

## Symmetric dimethylarginine (SDMA): new biomarker of renal function in cats and dogs (2016)

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Filtration, specifically its magnitude (glomerular filtration rate or GFR), is the central measure of the adequacy of renal function. Furthermore, the severity of most renal diseases, including both acute kidney injury (AKI) and chronic kidney disease (CKD), is judged by their effects on GFR. Although direct measurement of GFR is widely accepted as the reference method for assessment of renal function, clinicians frequently use surrogate markers, such as blood urea nitrogen concentration or blood (plasma or serum) creatinine, to determine the adequacy of GFR. However, mild to moderate decreases in GFR are difficult to detect with these commonly used diagnostic tests. While serial evaluation of blood creatinine concentration in the same animal increases the sensitivity of this test, baseline measurements are often unavailable.

There are several species of methylated arginine produced as a byproduct of intracellular protein methylation followed by protein degradation. Of interest are the dimethylated derivatives of arginine, symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA). While ADMA is metabolized enzymatically, SDMA is eliminated primarily by renal filtration and plasma SDMA concentration has been used as an alternate biomarker for estimating GFR in people. A meta-analysis of 18 studies involving human patients showed that  $1/\text{SDMA}$  concentrations correlated highly with GFR (inulin clearance;  $r = 0.85$ ), and SDMA concentrations correlated highly with blood creatinine ( $r = 0.75$ ). Plasma SDMA concentrations are increased in cats with CKD and correlate with blood creatinine concentrations.

At present, the available data suggest that plasma (or serum) concentration of SDMA reflects GFR in cats and dogs, may be more sensitive than blood creatinine for early detection of CKD, and is less affected by loss of lean body mass than blood creatinine. Clearly SDMA has utility for the diagnosis and management of dogs and cats with renal disease.

IRIS CKD staging is based on fasting blood creatinine concentrations, but there are indications that SDMA concentrations in blood may be a more sensitive biomarker of renal function. Accordingly, if blood SDMA concentrations are known, the IRIS Board has suggested that some modification to the guidelines might be considered, as follows:

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

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

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

These comments are preliminary and based on early data from the use of SDMA in veterinary patients. We expect them to be updated as the veterinary profession gains further experience using SDMA alongside creatinine, the long-established marker in diagnosis and monitoring of canine and feline CKD.

To date, published studies have investigated the utility of this biomarker in cats, dogs, and people. Citations for several studies of the utility of the measurement of serum or plasma SDMA as a biomarker to estimate GFR [and conclusions of the study authors] are provided below.

### Cats

Jepson RE, Syme HM, Vallance C, Elliott J. Plasma asymmetric dimethylarginine, symmetric dimethylarginine, l-arginine, and nitrite/nitrate concentrations in cats with chronic kidney disease and hypertension. *J Vet Intern Med* 2008;22:317-324. [*Plasma SDMA concentrations were increased in cats with CKD and correlated with blood creatinine.*]

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. *J Vet Intern Med* 2015;29:1036-1044. [*Serum SDMA concentration was more highly correlated with GFR than serum creatinine, and, unlike creatinine, was unaffected by muscle wasting.*]

Hall JA, Yerramilli M, Obare E, Yerramilli M, Jewell DE. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. *J Vet Intern Med* 2014;28:1676-1683. [*Using serum SDMA as a biomarker for CKD allowed earlier detection of CKD in cats compared with blood creatinine.*]

Braff J, Obare E, Yerramilli M, Elliott J, Yerramilli M. Relationship between serum symmetric dimethylarginine concentration and glomerular filtration rate in cats. *J Vet Intern Med* 2014;28:1699-1701. [*Increased serum SDMA concentrations were observed in cats with reduced renal function as determined by direct measurement of GFR. The relation between GFR and SDMA was of similar strength as the relation between GFR and blood creatinine.*]

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. *J Vet Intern Med* 2015;29:1036-1044. [*Serum SDMA concentration was more highly correlated with GFR than serum creatinine, and, unlike creatinine, was unaffected by muscle wasting.*]

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### Dogs

Hall JA, Yerramilli M, Obare E, Yerramilli M, Melendez LD, Jewell DE. Relationship between lean body mass and serum renal biomarkers in healthy dogs. J Vet Intern Med 2015;29:808-14. *[In Beagle dogs, blood creatinine but not SDMA concentrations were influenced by lean body mass.]*

Nabity MB, Lees GE, Boggess M, Yerramilli M, Obare E, Yerramilli M, Aguiar J, Relford R. Correlation of symmetric dimethylarginine with glomerular filtration rate in dogs with chronic progressive renal disease. J Vet Intern Med 2013;27:733(Abstract). *[SDMA correlated well with GFR in dogs with progressive renal disease.]*

Hall JA, Yerramilli M, Obare E, Yerramilli M, Almes K, Jewell DE. Serum concentrations of symmetric dimethylarginine and creatinine in dogs with naturally occurring chronic kidney disease. J Vet Intern Med 2016;30:794-802. *[SDMA was an earlier biomarker than serum creatinine reference ranges for diagnosing CKD in dogs.]*

### People

Kielstein JT, Salpeter SR, Bode-Boeger SM, Cooke JP, Fliser D. Symmetric dimethylarginine (SDMA) as endogenous marker of renal function – a meta-analysis. Nephrol Dial Transplant 2006;21:2446-2451.

*[SDMA was a reliable marker of renal function.]*

Protas PT, Tenderenda-Banasiuk E, Taranta-Janusz K, Filonowicz R, Zajac M, Wasilewska A. Is symmetric dimethylarginine a sensitive biomarker of subclinical kidney injury in children born with low birth weight? Biomarker 2014;19:231-235. *[SDMA correlated well with GFR.]*

Ei-Khoury JM, Bunch DR, Hu B, Payto D, Reineks EZ, Wang S. Comparison of symmetric dimethylarginine with creatinine, cystatin C and their eGFR equations as markers of kidney function. Clin Biochem 2016;49:1140-1143. *[SDMA concentrations were more highly correlated with GFR than blood creatinine concentration]*