UNIVERSITY OF CALGARY
FACULTY OF VETERINARY MEDICINE

This review accompanies the relevant episode of the Cutting Edge veterinary podcast. In each episode of this podcast, 3rd year students in the University of Calgary's veterinary medicine program fill you in on the most up-to-date literature and evidence-based practices on topics that matter to you, the practising veterinarian.

Using symmetric dimethylarginine (SDMA) as a renal biomarker to enhance diagnosis of early-stage chronic kidney disease (CKD) and management of last-stage CKD.

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Introduction

Chronic kidney disease (CKD) is defined as 'structural and/or functional impairment of one or both kidneys that has been present for more than approximately 3 months' duration (1). For some time, this impairment of kidney structure and function can be stable, but ultimately is progressive (1). In general, CKD occurs commonly in cats and dogs, and prevalence increases with age (2). In cats, prevalence of CKD in the general population is between 2-4% and increases to > 30-40% in cats over 10 years old and increases up to 80% in geriatric cats (2,3,4). In dogs, reported prevalence is more variable based on sample population and case criteria; some sources report prevalence of 0.5-1% of dogs and one source reported up to 10% of elderly dogs (2,5).

Serum creatinine (sCr) has traditionally been used in veterinary medicine to indirectly measure glomerular filtration rate (GFR) to detect decreases in kidney function and diagnose chronic kidney disease (CKD). Serum creatinine has many benefits such as being economical, available, and easy to measure. Serial monitoring of older cats using serum creatinine is valuable, since establishing a baseline and tracking changes over time helps to create a clinical picture. Further, a persistent increase of >15% above baseline likely indicates decreased renal function (3, 4).

Although sCr has been used traditionally, and is quick and easy, it has some important limitations that should be addressed. The first important limitation is that there is a non-linear relationship between sCr and GFR, meaning sCr has a low sensitivity for detecting early decreases in GFR (3). The second limitation is that sCr is affected by non-renal factors, specifically muscle mass (3). Creatinine is formed as a product of muscle metabolism and serum

concentrations are directly affected by muscle mass (5). This means that for patients in late stages of CKD with decreased muscle mass, sCr concentrations are naturally decreased, making it challenging to monitor progression of CKD. Another limitation is that in practice there can be misinterpretation of sCr values stemming from the highly variable nature of sCr between individuals based on muscle mass and variable reference ranges depending on the laboratory or method of analysis. These important limitations of sCr impact our ability to detect early CKD and monitor late stages of CKD. This review will investigate how to use a different indirect biomarker of GFR, symmetric dimethylarginine (SDMA), to increase diagnostic power (3).

SDMA is produced at a constant rate by all nucleated cells through protein methylation (6). SDMA is primarily excreted by glomerular filtration and is not affected by tubular reabsorption (7). Unlike sCr, SDMA does not appear to be affected by non-renal factors, such as muscle mass, making it a useful marker of GFR (3). Although it is unknown how fast SDMA increases post reduction in GFR, recent studies have shown SDMA to detect changes in GFR earlier than creatinine with veterinary studies (8). Veterinary studies have shown SDMA to decrease at 20-40% renal dysfunction compared to creatinine increasing at 75% dysfunction (9,2). This is where SDMA plays an important role in detecting early, non-azotemic CKD (10). SDMA has important implications on treatment decisions because the earlier we can detect CKD the more treatment options are available.

Diagnosis

Diagnosis of CKD requires a comprehensive look at the patient, piecing together history, clinical signs, physical exam findings, laboratory values, imaging, and histopathology when relevant. For animals with advanced kidney disease, these changes will be quite striking. On the other hand, patients with early kidney disease may just have one abnormal finding making it challenging to make a definitive diagnosis.

In terms of history and clinical signs, a relatively early clue of CKD is owners reporting polyuria and polydipsia. Once more advanced, patients may show signs of uremia such as vomiting, lethargy, hyporexia, weight and muscle loss.

On physical exam, some indications of kidney disease may be low body condition and muscling, pale mucous membranes, abnormal kidney palpation, and unexplained dehydration.

Abnormal kidney imaging may be appreciated on abdominal ultrasound or abdominal radiographs. This may be incidental if there is an unrelated issue which is being investigated.

When looking at laboratory tests to diagnose CKD it is important to look for evidence of elevated BUN, creatinine, and SDMA. It is also critical to perform a urinalysis including USG and cytology.

As with all conditions, it is important to consider any changes in laboratory values in light of physical exam and history findings. When diagnosing CKD, it is important to rule out pre or post renal azotemia and other renal diseases such as acute kidney injury (AKI). For example,

pre-renal causes of elevated SDMA include hypertension, renal toxins, and severe dehydration (11). These must be investigated prior to diagnosing CKD. Further, emerging data has highlighted that in certain conditions, such as canine and feline lymphoma, SDMA may be elevated without decreased GFR, and sCr is unaffected (12). A complete urinalysis must be performed if increased kidney values are detected to help distinguish between pre- renal, renal, and post-renal azotemia based on cytology and USG.

In early CKD, mild changes to SDMA may be the only abnormal finding. However, diagnosing CKD using solely a mild elevation in SDMA may be associated with reduced specificity (13). It is exceptionally important in these cases to thoroughly investigate all factors to support or refute the diagnosis of CKD. Given that the goal is early diagnosis, IRIS recognizes that it is inevitable that some patients will be falsely diagnosed with early CKD if they only have mild increases to SDMA and no other signs to refute the diagnosis (13). Treatments for stage 1 CKD are mainly management changes, as will be discussed below, therefore will have minimal impact on a falsely diagnosed patient (13). On the other hand, this is a safer tradeoff for patients that are truly in stage 1 CKD as treatment is most beneficial when the number of functional nephrons is not severely reduced (12).

Staging

The International Renal Interest Society (IRIS) has developed four stages for renal disease based on fasted blood serum SDMA and creatinine levels. Classically, these guidelines were based primarily on sCr values, however with the recent evidence of SDMA as a highly sensitive marker of GFR, the guidelines have been revised to include both SDMA and sCr to enhance diagnosis. Further, there are IRIS sub-stages based on proteinuria and hypertension (12). By staging CKD following diagnosis, this can make it easier for clinicians to create a treatment plan for their patients.

Stage 1 patients have normal blood creatinine levels and normal - mildly increased SDMA serum levels. Renal abnormalities may be present such as inadequate urine specific gravity without identifiable non-renal cause in cats, abnormal renal palpation, imaging, or biopsy, proteinuria from renal origin, or serially increasing serum SDMA or creatinine levels. A persistent increased SDMA (>14ug/dl) may be used to diagnose early CKD. In stage one, both feline and canine patients have SDMA <18ug/dl, canines have creatinine <125umol/l and felines <140umol/l (12).

Stage 2 patients have normal - mildly increased creatinine, mild renal azotemia, and mildly increased SDMA. These patients may display absent to mild clinical signs. In stage two, canine patients have SDMA between 18-35ug/dl and creatinine between 125-250umol/l. Feline patients have SDMA between 18-25ug/dl and creatinine between 140-250umol/l (12).

Stage 3 patients display moderate renal azotemia. These patients may present extrarenal signs, but their severity can vary. This allows for early and late classifications of stage 3, a patient with no clinical signs can be considered as ‘early stage 3’, versus, a patient with severe - systemic clinical signs can be considered as ‘late stage 3’. In stage three, canine patients have

SDMA between 36-54ug/dl and creatinine between 251-440umol/l. Feline patients have SDMA between 26-38ug/dl and creatinine between 251-440umol/l (12).

Stage 4 patients are at an increased risk of having systemic clinical signs and presenting in a uremic crisis. In stage four, canine patients have SDMA above 54ug/dl and creatinine above 440umol/l. Feline patients have SDMA above 38ug/dl and creatinine above 440umol/l (12).

It is important to note that there is some association between breed and size on sCr and SDMA. It is known that healthy greyhound dogs and Birman cats naturally display higher serum SDMA and creatinine levels (12).

There are some discrepancies that arise between creatinine and SDMA when staging patients for CKD. As discussed above, since SDMA is most likely a more sensitive biomarker that is less impacted by lean body mass, when a patient is in a lower stage for creatinine, and a higher stage for SDMA (for example stage 1 based on creatinine and stage 2 based on SDMA), the patient should be staged and treated depending on the SDMA status (14).

After staging, CKD is further sub-staged based on proteinuria and blood pressure. Substaging helps paint the clinical picture and allows clinicians to tailor monitoring, treatment and prognosis to that particular patient's needs. This further understanding allows for the highest quality of care and maximizes disease outcome (9).

Systemic hypertension is used for substaging and is present in 20% of feline patients with CKD and has detrimental effects on renal and extra-renal organ function (9). The cause of hypertension is unknown and multifactorial. Systemic hypertension can damage the kidneys, eyes, brain, and cardiovascular system primarily. It is also a negative prognostic indicator; therefore it is pertinent to monitor blood pressure and treat if needed (9, 14).

Proteinuria is used for substaging and is present in about 50% of feline patients with CKD. Proteinuria is detrimental because it increases the rate of kidney damage by causing tubular degradation and fibrosis. Proteinuria can be caused by pre renal, renal, and post renal factors therefore it is important to rule out these other causes when investigating CKD and proteinuria (9). Proteinuria is of clinical importance as it is a negative prognostic indicator and increases the relative risk of uremic crisis and mortality (15).

If proteinuria is present, the aim is to first determine if the cause is pre-renal, renal, or post renal. There is a preference to use a specific screening test - urine protein to creatinine ratio (UP/C) versus simply using urine dipsticks as these dipsticks can give false positives. A UP/C should be done on all felines and canines with CKD if there is no evidence of urinary tract inflammation, cystoliths, hemorrhage, or dysproteinemias. For ideal substaging, two urine samples should be collected over at least two weeks (12). There are three sub-stages based on proteinuria. First, non-proteinuric, where both canine and feline patients have a UP/C of less than 0.2. Second, borderline proteinuric, where canines have a UP/C between 0.2-0.5, and felines are between 0.2-0.4. If patients test as borderline proteinuric persistently, they should be

re-evaluated in 2 months. Lastly, proteinuric, where canines have a UP/C above 0.5, and felines are above 0.4 (12).

There are four substages based on multiple systolic blood pressure readings according to the degree of risk of target organ damage. It is ideal to take systolic blood measurements on different days, but this can also be done on the same day at least separated by two hours (12). The different substages based on systolic blood pressure measurements are described below.

Normotensive patients have a systolic blood pressure below 140mmHg and have minimal risk of future target organ damage. Prehypertensive patients have a systolic blood pressure between 140-159mmHg and have a low risk of future target organ damage. Hypertensive patients have a systolic blood pressure between 160-179mmHg and have a moderate risk of future target organ damage. Severely hypertensive patients have a systolic blood pressure equal to or above 180mmHg and have a high risk of future target organ damage. It is important to note that certain dog breeds, such as sight hounds, typically have higher blood pressure when compared to other dog breeds. For this reason, it is recommended to use breed-specific reference ranges if they are available. If the patient is a high-pressure breed, we sub-stage as shown below (12).

The risk of developing organ damage is correlated to how much higher the systolic pressure is above reference range; minimal risk if the patient's systolic pressure is less than 10mmHg above reference range. Low risk if the patient's systolic pressure is between 10-20mmHg above reference range. Moderate risk if the patient's systolic pressure is between 20-40mmHg above reference range. And lastly, high risk if the patient's systolic pressure is higher than 40mmHg above reference range (12).

It is important to re-evaluate patients and classify substages accordingly. For example, if a patient is treated with antihypertensive medications and the patient demonstrates a persistent decrease in systolic blood pressure measurement, the clinician should re-classify to the lower appropriate sub-stage (12).

Treatment

There are two main streams of treatment options for CKD. Firstly, there are treatments that slow the progression of disease and maintain kidney function for more time. Second, there are treatments which reduce the clinical signs of CKD to improve quality of life for the patient. The first treatment stream is mainly useful when CKD is diagnosed in the early stage of disease. Once patients are in the late stages of disease, treatments which slow disease progression are not nearly as useful, and limiting clinical signs becomes a top priority. This again highlights the benefit of early diagnosis (14).

Treatment decisions need to be tailored to each individual patient, however there are a series of IRIS guidelines to create a starting point. Additionally, serial monitoring of lab work (SDMA and sCr), physical exam parameters, and clinical signs is vital to managing these patients as CKD progresses and allows for fine-tuning of treatments (14).

Stage 1 treatments for cats and dogs include discontinuing nephrotoxic drugs, identifying any pre-renal or post-renal abnormalities, ruling out any treatable conditions such as ureteral obstruction or pyelonephritis with imaging, and measuring UPC ratio and blood pressure. In terms of pre-renal abnormalities, it is vital to maintain hydration in these patients as their renal concentrating ability may be impaired. This includes having fresh water available and prompt fluid administration in the face of clinical dehydration due to any illness. (14).

Clinical renal diets are a common treatment recommended for patients with CKD. Evidence suggests that reduction of dietary phosphate intake to maintain plasma phosphate within the IRIS target (0.9-1.5 mmol/L) is beneficial to CKD patients. In early CKD (stage 1), most animals have plasma phosphate below the upper limit. Some cats with phosphate within the target may have an increased risk of developing hypercalcemia when fed a phosphate restricted diet (16). In this case, FGF23 (Fibroblast Growth Factor 23) can be used to determine which animals may benefit from starting phosphate restriction when with plasma phosphate within the target. FGF23 is a bone derived hormone which plays a role in the regulation of phosphate and vitamin D metabolism. Increased FGF23 is an early indicator of mineral bone disturbance associated with CKD, and helps to predict the development of hyperphosphatemia and progression of CKD (16). Additionally, increased FGF23 can lead to reduced renal production of calcitriol and hypersecretion of parathyroid hormone (17, 18). For patients with phosphate levels within the IRIS target, measuring FGF23 is indicated to decide if a renal diet should be implemented. First, if plasma FGF23 is >400 pg/mL treatment with an early renal diet (moderate phosphate restriction) is indicated. Second, if plasma FGF23 is 300-400 pg/mL these patients should be closely monitored for increased FGF23 and need to begin a renal diet. Finally, if plasma FGF23 is <300 pg/mL there is no indication of mineral bone disturbance and a clinical renal diet is not needed at this point (16).

Stage 2 treatments include all the above options, additionally, plasma phosphate concentrations and FGF23 should be reassessed to add or change the degree of dietary phosphate restriction (clinical renal diet). If patients have a plasma phosphate concentration within the IRIS target (0.9-1.5 mmol/L), FGF23 should be used following the same recommendations outlined for stage 1. It is more likely that patients in stage 2 will have a plasma phosphate concentration above the IRIS target. In this case, there is no need to measure FGF23 and a clinical renal diet should be implemented. Monitoring plasma phosphate concentrations should be used to indicate response to treatment. Once plasma phosphate levels are below 1.5 mmol/L, measuring FGF23 is valuable to continue monitoring response to treatment and identify patients who may benefit from a more aggressive phosphate restriction. If FGF23 >700 pg/mL, it is indicated to more aggressively reduce phosphate with a further restricted diet or use of enteric phosphate binders. If FGF23 <700 pg/mL, then the phosphate restriction is appropriate and the patient can be maintained on that diet. If plasma phosphate concentrations are maintained above 1.5 mmol/L after introducing a clinical renal diet, enteric phosphate binders can be started to effect. There are various guidelines on the IRIS page to manage enteric phosphate binders (16, 14).

Other stage 2 treatments depend on the individual patient but can include managing hypokalemia with potassium gluconate, treating nausea, vomiting, hyporexia, weight / muscle loss with medication for antinausea, antiemetic, and/ or appetite stimulants. It is important to remember that muscle loss will affect sCr levels, so staging and treatments should be based on SDMA if there is substantial muscle loss (14).

Stage 3 includes many patients from presenting with mild clinical signs to quite marked clinical signs, therefore the treatments must be tailored to each individual. Treatments aimed towards slowing disease progression are still used, but treatments aimed towards improving quality of life become more important. All the treatments discussed above should be implemented. Additional treatments include managing metabolic acidosis with oral sodium bicarbonate, treating anemia if it is affecting quality of life, treating non-specific clinical signs such as vomiting, hyporexia, and managing gastric bleeding and esophagitis. Caution should be used with drugs that rely on primary renal metabolism and excretion for their function or clearance from the body in these patients as GFR can be severely reduced (14).

Stage 4 treatment is geared toward improving quality of life and limiting the extra-renal clinical signs. All the above treatments should be used. New treatments include intensifying efforts to prevent malnutrition, protein loss, and dehydration such as placing a feeding tube. IRIS guidelines note that omeprazole can be considered if GI bleeding is an issue. However, this treatment is controversial as a new veterinary study stated uremic gastropathy and CKD in cats differs from other species and that gastric ulceration was not observed in any CKD test cats (19). The most frequent and important gastric lesion observed was mineralization and fibrosis (19). Dialysis or renal transplantation is also an option, however, is not accessible for most patients (14).

For all stages, treatment of systemic hypertension should be considered. As discussed above, it is important to monitor blood pressure as systemic hypertension can induce extra-renal organ damage. Reduced blood pressure is an overarching goal of CKD treatment, where the aim is gradual and sustained reduction. If a patient is identified as persistently hypertensive, or if there is evidence or extra-renal organ damage, treatment is warranted. Treatments follow a stepwise approach. First dietary sodium reduction may be attempted, however there is little evidence to support its efficacy. Secondly, calcium channel blockers or RAAS inhibitors such as ACEI and angiotensin receptor blockers may be used separately or concurrently with doses adjusted based on protocol and response to treatment. Caution must be used when animals are dehydrated, especially animals in stage 4 CKD, as RAAS inhibitors are contraindicated in these cases as they may cause GFR to decrease substantially. Serial monitoring of blood pressure approximately every 3 months is recommended and allows tailoring of treatments (14).

For all stages, proteinuria should be investigated and treated if present. UPC ratios should be done and if >0.5 in dogs or >0.4 in cats proteinuria should be investigated. First, it is important to identify and treat any concurrent disease that may be causing proteinuria. Depending on the patient, kidney biopsies to identify disease processes can be considered.

Guidelines exist on the IRIS website to help decide when a biopsy is indicated as it is not useful in all patients, for example a biopsy is warranted in a young patient with CKD. Next, medications such as RAAS inhibitors and feeding a clinical renal diet should be attempted if these are not already done. Again, it is important to monitor all disease progression using UPC, SDMA, sCr and physical exam parameters to adjust treatments (14).

Conclusion

In conclusion, serum creatinine (sCr) concentrations have historically been used as the sole marker of GFR to diagnose and monitor CKD. sCr has many limitations, such as a low sensitivity for detecting early changes to GFR and its concentrations are directly affected by muscle mass (3). These limitations make it challenging to use sCr to diagnose early CKD and monitor late stages of CKD. SDMA is a highly sensitive marker which helps to fill the gaps where sCr is lacking. Recent literature shows SDMA to detect changes in GFR earlier than sCr allowing for earlier diagnosis of CKD (8). Additionally, SDMA may be the only marker which is elevated in early, non-azotemic CKD (10). SDMA is also not affected by muscle mass, which helps clinicians monitor the progression of late stage CKD in poorly muscled patients (3). Early diagnosis allows for clinicians to intervene early and use treatments that slow the progression of disease, whereas late diagnosis means clinicians are limited in their treatment options to decreasing clinical signs. SDMA is highly valuable in the monitoring and treatment of late stage CKD where patients have lost substantial amounts of muscle mass. This allows for better monitoring of disease progression and enhances a clinician's ability to tailor a treatment plan to each individual patient. Used together, SDMA, sCr, UPC ratio, blood pressure measurements, physical exam parameters and clinical signs are vital to diagnose and stage CKD (14).

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