0) years for cats, respectively. These 460 dogs and 239 cats included 131 male, 115 female, 86 neutered and 124 spayed dogs and 33 male, 58 female, 73 neutered and 75 spayed cats. All dogs and cats were classified into two groups on the basis of the mean of body weight (15 kg for dogs and 4 kg for cats).

Measurement of plasma creatinine (P-Cre) and urea (P-UN) concentrations: Blood samples were collected from the jugular vein and were heparinized before the PCio procedure. All blood samples were centrifuged at 3,000 g for 5 min, and the plasma was separated and stored at -20°C until analysis. All samples were analyzed within 7 days of being stored. P-UN and P-Cre were measured by an enzyme method using an automatic analyzer (7180 Automatic Analyzer, Hitachi). The reference ranges for P-UN and P-Cre were 9.2 to 29.2 and 0.4 to 1.4 mg/dl for dogs and 17.6 to 32.8 and 0.8 to 1.8 mg/dl for cats, respectively.

Plasma iohexol clearance (PCio): PCio was performed to determine GFR in all dogs as previously described [7, 15, 34]. These animals were well hydrated and fasted for half a day before the PCio study. The dosage of iohexol was 90 mg of iodine/kg for non-azotemic animals and 45 mg of iodine/kg for azotemic animals. A half-milliliter of heparinized blood was collected from the jugular vein before iohexol injection. Iohexol was administered via the cephalic vein (time 0), and then heparinized blood was sampled again at 120, 180 and 240 min for the non-azotemic dogs and 120, 240 and 360 min for the azotemic dogs. The plasma iodine concentration was determined by cerium arsenite colorimetric methods [34].

PCio was calculated using the 1-compartment model corrected with the Broschner-Mortensen formula [6]. The area under the curve (AUC) was estimated from the slope (α) and intercept (A) of the elimination phase of the curve, as determined by linear regression analysis of the final three plasma samples. Clearance values (Cl) were calculated as Cl = dose of iohexol/AUC (AUC=A/α). The PCio was then calculated as PCio=0.990778 × CI−0.001218 × Cl². The clearance values (ml/min) were standardized to BW (ml/min/kg) and body surface area (BSA, m²/min/m²). BSA (m²) was calculated from BW (g) using the formula: BSA=K × (BW)²/10², where K is a shape constant (10.1 for dogs and 10.0 for cats), and α is the mass exponent (0.71 for dogs and 0.66 for cats) [38]. The reference ranges in dogs and cats were 40.59 to 106.54 and 36.14 to 71.12 ml/min/m², respectively. These values were determined using PCio values obtained from healthy dogs (n=100) and cats (n=36) under the same conditions including fasting, environment and hydration state as in our previous study (unpublished data). In this study, a PCio of < 40 ml/min/m² (2.35 ml/min/kg) for dogs and < 35 ml/min/m² (2.11 ml/min/kg) for cats was considered to represent a decreased GFR [31].

Statistics: Statistical analysis was performed using commercial software (Dr. SPSS for Windows, SPSS Japan Inc.). Descriptive statistics were calculated for BW, age, sex, and each measurement parameter in the dogs and cats. Linear regression analysis and Pearson’s coefficient of correlation were used to assess the correlation among the markers and BW and age in the healthy dogs and cats. Sex differences of the markers were assessed using the Student’s t-test in healthy dogs and cats. Receiver operating characteristics (ROC) analysis was performed to assess the sensitivity and specificity of P-Cre and P-Urea for detecting decreases in
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The values are presented as means ± standard deviation (SD). A P value of < 0.05 was considered statistically significant.

RESULTS

The P-UN and P-Cre concentrations, PCio/BW and PCio/BSA for the healthy dogs and cats group are shown in Table 1. In the healthy dogs group, P-UN, P-Cre, PCio/BW and PCio/BSA were significantly correlated with BW. Only the PCio values were also significantly correlated with age, but a significant linear correlation was also detected between age and BW (r=0.224, P<0.01). When all healthy dogs were classified as high BW (≥ 15.1 kg) or low BW (≤ 15.0 kg), no significant correlation was found between age and BW in the high or low BW group (r=0.092, P=0.538, and r= – 0.013, P=0.867, respectively). The PCio/BW values in the low BW group were significantly correlated with age (r= – 0.296, P<0.001), but not in the high BW group (r= – 0.119, P=0.428; Fig. 1). The P-UN and P-Cre concentrations were not significantly correlated with age in the high (r= – 0.264, P=0.072, and r= – 0.159, P=0.285, respectively) or low BW group (r=0.087, P=0.261, and r= – 0.004, P=0.956, respectively).

In the healthy cats group, the PCio/BW and P-Cre concentration were significantly correlated with BW (Table 1). In contrast to the dogs group, no significant correlation was found between BW and the PCio/BSA or P-UN concentration. Only the P-Cre concentration was significantly correlated with age in cats (r= – 0.267, P<0.05). No significant correlation was detected between age and BW (r=0.041, P=0.715). No significant sex difference was observed among all parameters in the healthy dog or cat group (Table 1).

In all 699 dogs, the P-UN and P-Cre concentrations were significantly correlated with PCio/BW (r= – 0.349, P<0.001, and r= – 0.437, P<0.001, respectively; data not shown). In all 321 cats, the P-UN and P-Cre concentrations were significantly correlated with PCio/BW (r= – 0.341, P<0.001, and r= – 0.427, P<0.001, respectively) and PCio/BSA (r= – 0.380, P<0.001, and r= – 0.451, P<0.001, respectively). In the ROC analysis, these markers in both dogs and cats had poor sensitivity and specificity for use in detection of decreased GFR (Table 3).

In order to compare the diagnostic accuracy of P-UN and P-Cre after excluding the effect of BW, all 699 dogs and 321 cats were classified as high BW (≥ 15.1 kg for dogs and ≥ 4.1 kg for cats) or low BW (≥ 15.0 kg for dogs and ≥ 4.0 kg for cats). The P-UN, P-Cre, and PCio/BW for each group of dogs and cats are shown in Table 2. Significant differ-

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**Table 1. Means ± standard deviation (SD), range, correlation with body weight or age and sex difference for each marker in the healthy dogs and cats**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Correlation with body weight (kg)</th>
<th>Correlation with age (year)</th>
<th>Sex difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dog</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-UN (mg/dl)</td>
<td>16.2±7.4</td>
<td>3.2–50.3</td>
<td>r = –0.220†</td>
<td>r = –0.002</td>
<td>P=0.137</td>
</tr>
<tr>
<td>P-Cre (mg/dl)</td>
<td>0.78±0.25</td>
<td>0.14–1.53</td>
<td>r = –0.405*</td>
<td>r = 0.058</td>
<td>P=0.236</td>
</tr>
<tr>
<td>PCio/BW (m/min/kg)</td>
<td>4.39±1.81</td>
<td>1.78–11.48</td>
<td>r = –0.549*</td>
<td>r = –0.354**</td>
<td>P=1.000</td>
</tr>
<tr>
<td>PCio/BSA (m/min/m²)</td>
<td>58.8±18.3</td>
<td>35.6–127.0</td>
<td>r = –0.208†</td>
<td>r = –0.363**</td>
<td>P=0.970</td>
</tr>
<tr>
<td><strong>Cat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-UN (mg/dl)</td>
<td>25.4±5.8</td>
<td>4.4–39.7</td>
<td>r = –0.081</td>
<td>r = –0.094</td>
<td>P=0.918</td>
</tr>
<tr>
<td>P-Cre (mg/dl)</td>
<td>1.24±0.25</td>
<td>0.6–1.8</td>
<td>r = –0.372†</td>
<td>r = –0.267*</td>
<td>P=0.990</td>
</tr>
<tr>
<td>PCio/BW (m/min/kg)</td>
<td>3.20±1.02</td>
<td>2.0–7.7</td>
<td>r = –0.302†</td>
<td>r = 0.124</td>
<td>P=0.961</td>
</tr>
<tr>
<td>PCio/BSA (m/min/m²)</td>
<td>49.6±12.6</td>
<td>35.6–96.7</td>
<td>r = –0.102</td>
<td>r = 0.130</td>
<td>P=1.000</td>
</tr>
</tbody>
</table>

*: P<0.001. † P<0.01. **: P<0.05.
ences were detected for all values between the two groups in dogs and were detected in cats for P-Cre and PCio/BW between the two groups. The P-Cre concentration for the high BW dogs was more linearly correlated with PCio/BW \((r=–0.615, P<0.001)\) than that for the low BW dogs \((r=–0.403, P<0.001)\; \text{Fig. 2}\). In the ROC analysis, although the difference was not significant \((P=0.088)\), the sensitivity and specificity of P-Cre in the high BW dogs \((80\%\) and \(83\%\), respectively) were higher than those in the low BW dogs \((75\%\) and \(80\%\), respectively; Table 3). In cats, no difference in the sensitivity and specificity of P-UN or P-Cre was detected between the two groups.

To compare the frequency of abnormal values of P-UN and P-Cre between the high BW and low BW groups, CKD dogs with a decreased PCio/BW were classified as severely reduced GFR (PCio/BW < 1.0 ml/min/kg) or mildly reduced GFR (PCio/BW 1.1 to 2.0 ml/min/kg). In the severely reduced GFR and high BW groups \((n=46)\), the upper limits of the reference ranges \((> 29.2 \text{ mg/dl for P-UN, } >1.4 \text{ mg/dl for P-Cre})\) for both markers were exceeded in many dogs \((71.7\%)\), and no dogs presented isolated P-UN abnormality. However, in the severely reduced GFR and low BW groups \((n=61)\), 10 dogs \((16.4\%)\) presented isolated P-UN abnormality. In the mildly reduced GFR and high BW groups \((n=82)\), both markers in many dogs \((64.6\%)\) were within the reference ranges. In the mildly reduced GFR and low BW groups \((n=118)\), only P-UN exceeded the upper limits of the reference range, and this occurred in nearly half of the dogs \((48.3\%; \text{Fig. 3})\). Additionally, in the low BW groups with a severely reduced GFR, 38 \((62\%)\) dogs showed a P-Cre < 2.0 mg/dl, and 17 \((27\%)\) presented a P-Cre < 3.0 mg/dl. By contrast, in the high BW groups with a severely reduced GFR, 20 \((43\%)\) dogs presented a P-Cre > 2.0 mg/dl, and 15 \((33\%)\) presented a P-Cre > 3.0 mg/dl.

**DISCUSSION**

As shown in many studies including this study, renal function markers are affected by various extrarenal factors such as BW, age, protein intake and hydration state \([3, 9, 10, 12, 13, 24, 28, 30, 37, 40, 44]\). PCio in healthy dogs was also significantly related to BW in the present study. Although PCio/BW in healthy cats was similarly significantly correlated with BW \((r=–0.372, P<0.01)\), PCio/BSA was not related to BW \((r=–0.102, P<0.361)\). The present study showed that the utility of BSA did not differ from BW for standardization of GFR in dogs, as these procedures could not exclude the effect of BW on PCio. Unlike in healthy dogs, as the standardization of PCio by BSA in cats can counteract the effect of BW, PCio/BSA may be more adapted for assessment of GFR than PCio/BW in cats. In humans and animals, standardization procedures for GFR have been proposed because GFR depends on body size \([23, 24, 30]\). One of these procedures relates GFR to the extra-

**Table 2.** Means ± standard deviation (SD) of each marker in the healthy dogs and cats classified by BW group

<table>
<thead>
<tr>
<th></th>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High BW group</td>
<td>Low-BW group</td>
</tr>
<tr>
<td>n</td>
<td>61</td>
<td>178</td>
</tr>
<tr>
<td>P-UN (mg/dl)</td>
<td>13.6 ± 5.5</td>
<td>17.0 ± 7.8*</td>
</tr>
<tr>
<td>P-Cre (mg/dl)</td>
<td>0.92 ± 0.24</td>
<td>0.73 ± 0.32*</td>
</tr>
<tr>
<td>PCio/BW (ml/min/kg)</td>
<td>2.76 ± 0.75</td>
<td>4.95 ± 1.72*</td>
</tr>
<tr>
<td>PCio/BSA (ml/min/m²)</td>
<td>49.8 ± 12.3</td>
<td>61.9 ± 19.0*</td>
</tr>
</tbody>
</table>

*: \(P<0.001\). **: \(P<0.05\) for Hi-BW vs Lo-BW.

**Table 3.** Sensitivities, specificities and areas under the receiver operating characteristics (ROC) curve of P-UN and P-Cre in all dogs and cats classified by body weight. There was slightly higher sensitivity and specificity of P-Cre in the high BW dogs compared with the low BW dogs.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensitivity(%)</th>
<th>Specificity(%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-UN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>70</td>
<td>67</td>
<td>0.730</td>
</tr>
<tr>
<td>High BW group</td>
<td>76</td>
<td>69</td>
<td>0.817</td>
</tr>
<tr>
<td>Low BW group</td>
<td>76</td>
<td>67</td>
<td>0.782</td>
</tr>
<tr>
<td>P-Cre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>73</td>
<td>79</td>
<td>0.855</td>
</tr>
<tr>
<td>High BW group</td>
<td>80</td>
<td>83</td>
<td>0.902</td>
</tr>
<tr>
<td>Low BW group</td>
<td>75</td>
<td>80</td>
<td>0.859</td>
</tr>
<tr>
<td>Cats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-UN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>74</td>
<td>54</td>
<td>0.705</td>
</tr>
<tr>
<td>High BW group</td>
<td>70</td>
<td>55</td>
<td>0.643</td>
</tr>
<tr>
<td>Low BW group</td>
<td>73</td>
<td>62</td>
<td>0.744</td>
</tr>
<tr>
<td>P-Cre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>76</td>
<td>75</td>
<td>0.837</td>
</tr>
<tr>
<td>High BW group</td>
<td>73</td>
<td>69</td>
<td>0.797</td>
</tr>
<tr>
<td>Low BW group</td>
<td>71</td>
<td>73</td>
<td>0.812</td>
</tr>
</tbody>
</table>
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Heine et al. [23] showed that PCio standardized by the extracellular fluid volume (ECFV) in dogs results in the smallest coefficient of variation in a comparison with other standardization procedures (PCio/BW and PCio/BSA), but the PCio/ECFV value maintains its relationship with BW. In the present study, PCio could not be standardized by ECFV because plasma clearance using the 2-compartment model is needed to calculate ECFV.

In this study, PCio in healthy dogs in the low BW group was significantly correlated with age, but in healthy cats, no significant correlation was detected between age and PCio. In another study, aged dogs from 2 breeds showed no change in GFR between 7.5 and 11.5 years of age [16], and another study in dogs demonstrated that there was no trend towards a reduction in GFR with age except in small dogs (1.8 to 12.4 kg) [3]. The present study also demonstrated that the PCio values in the high BW dogs (> 15kg) were not correlated with age, as shown in a previous study [3]. A possible cause for this result is a slightly wider range of body weight (0.3 to 17.0 years) in the low BW dogs compared with the the high BW dogs (0.8 to 14.7 years). From a different point of view, this result suggests that small dogs are more likely to be affected by CKD than large dogs. Unfortunately, there are no reports confirming this hypothesis.

In the healthy dogs, the P-UN concentration was significantly inversely correlated with BW, but it was not inversely correlated in the healthy cats. P-UN is known to be affected by numerous extrarenal factors, and it greatly depends on protein supply [9, 12, 37]. In this study, it was difficult to compare precise protein intake between the small and large dogs, as these dogs were not fed the same diet. However, the relationship between P-UN and BW might have been caused by differences in protein intake between the small and large dogs. Usually, the amount of food given to an animal is determined by its BW; therefore, the protein intake per BW is higher in small dogs than in large dogs. In cats, no significant correlation was observed between P-UN and BW. This was attributed to the fact that the healthy cats group presented a relatively narrow range of BW (2.2 to 7.2 kg) compared with the healthy dogs (0.7 to 57.9 kg).

The P-Cre concentration was significantly and positively correlated with BW in both dogs and cats. This may be due to the differences of muscle mass as is well known. However, there is no method for directly measuring muscle mass in dogs and cats, comparison between P-Cre and muscle mass cannot be performed. In animals, the sex differences in muscle mass are also unknown, but, in the present study, no significant sex differences were observed in the P-Cre (P=0.990) concentration in either the healthy dog or cat group, and this result suggests that the sex differences in muscle mass were small. In several studies, P-Cre increased
from the first week to 1 year of age and then was stable up to 10 years of age [18, 19, 35]. However, Fukuda et al. [19] reported that P-Cre decreased with age in beagles, whereas BW remained unchanged. In the present study, P-Cre was not significantly correlated with age in the healthy dogs with a high or low BW. The variation of P-Cre with age might have been hidden by decreases in PCio because the PCio values were reduced with age in the low BW dogs. In cats, although a significantly negative correlation was detected between P-Cre and age (r = −0.267, P < 0.05), the variation was very small and may have little effect on diagnosis of CKD.

Many studies have shown that the diagnostic performance of P-Cre for CKD is not high in humans or animals [17, 18, 32, 42]. Although the efficiency of P-UN for diagnosis of CKD has not been reported, the presence of many extrarenal factors explains why P-UN is not recommended as a marker of GFR. In this study, the sensitivities and specificities of P-UN and P-Cre in all 699 dogs and 321 cats were poor for the detection of reduced GFR. In the ROC analysis, although the diagnostic accuracy of P-Cre for detecting reduced GFR (AUC; 0.855 for dogs, 0.837 for cats) was significantly higher (P < 0.001) than that of P-UN (AUC; 0.730 for dogs, 0.705 for cats), the sensitivities of both markers were lower than 80%, which is considered to be the minimum required sensitivity for a clinically diagnostic test. In the high BW dogs (n = 196), the sensitivity and specificity of P-Cre (80 and 83%) were higher than those of P-Cre in the low BW group (75 and 80%). Consequently, P-Cre in large dogs is more useful for detection of reduced GFR than in small dogs, and P-Cre in many small dogs might remain within the reference range even if 75% of GFR has been lost. In fact, 26.2% of the small dogs with a severely reduced PCio demonstrated a normal P-Cre value (< 1.4 mg/dL), and moreover, 62% presented a P-Cre < 2.0 mg/dL. In contrast, about half of the small dogs with a mildly reduced PCio presented an increase in P-UN concentration alone. The increase in the P-UN/P-Cre ratio has long been considered an indicator of the presence of prerenal components (e.g., dehydration, hemorrhage), but it cannot be used to identify specific diseases because of interindividual variations [18]. Although the P-UN concentration in dogs is not an appropriate marker for detecting a reduced GFR in small dogs, an increase in P-UN alone should lead to the suspicion of a decreased GFR. In cats, the diagnostic performance and P-Cre were not significantly different among the two BW groups. This means that the effect of BW on P-Cre and PCio/BW may have no clinical importance.

In regard to the limitations of this study, the differences in the P-Cre and PCio values between obese and non-obese animals could not be evaluated due to the lack of information on the degree of obesity in the animals. The ratio of muscle mass to BW in obese animals may be lower than that in non-obese animals with a similar BW. Neutering has been identified as important risk factor for obesity [11]. One study suggested that obesity in middle-aged dogs is responsible for age-related declines in exercise and metabolic efficiency [8]. The considerable individual variations in P-Cre and PCio in same the BW group might have been caused by differences in the degree of obesity.

Non-ionic low-osmolar contrast media including iohexol have few adverse reactions in humans, and most adverse effects are immediate or delayed allergic reactions [35, 39]. No temporary adverse effects were clinically evident in the animals in this study.

In conclusion, all markers of renal function (PCio, P-UN and P-Cre) used in this study were affected by body weight. Although P-UN and P-Cre have insufficient sensitivity for accurate diagnosis of renal dysfunction, the clinical utility of these markers could be enhanced by considering the effect of extrarenal factors, especially body weight. In smaller dogs, the increase of P-UN alone might warrant suspicion of a decreased GFR, but in contrast, P-Cre may be inefficient for detecting renal dysfunction or determining the severity of CKD compared with in larger dogs. P-Cre in larger dogs correlated better with PCio than in smaller dogs, suggesting that P-Cre in larger dogs might be a more sensitive marker of reduced GFR. In the cats, the clinical utility of P-UN and P-Cre could not be evaluated because they were less affected by body weight and age. It is necessary to define the reference ranges of these markers for different BW and age groups in order to detect CKD more accurately.

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REFERENCES


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