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Indirect markers of glomerular filtration rate in dogs and cats: a review

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ABSTRACT: Early diagnosis of kidney disease continues to be a subject of intense interest. Direct measurement of glomerular filtration rate is too complicated for first-line practices; thus, indirect markers of renal function have also been evaluated. Creatinine, traditionally measured as a readout of renal function, has limitations in its sensitivity. In dogs and cats, cystatin C became popular approximately 15 years ago, but recent reports question its usefulness, especially in cats. Symmetric dimethylarginine seems to be very promising as a marker of glomerular filtration rate with the ability to detect renal impairment earlier than creatinine. This article presents current knowledge of qualities, limitations, advantages and availability of novel and traditionally used biomarkers of glomerular filtration rate in dogs and cats.

Keywords: creatinine; SDMA; cystatin C; kidney disease; feline; canine; dog; cat

List of abbreviations

ADMA = asymmetric dimethylarginine, **AKI** = acute kidney injury, **CKD** = chronic kidney disease, **ELISA** = enzyme-linked immunosorbent assay, **GFR** = glomerular filtration rate, **HAC** = hyperadrenocorticism, **IRIS** = International Renal Interest Society, **MMA** = monomethylarginine, **PENIA** = particle-enhanced nephelometric immunoassay, **PETIA** = particle-enhanced turbidimetric immunoassay, **SDMA** = symmetric dimethylarginine

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1. Introduction

Chronic kidney disease (CKD) is one of the most common disorders in dogs and cats and represents a common cause of death. Regardless of the initiating cause, CKD tends to be progressive at a rate which is unpredictable. Appropriate management may be successful for months and years, especially when the disease is diagnosed early and the treatment starts at the beginning of the process (Ross et al. 2006).

In chronic kidney disease, a reduction of glomerular filtration rate is the early indicator of kidney damage. Direct measurement of GFR is accepted as the gold standard for evaluating renal function in dogs and cats. GFR may be measured directly by urine or plasma clearance methods using inulin, creatinine and iohexol (reviewed by Von Hendy-Willson and Pressler 2011). These methods are complicated, costly and time-consuming, thus making them impractical for clinical settings. Routinely used indirect measures of kidney function have fairly established limitations which result in lack of specificity or sensitivity. Efforts are now focused on finding biomarkers that allow recognition of renal problems earlier than with the use

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of standard renal parameters. An ideal biomarker of GFR is produced at a constant rate, eliminated by glomerular filtration and maintains constant plasma concentrations. There should be no plasma protein binding, no tubular secretion, no tubular reabsorption without catabolism and no extrarenal clearance; further, such a marker should exhibit low intra-individual variability (Seronie-Vivien et al. 2008). Early diagnosis of kidney disease is important in facilitating the timely implementation of renoprotective interventions aimed at slowing the progression of the problem. These markers are important not only for diagnosis, but also for improved patient monitoring, thus allowing the therapeutic approach to be adapted for specific patient needs.

The purpose of this article is to compare the current knowledge of serum/plasma markers of GFR, their ability to detect problems, their advantages and limitations and the use of markers in the diagnosis or monitoring of disease progression.

2. Creatinine

Creatinine is a small molecule (113 Da) produced by cyclisation from creatine phosphate and creatine. This conversion to creatinine occurs at an almost constant rate and affects about 2% of the total pool of body creatine daily (Wyss and Kaddurah-Daouk 2000). Creatinine may partly originate from the alimentary supply. This is more important in carnivores than in other animals because of the high concentration of creatine and creatinine in meat (Harris et al. 1997). After endogenous production or exogenous administration, creatinine diffuses into the total body water compartment and is not metabolised (Braun et al. 2003); creatinine is almost entirely excreted by the kidney. It is freely filtered by glomeruli, and its urinary elimination is constant over time with negligible tubular secretion or reabsorption.

Creatinine is the analyte most frequently measured in human and veterinary clinical chemistry laboratories as an indirect measure of glomerular filtration rate (Braun et al. 2003).

Creatinine concentrations have been measured using Jaffé's reaction, which is based on the formation of chromogen by the action of picrate ions on creatinine at alkaline pH. This reaction is nonspecific; bilirubin, lipids, acetone and glucose may alter the results (Jacobs et al. 1992). Jaffé's reaction overestimates the plasma concentration of creatinine by up to 45% in healthy dogs, but this overestimation is much less in dogs with renal failure (Balint and Visy 1965). The other possibilities for measurement of creatinine concentration are enzymatic reactions. These methods are based on the use of creatinine aminohydrolase or of creatinine iminohydrolase. Enzymatic reactions remain effective in the presence of all interferents except bilirubin. Incorrect results may occur when serum bilirubin concentrations exceed 50 μmol/l (Jacobs et al. 1991). Different results may be obtained among different laboratories and veterinary practices that may affect the interpretation of results as normal or abnormal (Braun et al. 2008; Ulleberg et al. 2011).

Creatinine concentrations in serum or heparinised plasma were stable for up to four days at room temperature (Thoresen et al. 1992). However, in whole blood at room temperature, creatinine concentrations increased by up to 35% on the fourth day (Fontaine et al. 1986). At –20 °C, creatinine is stable for up to three months. Long-term stability is better at –70 °C (Thoresen et al. 1995).

Creatinine concentrations are about 5–10 mmol/l higher in serum than in the plasma of the same animal (Thoresen et al. 1992). Plasma creatinine concentrations are generally slightly higher in jugular blood than in cephalic venous samples (Jensen et al. 1994). A circadian rhythm in creatinine concentrations was observed in dogs (Singer and Kraft 1989) and cats (Reynolds et al. 2015) with higher values in the afternoon. Creatinine concentrations are influenced even by season: in laboratory Beagles, higher levels were found in summer and autumn than in winter and spring (Strasser et al. 2001).

The relationship between creatinine and GFR is curvilinear (rectangular hyperbola). At both ends of the curve, large changes in one correspond to very small changes in the other. Thus, in the early stages of kidney disease, substantial reductions in GFR have little effect on plasma creatinine concentrations, which remain within the reference range. On the other hand, in advanced renal failure, a mild deterioration of GFR causes a significant increase of creatinine (Braun et al. 2003).

Several studies show that there is little or no clinically irrelevant effect of sex on serum/plasma creatinine concentrations in dogs (Matsuzawa et al. 1993; Mundim et al. 2007; Misbach et al. 2014). Only Craig et al. (2006) found a significant effect of

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gender with male dogs having a higher mean plasma creatinine than female dogs (Craig et al. 2006). In cats, sex appears to be a minor factor for variations in plasma creatinine (Reynolds et al. 2010).

Available data about the influence of age on plasma creatinine concentrations are conflicting. When compared to values of adult dogs, puppies (from birth to eight weeks, or 60 days) have lower plasma creatinine concentrations (Rosset et al. 2012; Rortveit et al. 2015). The creatinine concentration subsequently increases and becomes stable by approximately six months of age (Wolford et al. 1988). In healthy adult dogs, creatinine concentrations are very stable (Vajdovich et al. 1997; Misbach et al. 2014). According to Lowseth et al. (1990) and Fukuda et al. (1989), creatinine concentrations decrease in older dogs from the age of eight to ten years onwards (Fukuda et al. 1989; Lowseth et al. 1990).

In kittens, plasma creatinine was higher at birth than in adults, and subsequently decreased to levels that were equivalent to or less than adult reference intervals by eight weeks of age (Levy et al. 2006). There is no effect of age on plasma creatinine concentrations in healthy adult cats (Reynolds et al. 2008; Reynolds et al. 2010). Miyagawa et al. detected a significant negative correlation between plasma creatinine and age in cats; nevertheless, this variation was very small and had little clinical impact (Miyagawa et al. 2010).

Serum/plasma creatinine concentration is affected by breed (Craig et al. 2006). Several studies have reported higher creatinine in Greyhounds and other sighthounds when compared to other breeds (Freeman et al. 2003; Dunlop et al. 2011; Zaldivar-Lopez et al. 2011; Uhrikova et al. 2013). A possible explanation for the high creatinine concentrations in sighthounds may be their large muscle mass. In cats, Holy Birman have higher creatinine concentrations than other breeds. The cause is unknown, since this breed does not have increased muscle mass (Gunn-Moore et al. 2002; Paltrinieri et al. 2014).

There is a significant positive correlation between plasma creatinine concentration and body weight in both dogs and cats (Craig et al. 2006; Miyagawa et al. 2010; Reynolds et al. 2010; Misbach et al. 2014). Thus, the reference intervals in dogs should be based on body weight categories specific for small-, medium- or large-breed dogs. According to Craig et al. (2006), in miniature dogs the cut-off value of IRIS (International Renal Interest Society) Stage 1 could delay early diagnosis of renal dysfunction, and, conversely, might be too low in giant dogs. Recently, a pilot study of reference intervals in adult small-sized dogs was published (Misbach et al. 2014). Plasma creatinine concentrations decreased in formerly obese dogs after weight loss (Tvarijonaviciute et al. 2013); however, a prior study did not reveal any effect of weight loss in obese dogs on creatinine concentrations (Diez et al. 2004). Creatinine levels should always be interpreted in the light of the patient muscle mass and body condition score.

Creatinine concentrations are increased from 1–12 hours after meals of raw or cooked meat (Watson and Church 1980; Watson et al. 1981). In dogs fed with commercial food, postprandial concentrations of creatinine were reported to be increased (Evans 1987), decreased (English et al. 1980; Watson et al. 1981) or unchanged (Epstein et al. 1984). Similar results are reported in cats: pre- and postprandial creatinine concentrations were comparable (Ghys et al. 2015a) or lower (Reynolds et al. 2015). This postprandial decrease of creatinine can be explained by increases in glomerular filtration rate and urinary excretion of creatinine after a meal rich in protein (O'Connor and Summerill 1976; Woods 1993; Simon et al. 1998).

In healthy dogs and dogs with CKD, the amount of protein in canine food had no effect on creatinine concentrations (Bovee et al. 1979; Polzin et al. 1991; Hansen et al. 1992). Diets enriched with fish oil, antioxidants (vitamin C and E), L-carnitine, vegetables, highly bioavailable protein and amino acid supplements decreased serum creatinine concentrations in dogs and cats (Hall et al. 2016b, Hall et al. 2016c). Reduced-protein diets with fish oil, L-carnitine and medium-chain triglycerides did not alter creatinine concentrations (Hall et al. 2014a).

Available reports showed differing effects of exercise on creatinine concentrations, with mild to moderate exercise having no impact. Creatinine was increased in Greyhounds immediately after sprinting (Rose and Bloomberg 1989), after exhaustive exercise in sled dogs (Hammel et al. 1977), unchanged in sled dogs after very long races (Hinchcliff et al. 1993) and decreased in untrained Beagles 8–10 hours after running for one hour (Chanoit et al. 2002).

Creatinine has a high degree of individuality, with inter-individual variations found to be more sig-

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nificant than intra-individual ones. This indicates that comparison of an individual to a population-based reference interval is of limited utility and increases the risk of missing important biological change (Ruaux et al. 2012; Baral et al. 2014). The same creatinine concentration in different animals can correspond to either normal or reduced GFR. Thus, subject-base reference values are more appropriate.

For the diagnosis of chronic kidney disease, it is generally accepted that at least 75% of the renal mass must be non-functional before plasma creatinine concentrations are increased above the upper limit of the reference interval (Braun et al. 2003). Creatinine is thus considered as a relatively insensitive marker of early chronic kidney disease. Higher sensitivity of creatinine concentration measurement may be reached by serial creatinine measurements in an individual patient. Serial creatinine measurements over time in the same animal provide more precise information about the renal function than a single evaluation. Serial evaluation of creatinine increases the sensitivity of this test and may detect progressive changes in GFR. To minimise variations and for better comparison of the results, the patient should be well hydrated and fasted, the sample should be evaluated in the same laboratory and body weight, body and muscle condition score and urine specific gravity should be determined.

Similarly, we can use serial evaluation of creatinine for the detection of acute kidney injury. According to the AKI (Acute Kidney Injury) grading scheme of the IRIS, a significant increase of serum/plasma creatinine levels ≥ 26.5 μmol/l within 48 hours is suggestive of renal damage (Thoen and Kerl 2011). This is very important, because acute kidney injury may exist without azotaemia. Acute kidney injury is not a stable condition and early recognition of this problem may considerably improve the outcome for the patient and improve the overall prognosis by allowing initiation of adequate treatment strategies (decontamination, discontinuation of nephrotoxic agents, fluid therapy, etc.).

Creatinine will remain a standard surrogate for estimation of GFR because it is readily available, cheap and easily measured. Nevertheless, the different circumstances that may affect creatinine concentration require that results be evaluated with caution. Use of age- and breed-specific reference limits of the patient should be considered.

3. Cystatin C

Cystatin C (cysC) is a small (MW 13 350 Da) non-glycosylated protein of 120 amino acids that is produced by all nucleated cells at a constant rate (Turk and Bode 1991) and is independent of age and gender (Simonsen et al. 1985). It is a member of the cystatin superfamily of cysteine protease inhibitors, is involved in intracellular protein catabolism and protects host tissue against destructive proteolysis (Bobek and Levine 1992). The major function of cysC is to control inflammation by inhibiting lysosomal proteases (Warfel et al. 1987). The first reports about cysC are from the early 1960s, when the protein was discovered in normal human cerebrospinal fluid and in the urine of patients with proteinuria (Butler and Flynn 1961; Clausen 1961). Its expression was observed in kidney, liver, pancreas, intestine, stomach, lungs, placenta, seminal vesicles and the parotic salivary gland (Abrahamson et al. 1990). High concentrations can be found in serum, seminal fluid, cerebrospinal fluid and synovial fluid (Brzin et al. 1984). Because of its low molecular weight, its positive charge at normal pH and lack of plasma protein binding, it is freely filtered by the glomerulus without restriction (Tenstad et al. 1996). It is then reabsorbed in the proximal tubules by megalin-mediated endocytosis and is completely catabolised (Kaseda et al. 2007). In comparison with other low-molecular weight proteins (beta-2 microglobulin, retinol binding protein, factor D) a better correlation between the reciprocal of cysC and GFR was observed (Grubb et al. 1985; Simonsen et al. 1985).

Serum cysC is considered superior to serum creatinine as a marker of GFR and thus is a better mean of detecting renal dysfunction in humans (Dharnidharka et al. 2002). Meta-analysis showed the ability of cysC to accurately determine renal impairment in patients in whom this is suspected (Roos et al. 2007).

Three methods for measurement of cysC concentrations are available in humans: an ELISA (enzyme-linked immunosorbent assay), PETIA (particle-enhanced turbidimetric immunoassay) and PENIA (particle-enhanced nephelometric immunoassay) (Ishiguro et al. 1989; Kyhse-Andersen et al. 1994; Finney et al. 1997). Currently, no commercial veterinary assay for measurement of cysC is available. Results in animals obtained using human assays do not reflect exact cysC concentrations.

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Thus, the human assays need to be validated for different species (Ghys et al. 2014a). Amino acid sequence homology between human and feline cysC was found to be 67.3% (Nakata et al. 2010) and 44–79% in dogs (Poulik et al. 1981). In dogs, PETIA was validated in several studies (Jensen et al. 2001; Almy et al. 2002; Wehner et al. 2008). PENIA was validated both in cats and dogs (Ghys et al. 2014b, Marynissen et al. 2016). Jonkisz et al. (2010) compared the results of cysC analysis obtained by PETIA and PENIA assays and found PENIA to be more sensitive than PETIA. According to these findings, PENIA and PETIA should be validated in parallel and correlated with GFR to determine which assay is better for veterinary use. The disadvantage of the PENIA assay is that it can only be used with a specialised automated immunonephelometer, whereas PETIA can be used with several analysers (Ghys et al 2014a).

CysC is a stable protein. It was stable in human serum for six months, in canine serum for 12 months at –80 °C, for seven days at temperatures ranging from 20 to –20 °C (Erlandsen et al. 1999; Wehner et al. 2008), for up to one month at 2–8 °C but only one day at room temperature (19–23 °C) (Sunde et al. 2007). In cats, serum cysC levels significantly increased during storage at room temperature. Serum cysC concentrations significantly decreased after five and 12 months of freezing at either –20 °C or –80 °C (Ghys et al 2015a).

CysC has been evaluated as an endogenous marker of GFR in dogs in several studies (Jensen et al. 2001; Almy et al. 2002; Braun et al. 2002; Wehner et al. 2008). The correlation between cysC and GFR was found to be stronger than that between creatinine and GFR (Almy et al. 2002; Wehner et al. 2008). CysC was less well correlated with GFR in volume-depleted dogs and may not be a sensitive indicator of decreased GFR associated with prerenal causes (Almy et al. 2002). CysC was shown to have better sensitivity (76%) than creatinine (65%) and specificities were similar (87% and 91%, respectively); nevertheless, cysC had a higher negative predictive value (69%) compared with that of serum creatinine (62%) (Wehner et al. 2008). Miyagawa et al. (2009) compared the diagnostic accuracy of cysC and creatinine in dogs with normal and decreased GFR (determined by plasma iohexol clearance). They found an even higher sensitivity of cysC (90.3% vs 73.6% for creatinine) and the same specificity for both (88.2%). Therefore, the serum cysC concentration had higher sensitivity for detecting decreased GFR than creatinine in dogs. In a very recent study, a close correlation between cysC and symmetrical dimethylarginine was found (Choi et al. 2017).

In humans, cysC concentrations are not affected by non-renal factors, such as infection or inflammation (Grubb et al. 1985; Simonsen et al. 1985; Grubb 1992). Nevertheless, serum cysC concentrations are influenced by thyroid dysfunction in humans: in the hypothyroid state cysC levels are lower, while in the hyperthyroid state levels are higher compared with the euthyroid state (Fricker et al. 2003). Furthermore, Kos et al. showed changes in serum cysC concentrations during malignant progression in patients with colorectal cancer and melanoma. The correlation between serum cysC and serum creatinine was much weaker in cancer patients than in healthy controls (Kos et al. 1998).

In dogs with chronic kidney disease, significantly higher serum cysC levels were reported when compared to healthy animals or dogs with non-renal diseases (cardiologic, dermatologic, endocrine, inflammatory, neoplastic, immune-mediated) (Jensen et al. 2001; Almy et al. 2002; Braun et al. 2002; Wehner et al. 2008; Miyagawa et al. 2009). Yet, there was an overlap in serum cysC concentrations between dogs with CKD and healthy dogs in some studies (Braun et al. 2002; Antognoni et al. 2005). However, no GFR measurements were performed and renal status was determined only by serum creatinine concentrations. Thus, early kidney disease with decreased GFR and without creatinine elevation cannot be excluded in the animals investigated in these studies.

The influence of corticosteroids on serum cysC concentrations is questionable, both in people and dogs. Bokenkamp et al. (2002) reported that a standardised high-dose corticosteroid therapy did not affect concentrations of cysC in humans, but Risch and Huber (2002) found higher cysC concentrations and Zhai et al. (2016) reported a significant increase of cysC in patients with symptomatic heart failure treated with prednisone but without effects on renal function. Higher serum cysC concentrations were also found in canine patients receiving glucocorticoid medication due to steroid responsive-meningitis, but not in dogs with hyperadrenocorticism (HAC) (Munoz et al. 2016). In a different study of dogs with HAC, it was similarly found that there were no significant differences for cysC in

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dogs with HAC and healthy controls (Marynissen et al. 2016). Moreover, there was an absence of an increase of serum cysC concentrations in association with a significant post-treatment decrease of GFR in HAC dogs. In the same study, serum cysC was also evaluated in dogs with diabetes mellitus. There was a significant decrease of serum cysC over a six-month period despite no significant change of GFR as measured by plasma clearance of creatinine. The question arose, whether cysC levels can report on minor changes in GFR in these patients.

According to available reports, serum cysC concentrations are not influenced by sex (Braun et al. 2002; Wehner et al. 2008; Miyagawa et al. 2009). Braun et al. (2002) found a relationship between cysC and age as well as between cysC and body weight: cysC concentrations were moderately lower in one to eight-year-old dogs than in younger or older ones, while cysC levels were lower in 88 dogs weighing less than 15 kg than in 91 heavier dogs. Similar findings were reported by Miyagawa et al. (2009): cysC concentrations were lower in dogs that weighed less than 5 kg (11 dogs) than in 65 heavier dogs. In contrast, this dependency of cysC concentration on age or body weight was not found in other studies (Pagitz et al. 2007; Wehner et al. 2008; Miyagawa et al. 2009). In cats, age, sex and body weight do not affect the serum concentration of cysC (Poswiatovska-Kaszczyszyn 2012; Ghys et al. 2015b). No differences were found among purebred and domestic short- and long-haired cats (Ghys et al. 2015b).

No significant changes were found in cysC concentrations in fasted dogs. A meal produced a dramatic decrease in plasma cysC concentrations, which started during the first hour and lasted for up to nine hours after the meal, returning to baseline values by 12 hours (Braun et al. 2002). Although Miyagawa et al. (2009) did not confirm this observation and found cysC to be stable for one, three, six and 10 hours after feeding, it might be recommended to sample dogs fasted for at least 12 hours. Subsequent decreases in cysC concentrations may be explained by a significant increase in GFR caused by the meal as in the case of creatinine (O'Connor and Summerill 1976), but this has not yet been confirmed. In cats, pre- and postprandial cysC concentrations did not change significantly; thus, it is not mandatory to fast cats before evaluation of cysC (Ghys et al. 2015b).

Only a few studies are available on cysC in cats. Martin et al. (2002) tested 99 healthy cats and 110 cats with clinical or biological signs of renal failure. In cats with renal failure, cysC concentrations were significantly higher, but there was a significant overlap of cysC concentrations between healthy cats and cats with renal failure. According to their results, the specificity of creatinine and cysC in diagnosis of kidney disease was similar (97.6% for creatinine and 98.4% for cysC), but the sensitivity of cysC was much lower in comparison with creatinine (15.3% and 46.8%, respectively) (Martin et al. 2002). They did not recommend using cysC for the diagnosis of kidney failure in cats. In this study too, no GFR was measured. Similar results were reported by Farace et al. (2015) based on analysis of 65 samples of feline serum. Nevertheless, in these studies, renal status was assessed only by creatinine concentration. Ghys et al. (2014b; Ghys et al. 2016a) found significantly higher serum cysC concentrations in CKD cats, but the sensitivity and specificity of serum cysC for detection of decreases of GFR were 22% and 100% (the values for serum creatinine were 83% and 93%). Thus, they did not recommend cysC evaluation, because it is does not allow discrimination of healthy cats from CKD cats, or normal cats from those with low GFR (Ghys et al. 2016a). In another study where GFR was determined, no correlation between GFR and cysC concentration was reported. In hyperthyroid cats, higher serum cysC concentrations were found (Ghys et al. 2016b). In a further study, hyperthyroid cats were examined prior to and after therapy with ^{131}I and no changes in serum cysC concentrations were observed, whereas GFR decreased after the treatment (Jepson et al. 2006). Only Poswiatowska-Kaszczyszyn (2012) found a better correlation between serum cysC concentrations and GFR (calculated on the basis of plasma clearance of iohexol). As of now, the majority of available reports on serum cysC do not recommend it as a marker of GFR in cats.

The contrasting results from available reports are summarised in Table 1.

4. Symmetric dimethylarginine

Symmetric dimethylarginine (SDMA) is derived from intracellular methylation of L-arginine residuals by protein-arginine methyltransferase and is released into circulation after proteolysis (Kakimoto and Akazawa 1970). There are three main spe-

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Table 1. Summary of available studies of cystatin C (cysC) in dogs and cats together with animal characteristics, method of cysC determination, level of cysC (range or mean ± standard deviation) and conclusions of the study

Study	Animals and their characteristics	Method of cysC determination	Level of cysC (mg/l)	Conclusion of the study	Commentary
Jensen et al. 2001	**17 clinically healthy dogs** creatinine 48–106 µmol/l	PETIA	1.036 ± 0.25 (0.4–1.375)	Dog with clinical renal insufficiency had significantly higher serum cysC levels.	GFR by clearance method was not determined. Thus, dogs with early kidney disease with decreased renal function but still normal creatinine concentration may be incorrectly assigned to the group of healthy dogs. There is an overlap in cysC concentrations between the group of healthy dogs and dogs with renal failure. The variability of serum cysC levels in dogs with nonrenal diseases remains unclarified.
	12 dogs with nonrenal diseases creatinine 44–112 µmol/l		1.85 ± 1.42 (0.4–6.25)		
	8 azotemic dogs creatinine 203–860 µmol/l		5.11 ± 1.18 (3.39–7.35)		
Almy et al. 2002	**20 dogs (15/16 remnant kidney model)** GFR: 0.5 ± 0.15 ml/min/kg GFR: 0.26–0.76 ml/min/kg	PETIA	4.42 ± 1.05 (2.24–6.9)	In the remnant kidney model, serum cysC was better correlated with GFR than creatinine. cysC was less well correlated with GFR in volume-depleted dogs.	15/16 remnant kidney model was used; thus, the ability to detect a mild decrease of GFR was not evaluated.
	10 healthy volume-depleted dogs GFR: 2.41 ± 0.41 ml/min/kg GFR: 1.55–2.99 ml/min/kg		0.85 ± 0.15 (0.55–1.02)		
	10 healthy dogs		0.76–1.44		
Braun et al. 2002	**179 healthy dogs – no signs of disease** creatinine less than 133 µmol/l	PETIA	0–1.73	Upper limit of the reference range for cysC was established to be 1.3 mg/l.	In this study, GFR was not determined using a clearance method.
	47 dogs with renal failure clinical signs of renal failure with azotaemia, clinical signs of renal failure without azotaemia, no clinical signs but increased concentrations of creatinine and/or urea		0–8.6	CysC may be a useful indicator of renal insufficiency in clinically relevant dogs with borderline plasma creatinine values.	
Antognoni et al. 2005	**28 clinically healthy dogs** creatinine 86.6 ± 37.1 µmol/l	PENIA	0.25 ± 0.14	According to the authors, cysC levels can determine renal failure in a more appropriate manner than the concentrations of creatinine.	In this study, GFR was not determined using a clearance method.
	39 dogs with nonrenal pathology creatinine 115.8 ± 27.4 µmol/l		0.29 ± 0.15		
	82 dogs with clinical signs of renal failure and azotaemia creatinine 465 ± 335.9 µmol/l		0.89 ± 0.68		

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Table 1 continued

Study	Animals and their characteristics	Method of cysC determination	Level of cysC (mg/l)	Conclusion of the study	Commentary
Wehner et al. 2008	**99 healthy dogs** normal haematology, biochemistry and urinalysis results (no GFR was measured)	PETIA	0.49–1.81 (1.144 ± 0.23)	Reference range was established as 0.68–1.6 mg/l.	
	60 dogs where GFR was determined by exogenous creatinine plasma clearance creatinine 42–590 mmol/l GFR: 0.3–0.5 ml/kg/min normal (> 3 ml/kg/min) in 23 abnormal (≤ 2.99 ml/kg/min) in 37		0.79–5.97	In the 60 dogs, where exogenous creatinine plasma clearance was evaluated, a significant inverse correlation between ECPC and serum cysC was found. Sensitivity and specificity of cysC for detecting decreased GFR was 76% and 87%, in creatinine it was 65% and 91%, respectively.	
Miyagawa et al. 2009	**76 clinically healthy dogs**	ELISA	0.85 ± 0.15 (0.52–1.18)	The reference range for cysC concentration was 0.55–1.15 mg/l. CysC concentrations were significantly correlated with plasma iohexol clearance and to a greater extent than creatinine levels. Specificity and sensitivity of cysC for detection of decreased plasma clearance of iohexol was 90.3% and 88.2%, whereas in creatinine it was 73.6% and 88.2%, respectively. The sensitivity of cysC was significantly higher for detecting decreased GFR.	Human ELISA was used, canine serum cysC might show a different response to anti-human cysC antibody.
	88 dogs with CKD diagnosed by detection of proteinuria (UPC > 0.5) and/or plasma iohexol clearance < 30 ml/min/m2		1.23 ± 0.21 (0.62–1.58)		
Marynissen et al. 2016	**14 dogs with diabetes mellitus** GFR: 1.3–4.5 ml/min/kg	PENIA	0.2–0.6	Serum cysC was not effective for detecting minor but significant changes of GFR in dogs with hyperadrenocorticism.	
	22 dogs with hyperadrenocorticism GFR: 1.1–4.3 ml/min/kg		0.1–0.8		
	17 healthy dogs GFR: 1.8–3.6 ml/min/kg		0.2–0.4		
Martin et al. 2002	**99 healthy cats (control group)** creatinine < 229 µmol/l	PETIA	0.19–4.37	The reference interval was established as 0.34–4.11, where the upper limit was much higher than in humans or dogs. Sensitivity and specificity of cysC for diagnosis of renal failure was 15.3% and 98.4%, of creatinine 46.8% and 97.6%, respectively. The authors do not recommend using cysC for the diagnosis of kidney failure in cats.	In this study, GFR was not evaluated using a clearance method. In the control group, a higher upper limit for creatinine than usual was used.
	75 cats with elevated creatinine and urea		0.35–9.52		

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Table 1 continued

Study	Animals and their characteristics	Method of cysC determination	Level of cysC (mg/l)	Conclusion of the study	Commentary
Poswiatowska-Kaszczynczyn et al. 2012	**24 healthy cats** creatinine 131.0 ± 34.3 µmol/l GFR: 2.4 ± 0.8 ml/min/kg	PENIA	0.7 ± 0.2	Strong correlation between GFR and cysC concentration was found.	GFR was determined by plasma iohexol clearance.
	46 cats with CKD creatinine 340 ±437.7 µmol/l GFR: 1.2 ± 0.7 ml/min/kg		1.3 ± 0.6		
	IRIS 1 (16 cats): creatinine: 117.8 ± 13.1 µmol/l GFR: 1.5 ± 0.7 ml/min/kg		1.1 ± 0.3		
	IRIS 2 (16 cats): creatinine: 178.9 ± 29 µmol/l GFR: 1.4 ± 0.5 ml/min/kg		1.0 ± 0.5		
	IRIS 3 (6 cats): creatinine 351.3 ± 53.4 µmol/l GFR: 0.7 ± 0.3 ml/min/kg		1.4 ± 0.3		
	IRIS 4 (8 cats): creatinine: 1099.3 ± 629.3 µmol/l GFR: 0.5 ± 0.4 ml/min/kg		2.0 ± 0.7		
Ghys et al. 2015	**130 healthy cats** creatinine 106.2 ± 19.3 µmol/l	PENIA	1.2 ± 0.4	A reference interval of 0.58–1.95 mg/l was established. The majority of cats with CKD in previous studies fall within the reference interval calculated in this study.	GFR was estimated only by serum creatinine concentration, no clearance tests were performed.
Ghys et al. 2016	**41 healthy cats** creatinine 88.4 ± 23 µmol/l	PENIA PETIA	1.0 ± 0.3	Serum cysC was significantly higher in cats with CKD compared to healthy cats but an important overlap was present. Serum cysC could not be used to distinguish healthy from CKD cats, nor normal from borderline or low GFR. There was significant correlation between GFR and serum cysC, the correlation between GFR and creatinine was weaker. CysC was not a reliable marker of reduced GFR. PENIA and PETIA methods were highly correlated, but serum cysC measured with PETIA was significantly higher than levels measured with PENIA.	
	49 cats with CKD creatinine 358.9 ± 223.7 µmol/l plasma exogenous creatinine clearance test in 17 CKD cats and 15 healthy cats		1.4 ± 0.5		

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Table 1 continued

Study	Animals and their characteristics	Method of cysC determination	Level of cysC (mg/l)	Conclusion of the study	Commentary
Williams et al. 2016	**24 healthy cats** creatinine 106–141.4 µmol/l	PETIA	0.5–2.7	There was no significant difference in serum cysC between cats with CKD and healthy older cats and there were no differences between preazotaemic and nonazotaemic hyperthyroid cats.	No GFR was measured.
	12 azotaemic cats with CKD creatinine 168–247.5 µmol/l		1.0–1.9		
	55 hyperthyroid cats				
	preazotaemic creatinine 97.2–141.4 µmol/l		1.1–2.2		
	nonazotaemic creatinine 79.6–114.9 µmol/l		0.8–1.4		

CKD = chronic kidney disease, cysC = cystatin C, ELISA = enzyme-linked immunosorbent assay, GFR = glomerular filtration rate, IRIS = International Renal Interest Society, PENIA = particle-enhanced nephelometric immunoassay, PETIA = particle-enhanced turbidimetric immunoassay

cies of methylated arginine: monomethylarginine (MMA), asymmetric dimethylarginine (ADMA), and SDMA (Bedford and Richard 2005). ADMA is largely cleared by enzymatic hydrolysis; most ADMA is converted to L-citrulline and dimethylarginine. SDMA is primarily (≥ 90%) eliminated by renal excretion. Thus, the plasma concentrations of SDMA are affected by changes in GFR (McDermott 1976), suggesting SDMA as a potential endogenous marker of GFR (Schwedhelm and Boger 2011). The true importance of SDMA in kidney disease is not known. It has proinflammatory effects (stimulation of production of reactive oxygen species) and thus may play a role in progression of the process (Kielstein et al. 2009). Large meta-analysis of SDMA in humans supported its use as a marker of renal disease (Kielstein et al. 2006). It is also an accurate and precise biomarker for calculating estimated GFR in humans (Bode-Boger et al. 2006) and a more precise biomarker than serum creatinine concentration for evaluating kidney dysfunction (Dixon et al. 2013). In humans, non-renal influences (obesity, sex, age) on SDMA concentration appear to be minor (Siroen et al. 2005; Marliss et al. 2006; Atzler et al. 2014).

In dogs and cats, liquid chromatography-mass spectrometry has been validated for SDMA measurement (Jepson et al. 2008; Padmanabhan et al. 2013; Nabity et al. 2015). The reference range limit for SDMA concentration in healthy adult dogs and cats is < 14 µg/dl; in puppies and kittens, SDMA levels may be slightly higher (Rentko et al. 2013; Relford et al. 2016). SDMA is highly stable in serum and plasma (Nabity et al. 2015); multiple freeze-thaw cycles did not significantly alter its concentrations at 4 °C and room temperature for seven days (Yerramilli et al. 2013). Haemoglobin, bilirubin, lipids, MMA and ADMA all exerted no effects on SDMA measurement (Nabity et al. 2015).

The concentration of SDMA is significantly correlated with GFR in healthy dogs and cats (Hall et al. 2014a) and dogs and cats with chronic kidney disease (Nabity et al. 2013a; Nabity et al. 2013b; Braff et al. 2014; Hall et al. 2014b; Nabity et al. 2015). The upper limit for the serum SDMA reference interval corresponded to a 49% decrease in GFR in dogs (Hall et al. 2016a) and a 24% decrease in GFR in cats (Hall et al. 2014a). The concentration of SDMA increases earlier than creatinine in dogs and cats with CKD (on average with 40% loss of kidney function and in some cases already when

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there is a 25% loss in renal function) (Hall et al. 2014a; Nabity et al. 2015). In cats with CKD, an increase of SDMA was noted on average 17 months earlier (and up to 48 months earlier) than an increase of creatinine (Hall et al. 2014b). In dogs with CKD, serum SDMA increases on average (mean) 9.8 months earlier than serum creatinine (range 2.2–27 months) (Hall et al. 2016a). In a group of dogs with X-linked hereditary nephropathy, SDMA increased on average 4.8 weeks earlier than creatinine. The difference can be explained by the more progressive nature of the disease in juvenile dogs with hereditary disease (Nabity et al. 2015).

When compared to the gold standard of GFR, the sensitivity of SDMA was found to be 100% and the specificity to be 91% (Hall et al. 2014b). In comparison to serum creatinine concentrations, SDMA is better-suited for use with population-based reference intervals. Nevertheless, moderate individuality was found, and serial monitoring is thus recommended. The critical difference should be more than 1.34 μg/dl to ensure that variation between sequential measurements is not because of biological variability (Kopke et al. 2018).

SDMA strongly correlates with GFR, which may be affected by pre-renal or post-renal disorders. In dehydrated animals, where a reduction in GFR causes pre-renal azotaemia, SDMA should also increase. Thus, patients submitted to SDMA evaluation should be ideally well-hydrated and other causes of pre-renal and post-renal azotaemia should be considered. SDMA does not help in localising the problem in kidneys or in identifying the cause of kidney disease. SDMA is suitable for identifying acute kidney injury as well, but it cannot be used to differentiate between AKI and CKD (Dahlem et al. 2017).

In comparison with serum creatinine concentration, SDMA seems to be a more precise marker of GFR, because it is not impacted by lean body mass (Jewell et al. 2014a; Hall et al. 2015). Thus, it can be a more useful marker of kidney function especially in geriatric animals, where creatinine concentration may be lower due to decreased lean body mass. The concentration of SDMA is not affected by age in adult dogs, breed, sex or exercise (Pedersen et al. 2006; Moesgaard et al. 2007). In contrast to these studies, Martinez et al. (2017) found higher SDMA concentrations in Greyhounds compared to non-Greyhound dogs. Nevertheless, this study was conducted in 20 Greyhounds only, and thus further studies in this field are needed.

Evaluation of SDMA concentration instead of creatinine may be used as a better indicator of GFR during the therapy of feline hyperthyroidism (Vaske et al. 2015). In a prospective before and after study of hyperthyroid cats, Peterson et al. (2018) found that high serum levels of SDMA were predictive of the development of azotaemia after treatment. It had high diagnostic specificity but relatively low sensitivity. A finding of increased serum SDMA indicates that further evaluation (e.g. diagnostic imaging) of kidneys should be performed. SDMA may be a better indicator of undiagnosed renal disease than serum concentrations of creatinine (Hall et al. 2017). SDMA concentration may be used to evaluate the effects of nutritional interventions in dogs and cats with normal creatinine concentrations and increased SDMA (Hall et al. 2016b; Hall et al. 2016c), or during feeding of low-protein and low-phosphorus diets in animals with chronic kidney disease (Jewell et al. 2014b).

According to Yerramilli et al. (2015), the SDMA-to-creatinine ratio may have prognostic value in animals with chronic kidney disease: the larger the ratio (> 10), the greater the chance of mortality. Nevertheless, a very recent study of Dahlem et al. (2017) did not confirm this finding.

In conclusion, SDMA seems to be a useful and very promising test for both identifying and monitoring decreased renal function in dogs and cats. It has already been incorporated into new IRIS CKD guidelines for better description of patients and subsequent improvement of management, thus slowing progression of the disease. Its advantage lies in its commercial availability and good stability in samples typically submitted for analysis; this allows veterinarians to precisely identify early chronic kidney disease. As a new marker, further studies of animals with non-renal disorders and their influence on SDMA concentration are needed.

5. Conclusions

Creatinine is a traditional indirect marker of GFR. While it has its drawbacks (lower sensitivity, influenced by muscle mass, body weight or breed), it will remain as a part of biochemistry analysis and detection of kidney disease. IRIS classification is still primarily based on serum creatinine concen-

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trations. The advantages of creatinine are its wide availability, cheapness and ease of measurement. We can improve the quality of this parameter by using reference ranges based on body weight and breed and registering the amount of muscle mass in evaluated patients. The sensitivity of creatinine may be increased by serial measurements over a short period for detection of acute kidney injury or over a period of time as a part of preventive care and as a basis for individual reference ranges.

CysC is another indirect marker of GFR. The first studies from canine and feline medicine were carried out at the beginning of millennium, but no consensus emerges from the results reported by different authors. In most studies of cysC, GFR was not determined by clearance methods and the animals were characterised only by the serum creatinine concentration. Thus, it was not possible to distinguish patients with decreased GFR but still normal concentrations of creatinine. In a majority of later studies, it was found that cysC cannot be used to reveal mild but significant changes of GFR. Currently, we have no convincing evidence that serum cysC is superior to creatinine in detection of renal problem.

Symmetric dimethylarginine is a relatively new and promising indirect marker of GFR. It can be used to reveal a decrease of GFR earlier than creatinine and in addition, it is not impacted by muscle mass. Determination of SDMA is thus suitable for cachectic patients, in patients predisposed to kidney disease or in patients at risk of kidney damage (e.g. geriatric patients, patients with concurrent diseases, exposed to ischaemia or nephrotoxic agents). Nevertheless, it is to be expected that future studies of SDMA will enhance our understanding further.

A combination of the traditional marker creatinine and SDMA provides more precise description of GFR. Early diagnosis of kidney disease is essential for successful management. Other markers of renal function, both glomerular and tubular (e.g. proteinuria, urine specific gravity, activity of urine enzymes etc.), should be considered for better characterisation of renal function.

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