

The new standard of care from IDEXX

Symmetric dimethylarginine (SDMA) is a new renal biomarker that should be run alongside creatinine, BUN and a urinalysis to help diagnose kidney disease earlier and with more confidence. The International Renal Interest Society (IRIS) has also added SDMA to their staging guidelines for chronic kidney disease (CKD). Therefore, IDEXX Reference Laboratories has added SDMA to routine chemistry panels, creating a new standard for chemistry panels.

What is SDMA?

SDMA is a methylated form of the amino acid arginine, which is released into the circulation during protein degradation and is excreted by the kidneys.

What is the benefit of measuring SDMA on canine and feline patients?

There are three key attributes of SDMA:

- **SDMA is a biomarker for kidney function.** Because SDMA is almost exclusively eliminated by renal filtration, it is a good estimate of glomerular filtration rate (GFR). It can be used along with creatinine, BUN and urinalysis to evaluate kidney function.
- **SDMA increases earlier than creatinine in CKD.** SDMA increases on average with 40% loss of kidney function versus creatinine, which does not increase until 75% of kidney function is lost.¹
- **SDMA is specific for kidney function.** SDMA is not impacted by extrarenal factors that impact creatinine. In particular, it is not impacted by lean body mass and, therefore, will more accurately reflect GFR in underweight dogs and cats (e.g., geriatric and cachectic animals).

What is the evidence to support the three key attributes of SDMA?

- **SDMA as a biomarker for kidney function.** Performing a GFR clearance test is the gold standard for estimating GFR and assessing kidney function, but it is cumbersome to perform and rarely done in practice. SDMA has been shown to strongly correlate with GFR (R^2 of 0.82 in cats²; $r = -0.95$ in dogs³).
- **SDMA as an early indicator of CKD.** A recently published study found that SDMA increased on average 17 months earlier than creatinine in cats with CKD which on average occurred when 40% of GFR was lost.¹ A similar study in dogs with CKD found that SDMA increased on average 9.5 months earlier than creatinine.⁴

- **SDMA not impacted by other diseases or lean body masses.**

SDMA, like creatinine in most cases, is specific to kidney function. SDMA is not increased in animals with various diseases, including liver disease, Cushing's disease and heart disease, unless there is concurrent kidney disease.

Unlike creatinine, SDMA is not impacted by lean muscle mass. Loss of total lean body mass associated with aging and chronic disease can lower creatinine concentrations, resulting in a poor estimation of renal function. A study in older cats confirmed that, as cats aged, they lost muscle mass and creatinine decreased even as the GFR decreased. SDMA increased as kidney function declined with no correlation to lean body mass.⁵ A study in dogs showed that creatinine correlated with lean body mass, whereas SDMA did not.⁶

What are the next steps if SDMA is increased and creatinine is within the reference interval?

In patients with these results, follow the recommended "investigate, manage, and monitor" (IMM) protocol:

1. Investigate

Evaluate the history, physical examination, urinalysis or other findings that could suggest kidney disease:

- Is the dog or cat polyuric and/or polydipsic?
- Do the kidneys palpate small or irregular? Or is one kidney much bigger than the other?
- Is the pet geriatric, underweight or poorly muscled?
- Has a urinalysis been performed? (If not, this is the next step.) Is the urine appropriately concentrated? Is there proteinuria? Is there an active urine sediment?
- Are there any other findings on the CBC or chemistry panel that suggest kidney disease?
- Could the dog or cat have an early acute kidney injury? If so, is there a possibility of exposure to a renal toxin?

Consider additional diagnostics to investigate and stage kidney disease:

- Urine protein:creatinine ratio.
- Urine culture and sensitivity.
- Blood pressure measurement.
- Investigation for infectious diseases (e.g., Lyme disease, leptospirosis, ehrlichiosis).
- Diagnostic imaging for uroliths, structural changes, etc.

2. Manage

- Use with caution any potentially nephrotoxic drugs (NSAIDs, aminoglycosides, cisplatin, etc.)

- Consider kidney-supportive diet. Includes diets that are phosphorus and sodium restricted, high in polyunsaturated fatty acids and supplemented with antioxidants. Renal therapeutic diets have these attributes and are also protein restricted. Renal diets should be considered in IRIS CKD Stage 2 patients and in IRIS CKD Stage 1 patients with proteinuria (urine protein to creatinine ratio >0.5 in dogs and >0.4 in cats).
- Consider renal-protective drugs when available and evidence supports their use (e.g., Pronefra[®], Semintra[®]).
- Provide a variety of water sources (e.g., bowls in several locations, water fountain, dripping tap).
- During anesthesia monitor and maintain blood pressure and ensure good perfusion with intravenous fluids.

3. Monitor

- Based on clinical signs
- Initial recheck in 2 weeks to determine progression
- Follow-up recheck in 2–3 months if stable
- Follow-up recheck earlier if indicated

IRIS CKD Staging Guidelines now include SDMA

SDMA has been recognized by the International Renal Interest Society (IRIS), a multinational board of 15 independent veterinarians with particular interest in veterinary nephrology, as a valuable tool to help detect dogs and cats with IRIS CKD Stage 1 disease and to help correctly stage CKD in underweight patients.

The following interpretive comments for the diagnostic and therapeutic utilization of SDMA were incorporated into the 2015 IRIS CKD Staging Guidelines, which are available in their entirety at www.iris-kidney.com.

SDMA concentrations in blood (plasma or serum) may be a more sensitive biomarker of renal function than blood creatinine concentrations. A persistent increase in SDMA above 14 $\mu\text{g}/\text{dl}$ suggests reduced renal function and may be a reason to consider a dog or cat with creatinine values <1.4 or <1.6 mg/dl , respectively, as IRIS CKD Stage 1.

In IRIS CKD Stage 2 patients with low body condition scores, SDMA $\geq 25 \mu\text{g}/\text{dl}$ may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 3 for this patient.

In IRIS CKD Stage 3 patients with low body condition scores, SDMA $\geq 45 \mu\text{g}/\text{dl}$ may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 4 for this patient.

These additions to the guidelines are preliminary, based on early data derived from the use of SDMA in veterinary patients. The IRIS board fully expects them to be updated as the veterinary profession gains further experience using SDMA alongside the long-established marker, creatinine, in the diagnosis and therapeutic monitoring of canine and feline CKD.

Conclusion

Chronic kidney disease is a common condition in dogs and a leading cause of death in cats. SDMA helps identify disease earlier and is complementary to existing kidney tests. Early identification should prompt investigation for an underlying cause, giving the potential for specific treatment. Early management may slow the progression of the disease. Closer monitoring will help identify progression and indicate when additional therapies should be initiated.

References

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3. Nabity MB, Lees GE, Boggess M, et al. SDMA assay validation, stability, and evaluation as a marker for early detection of chronic kidney disease in dogs. *J Vet Intern Med.* 2015;29(4):1036–1044.
4. Yerramilli M, Yerramilli M, Obare E, Jewell DE, Hall JA. Symmetric dimethylarginine (SDMA) increases earlier than serum creatinine in dogs with chronic kidney disease (CKD). [ACVIM Abstract NU-42]. *J Vet Intern Med.* 2014;28(3):1084–1085. <http://onlinelibrary.wiley.com/doi/10.1111/jvim.12361/abstract>. Accessed January 14, 2015.
5. Hall JA, Yerramilli M, Obare E, Yerramilli M, Yu S, Jewell DE. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in healthy geriatric cats fed reduced protein foods enriched with fish oil, L-carnitine, and medium-chain triglycerides. *Vet J.* 2014;202(3):588–596.
6. Hall JA, Yerramilli M, Obare M, Yerramilli M, Melendez LD, Jewell DE. Relationship between lean body mass and serum renal biomarkers in healthy dogs. *J Vet Intern Med.* 2015;29(3):808–814.

The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment, you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical presentation and complete laboratory data. With respect to any drug therapy or monitoring program, you should refer to product inserts for a complete description of dosages, indications, interactions and cautions. Diagnosis and treatment decisions are the ultimate responsibility of the primary care veterinarian.