

Frequently asked questions about SDMA



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Answers

SDMA background

1. What is SDMA?

Symmetric dimethylarginine (SDMA) is a methylated arginine amino acid. SDMA along with its structural biologically active isomer, asymmetric dimethylarginine (ADMA), are derived from intranuclear methylation of L-arginine residues and are released into the cytoplasm after proteolysis. SDMA is excreted by the kidneys, whereas ADMA is largely metabolized.

2. What are the 3 key attributes of SDMA?

There are 3 key attributes of SDMA:

- SDMA is a biomarker of kidney function. It correlates extremely well with glomerular filtration rate (GFR).
- SDMA increases earlier than creatinine in CKD. On average, SDMA increases with 40% loss of kidney function and as early as with 25% kidney function loss. However, creatinine does not increase until 75% of kidney function is lost. SDMA will enable veterinarians to diagnosis CKD months or even years earlier than traditional tests.
- SDMA is specific for kidney function. SDMA is not affected by other diseases if kidney function is not affected. This includes liver disease, cardiovascular disease, inflammatory disease, and endocrine diseases. In addition, an exciting feature of SDMA is that it is not impacted by lean body mass whereas creatinine is.

3. Did IDEXX discover SDMA?

No, IDEXX did not discover SDMA. Numerous studies have been previously performed and published evaluating SDMA as a kidney biomarker.

4. What is unique about IDEXX's SDMA test?

IDEXX has developed a commercial test for SDMA. It is an immunoassay that can be performed on a high-throughput chemistry analyzer at our reference laboratories. In this way, we can provide SDMA results as part of our routine chemistry panel alongside creatinine.

5. Why did IDEXX develop the SDMA test? Why did IDEXX Reference Laboratories add SDMA to all routine chemistry panels?

CKD is a common disease in dogs and cats, and it is well recognized that traditionally available diagnostic tests detect kidney disease late. At IDEXX, we are committed to enhancing the health and well-being of pets by providing veterinarians with tools and diagnostics to support the practice of best medicine. Because SDMA is a valuable tool to help recognize kidney disease early, often before any clinical signs develop, we believed it was important to add it to all routine chemistry panels.

6. Is SDMA available to run in-house on the Catalyst Dx® and Catalyst One™ chemistry analyzers?

Currently, SDMA is a reference laboratory-only test, but the IDEXX Reference Laboratories offering is just the beginning. IDEXX has a long history of introducing new tests at our reference laboratory first and then introducing them in-house (e.g., the SNAP® Feline proBNP Test and the Catalyst® Fructosamine Test). Until then, all in-house chemistry customers who use IDEXX Reference Laboratories can easily order a stand-alone SDMA test.

Comparison of SDMA to other kidney diagnostics

7. How does SDMA relate to glomerular filtration rate (GFR)?

SDMA is excreted from the kidneys; therefore, as kidney function or GFR decreases, SDMA increases. Studies have shown a very strong correlation between SDMA and GFR (R^2 of 0.82 in cats; R^2 of 0.85 in dogs). The benefit of using SDMA along with creatinine, which typically increases above the reference interval only after a 75% reduction in GFR, is that SDMA increases when there is on average a 40% decrease in GFR. In some cases, SDMA increases earlier when there is 25% reduction of GFR, representing 25% loss of kidney function.

Performing a GFR clearance test is the gold standard for estimating GFR and assessing kidney function. However, performing a GFR clearance test is expensive and not routinely done in practice.

8. How does SDMA compare to traditional kidney tests?

- Creatinine—SDMA increases earlier than creatinine in dogs and cats with CKD. SDMA increases on average with 40% loss of kidney function versus creatinine, which does not increase until 75% of kidney function is lost. In addition, creatinine is impacted by lean body mass, whereas SDMA is not. Therefore, SDMA is a more sensitive indicator of kidney function in animals with poor body condition.
- BUN—BUN is also a late marker of kidney dysfunction in contrast to SDMA. In addition, BUN can be influenced by decreased production in liver disease and increases with high-protein meals or gastrointestinal bleeding versus SDMA, which changes only with changes in GFR.
- Urine specific gravity—Natural fluctuations are normal and can be influenced by how much the animal drinks the day the urine is collected as well as the time of day of collection. Poor urine concentration is not specific to the kidney and can be influenced by other diseases like diabetes, liver disease, and Cushing's disease versus SDMA, which is only influenced by changes in kidney function.
- UPC—The urine protein:creatinine (UPC) ratio is a urine test. It is used to fully quantify protein detected in the urine once transient proteinuria, urinary tract infection, inflammation, or significant hematuria has been ruled out. UPC may detect

CKD earlier than creatinine if the primary target of the disease is the glomerulus and with some cases of tubulointerstitial disease. However, it is also common for the UPC to remain normal in animals with CKD, especially in early stages when SDMA may be increased. Persistent proteinuria that results in UPCs greater than 0.4 in cats and 0.5 in dogs, where prerenal and postrenal proteinuria have been ruled out, are consistent with glomerular or tubulointerstitial CKD, whereas UPCs greater than 2.0 are strongly suggestive of glomerular disease. In animals with proteinuria, UPC should be used to monitor progression and response to therapy.

- **Microalbuminuria**—Microalbuminuria is a urine test. It is an early marker only in some cases of CKD. Physiologic transient increases are common. It will also be positive with urinary tract inflammation, so additional testing is needed to rule out urinary tract infection, inflammation, or significant hematuria. Once persistence has been established and false positives eliminated, microalbuminuria will be the earliest indicator of glomerular disease. In early glomerular disease when GFR may still be normal, SDMA may also remain normal. Similarly, microalbuminuria may be an early indicator of some but not all tubulointerstitial CKD, and as GFR decreases, SDMA will increase. A positive result should always be followed by a UPC test to determine quantitative value. It is common for the microalbuminuria test and UPC to be normal, especially in early CKD.

9. Will SDMA replace creatinine in diagnosing CKD? Do I still need to use creatinine if I have SDMA?

SDMA and creatinine are complementary. SDMA will not replace creatinine; it is another more sensitive tool to evaluate kidney function. A complete kidney evaluation should consist of a thorough history, physical examination, and evaluation of minimum database, including CBC, chemistry panel with SDMA, and complete urinalysis. IDEXX will include the SDMA kidney test in all routine reference laboratory chemistry profiles this summer at no additional cost and with the same turnaround time, so creatinine will be readily available for comparison. Creatinine is needed for International Renal Interest Society (IRIS) staging of CKD, so it will continue to be important for clinical characterization of CKD patients.

10. Does SDMA increase before proteinuria? Does SDMA correlate with proteinuria?

SDMA is a serum test and a good marker of GFR; it increases as kidney function decreases, regardless of underlying cause. It is both sensitive and specific for loss of kidney function. Unlike SDMA, the microalbuminuria test and UPC are urine tests. They detect protein in the urine, which can be from anywhere in the urinary tract, so it's important to eliminate false-positive results, especially with urinary tract infections, other inflammation, or significant hematuria. Transient increases that can also result from physiologic causes, such as strenuous exercise, fever, exposure to extreme cold or heat, and stress, must first be eliminated.

Patients with glomerulopathy may develop proteinuria long before a significant change in GFR so their SDMA may remain

normal until disease is more advanced and GFR decreases. However, patients with tubulointerstitial disease may have only mild proteinuria or no proteinuria at all; in these cases, SDMA will usually be an earlier indicator of CKD.

11. Is SDMA too sensitive? Does SDMA have the same potential pitfalls as the microalbuminuria test?

The microalbuminuria test detects very small amounts of protein in the urine. A positive microalbuminuria test can result from physiologic or pathologic conditions. Transient physiologic increases can occur with fever, strenuous exercise, seizures, exposure to extreme heat or cold, and stress. Pathologic urinary proteinuria can be from anywhere in the urinary tract; therefore, false positives are common especially with urinary tract inflammation. Additional testing is needed to rule out urinary tract infection, inflammation, or significant hematuria. Only after nonpathologic causes and urinary tract inflammation have been ruled out and persistence established can microalbuminuria be considered an early indicator of kidney disease. Microalbuminuria of renal origin occurs with glomerulopathies and in some, but not all, animals with tubulointerstitial disease. SDMA, on the other hand, is a serum test and a biomarker for GFR, increasing only when there is on average a 40% loss of GFR, regardless of underlying etiology of the kidney disease.

12. What is the sensitivity and specificity of SDMA for confirming kidney dysfunction?

A [published study](#) in cats found the sensitivity of SDMA to be 100% and the specificity to be 91% when compared to the gold standard of GFR. There were 2 “false positives” in this study, but these 2 cats actually did have a 25% reduction in their GFR; the GFR cut off to define kidney disease in this study was only a 30% reduction in GFR.

13. Wouldn't creatinine be just as good as SDMA if the upper end of the reference interval was just lowered?

No. In the [feline study](#) mentioned above, the sensitivity of creatinine, using the reference interval established for their laboratory, was only 17%. However, when the IRIS stage 1 cut off for creatinine of 1.6 mg/dL was used instead, the sensitivity still only increased to 50%. SDMA is better correlated with GFR and is more sensitive than creatinine. At IDEXX, we established our creatinine reference intervals by performing a true reference interval study with clinically healthy dogs and cats following Clinical and Laboratory Standards Institute (CLSI) guidelines. SDMA reference intervals were established the same way.

14. Has there been any correlation between SDMA and different types of kidney disease, based on histologic diagnosis (e.g., glomerular versus tubular disease, membranoproliferative glomerulonephritis versus other)?

SDMA does not help localize kidney disease or the cause of kidney disease. It increases as GFR decreases, reflecting overall nephron function, regardless of lesion localization or etiology.

SDMA basics

15. What are the main advantages of SDMA?

SDMA increases earlier than creatinine in dogs and cats with kidney disease. It is also not impacted by lean body mass, making it a more sensitive test for assessing kidney function in older and underweight animals.

16. What is the benefit of diagnosing CKD early? What do you do differently?

Early diagnosis provides the opportunities to:

- **Investigate** for an underlying cause, especially more treatable conditions such as infection and obstruction, and to IRIS substage the CKD for proteinuria and hypertension.
- **Manage** or treat those causes, attending to hydration, proteinuria, and hypertension, with consideration for initiating kidney-supportive diet and drugs as indicated, and implementing practices to avoid future insults to the kidneys, e.g., taking precautions with prescribed drugs and when anesthetizing pet.
- **Monitor** the patient as an individual. The frequency of recheck visits will depend on clinical status, whether an underlying disease was identified and what treatments were initiated. An initial recheck 2 weeks after kidney disease is first suspected or identified would be reasonable to determine if disease is stable or progressing. After this initial recheck, in a stable animal with early CKD and no hypertension or proteinuria, a recheck in 2–3 months would be reasonable.

For more information, refer to [the SDMA algorithm](#) and the white paper, “[Introduction to a New Kidney Test: SDMA.](#)”

17. Is the utility of SDMA limited to CKD or is it also helpful in acute cases?

SDMA correlates with GFR and therefore will increase in acute kidney injury (AKI). Because it increases when there is on average 40% loss of GFR and as early as 25% kidney function loss versus creatinine, which is not increased until up to 75% loss of GFR, it will likely increase earlier in AKI. By the time an animal presents with clinical signs and is azotemic, SDMA will be clearly increased. SDMA might add value to help confirm toxin exposure when suspected, e.g., a scenario of possible lily exposure where the cat is hospitalized and being serially monitored for evidence of kidney injury. Demonstrating an increase in SDMA would confirm altered GFR, likely because of acute injury from the toxic plant, justifying continued hospital care.

18. What is the reference interval for SDMA and how was it established?

The reference interval for dogs and cats is the same; 0–14 $\mu\text{g}/\text{dL}$. Reference intervals were established following the Clinical and Laboratory Standards Institute (CLSI) guidelines for determining reference intervals. Adult (1 year and older) animals characterized as healthy based on history and physical examination were enrolled into the study. Animals received no medications except for routine heartworm and parasite prophylaxes. Males and females were equally represented and were of various breeds and sizes.

19. Have the reference intervals for puppies and kittens been determined?

On a population basis, median SDMA results appear to be slightly higher (approximately 1 $\mu\text{g}/\text{dL}$) in puppies and kittens. Most puppies and kittens will still have SDMA results within the reference interval, but if results are just above the reference interval (0–14 $\mu\text{g}/\text{dL}$), then they should be interpreted in light of other findings. The cause of this slight increase is unknown at this time but physiological roles for protein arginine methylation include signal transduction, mRNA splicing, transcriptional control, DNA repair, and protein translocation. It is postulated that in growing animals, there is an increase in these processes, resulting in increased SDMA generation when the methylated proteins are degraded.

20. Are there any breed differences recognized for SDMA? What about greyhounds?

Other than greyhounds, no breed differences have been recognized for SDMA. On a population basis, median SDMA results appear to be slightly higher (approximately 1 $\mu\text{g}/\text{dL}$) in greyhounds; however, most healthy greyhounds with normal kidney function will have SDMA results within the reference interval. It is also common for greyhounds to have creatinine concentrations just above the reference interval, which is believed to be a result of their high muscle mass. Therefore, in greyhounds, both creatinine and SDMA may be near the upper end or just above their respective reference intervals, and the results of both should be evaluated together, along with a complete urinalysis.

21. Has SDMA been validated in species other than dogs and cats? If so, what is the reference interval for other species?

SDMA has not been validated nor reference intervals established yet for species other than dogs and cats. Validating SDMA and establishing reference intervals for other species will be the focus of future studies. However, SDMA results will be provided on routine nonspecies-specific chemistry panels. For species other than dogs and cats, no reference interval will be provided, and the following statement will be given with the SDMA result: SDMA is a new kidney test for dogs and cats. No information is currently available on how to interpret SDMA in other species.

22. What constitutes a significant increase in SDMA?

Any increase of SDMA above the reference interval (greater than 14 $\mu\text{g}/\text{dL}$) is considered meaningful. Most animals with early kidney disease have a SDMA of 15–20 $\mu\text{g}/\text{dL}$. Since SDMA increases as kidney function decreases, an SDMA concentration greater than 20 $\mu\text{g}/\text{dL}$ is typically seen in more advanced disease, along with an increased creatinine concentration. Less than 1% of all results will be above 50 $\mu\text{g}/\text{dL}$ and the linearity of the assay is up to 100 $\mu\text{g}/\text{dL}$.

23. If a cat has already been diagnosed with CKD, would running an SDMA test provide any additional information?

CKD is common in older cats. Lean body mass decreases as cats age. SDMA is not impacted by lean muscle mass like creatinine is, which makes SDMA a more sensitive indicator of kidney function in older cats. Therefore, not only will SDMA help to detect CKD in older cats, it should be helpful to monitor

kidney function in cats with CKD as their disease progresses and they continue to lose muscle mass.

24. Does an increased SDMA mean that the patient has renal failure?

Renal failure is an outdated term. Current terminology for acute disease is acute kidney injury (AKI). Current terminology for chronic disease is chronic kidney disease (CKD) and the International Renal Interest Society (IRIS) staging system should be used to stage chronic stable disease from stage 1 through stage 4. Please see the [IRIS guidelines](#) for more information. SDMA offers another tool for recognition of dogs and cats with early CKD.

25. How do SDMA and GFR correlate to urine specific gravity (USG)?

SDMA correlates well with GFR, increasing when there is on average a 40% loss, and as little as 25% loss, of GFR. Reduced urine concentrating ability typically appears when there is, on average, a 67% loss of GFR, but this is variable. Cats with experimentally induced kidney disease, for example, showed poor correlation between maximum urine concentration and GFR, with some azotemic cats retaining concentrating ability despite severe reduction in GFR. Given the lack of correlation between GFR and USG, a linear relationship between SDMA and USG could not be expected.

SDMA will typically increase before isosthenuria associated with renal dysfunction develops. In many cases of early CKD, where SDMA is increased but creatinine is normal, the dog or cat will have an inappropriate USG (i.e., less than 1.030 for dogs or less than 1.035 for cats). However, in more than 25% of dogs and cats with an increased SDMA, significant urine concentrating ability will still remain because their GFR is only mildly decreased, or because of the variable timing of loss of concentrating ability.

26. What specimen type is needed to order SDMA?

SDMA can be run on serum (preferred); lithium heparin or EDTA plasma is also acceptable.

27. Does specimen quality, including such factors as lipemia, hemolysis, or icterus, affect the SDMA result?

Studies were done to confirm that lipemia, hemolysis, and icterus do not affect the SDMA result. However, rarely in specimens with extreme hemolysis and lipemia SDMA cannot be measured. As with all laboratory testing, quality specimens free of lipemia and hemolysis are preferred to provide the most accurate results.

28. What is the turnaround time for SDMA results?

SDMA results will be included with all routine chemistry profile results with the same turnaround time. SDMA will not impact the turnaround time of any routine chemistry profile result. Stand-alone SDMA results will be provided daily.

29. How does storage affect SDMA?

SDMA is stable for 4 days at room temperature and 14 days refrigerated. It is also stable for years in specimens that remain frozen and do not undergo freeze thaw cycles. Accordingly,

whole blood, serum or plasma specimens discovered in the centrifuge or on the counter that remained at room temperature for 24 hours or less should be acceptable to submit for SDMA testing. Because SDMA is a stable analyte it is acceptable to add on an SDMA test to serum or plasma specimens being held in the lab, or to submit specimens used for in house diagnostic testing. It is always best to interpret a SDMA result along with a paired creatinine result and a urinalysis.

SDMA in nonrenal diseases

30. Other than kidney disease, are there any specific reasons or conditions that could cause an increased SDMA?

SDMA correlates strongly with GFR. There are no known interferences that are expected to cause a falsely increased SDMA. SDMA increases only when GFR is reduced. However, if GFR is reduced with prerenal or postrenal azotemia, then SDMA will increase accordingly.

31. Does dehydration impact SDMA?

If dehydration results in a prerenal azotemia reflecting a reduction in GFR, then SDMA should also increase.

32. Do endocrinopathies, including hyperadrenocorticism and diabetes, affect SDMA?

SDMA correlates strongly with GFR. Therefore, if GFR is normal in an animal with an endocrinopathy, the SDMA will also be normal. IDEXX has evaluated SDMA in several dogs with confirmed hyperadrenocorticism and hyposthenuria or isosthenuria, and SDMA was well within the reference interval. In animals evaluated with confirmed diabetes mellitus and no evidence of kidney disease, SDMA results have also been normal. Finding an increased SDMA in patients with these endocrine diseases would indicate concurrent kidney disease.

33. Would SDMA be helpful in ruling out early kidney disease as the cause of polyuria/polydipsia (PU/PD) in nonazotemic patients without another apparent diagnosis?

Because SDMA increases early in CKD when there is on average a 40% loss and as early as a 25% loss of GFR, it is unlikely that an animal with a normal SDMA would have PU/PD or loss of urine concentrating ability associated with renal tubular dysfunction and nephron loss. Typically, PU/PD of renal tubular dysfunction appears when there is a more significant reduction in GFR, on average with 67% loss of GFR and USG becomes inappropriate (less than 1.030 for dogs, less than 1.035 for cats). In animals with a secondary nephrogenic diabetes insipidus (DI) caused by pyometra, bacteremia, glucocorticoids, or other metabolic diseases, SDMA concentrations would be expected to be normal because their GFR would remain normal. In these animals, their inappropriately concentrated urine that is hyposthenuric to isosthenuric is a result of tubular resistance to antidiuretic hormone.

However, a patient with pyelonephritis could have aspects of nephrogenic DI, as well as nephron loss from inflammation, so the GFR and SDMA could be normal or increased, depending on to the extent the GFR is affected.

34. Does SDMA accumulate in inflammatory diseases, such as pancreatitis or inflammatory bowel disease (IBD), etc.?

SDMA is specific for kidney function and reflects GFR. SDMA does not increase due to pancreatitis alone, and there is no correlation between SDMA and the Spec cPL® and Spec fPL® tests, which are sensitive markers for canine and feline pancreatitis, respectively. In well-characterized cats with IBD, SDMA only correlated with GFR and not the magnitude of gastrointestinal disease. In human studies SDMA is not impacted by acute inflammatory response, hepatic disease, stroke, or cardiovascular disease unless there is concurrent compromise of kidney function. It should be surmised that demonstrating an increased SDMA in a stable patient with IBD, pancreatitis, or other systemic illness suggests alterations in GFR as a result of kidney disease.

35. Will SDMA help us determine which hyperthyroid cats will develop azotemia with treatment, especially after I-131 therapy?

Untreated hyperthyroid cats have an increased GFR secondary to their hyperthyroidism, which can hide underlying CKD. SDMA may help in some cases to predict the impact of thyroid treatment on kidney function, depending on how much the GFR is decreased prior to treatment.

If the pretreatment GFR in a nonazotemic cat is decreased by on average 40% or more in the face of untreated hyperthyroidism, then we expect increased SDMA to alert us to the probability of underlying kidney disease, suggesting a more cautious approach to the treatment of hyperthyroidism.

If a cat's pretreatment GFR is not reduced by on average 40%, but is on average 60% normal or better, then the SDMA will likely be normal. If with treatment, the GFR decreases to on average 40% of normal, then the SDMA will increase above normal, and as GFR loss approaches 75%, azotemia will also develop. Therefore, a normal pretreatment SDMA definitely does not rule out the possibility of the cat developing azotemia with treatment, and routine precautions should still be taken.

In a study evaluating hyperthyroid cats on Hill's® Prescription Diet® y/d® Feline, SDMA better correlated with GFR than did creatinine, but none of the cats became azotemic.

36. Is SDMA influenced by the amount of arginine in the diet?

This has not been studied specifically in animals, but it has been confirmed that there is no correlation in dogs and cats between SDMA and serum arginine concentrations. In addition, in pregnant women with preeclampsia receiving prolonged supplementation with L-arginine, there was no impact on serum SDMA concentrations.

Interpreting SDMA results and what to do next

37. How often will SDMA be increased?

CKD is common with 1 in 3 cats¹ and 1 in 10 dogs² developing some form of kidney disease over their lifetime. Recent studies suggest kidney disease is even more common and until now has been under-recognized.^{3,4} SDMA will help to recognize CKD in more animals earlier with prevalence increasing with age. As CKD advances, creatinine will also be increased.

• Prevalence of increased SDMA in dogs

Approximately 10% of adult dogs less than 10 years of age, approximately 20% of dogs 10–15 years of age, and approximately 50% of dogs over 15 years of age will have increased SDMA.

• Prevalence of increased SDMA in cats

Approximately 15% of adult cats less than 5 years of age, approximately 20% of cats 5–10 years of age, approximately 30% of cats 10–15 years of age, and approximately 60% of cats over 15 years of age will have increased SDMA.

38. What should I do if the SDMA is increased?

SDMA is a sensitive and specific biomarker of kidney function, so we recommend reviewing your patient's history, physical examination findings, and other laboratory results for any evidence of kidney disease. If a urinalysis has not been performed, then performing a urinalysis is the next step in the diagnostic plan.

• What to do in patient with high SDMA and normal creatinine with no other findings to support kidney disease

History, physical examination, creatinine, and urinalysis are normal with appropriate concentration (USG greater than or equal to 1.030 for dogs, USG greater than or equal to 1.035 for cats), no proteinuria, no glucosuria, and inactive urine sediment.

SDMA increases when there is on average 40% loss of kidney function and as early as 25% loss of kidney function. Whereas urine concentrating ability decreases when approximately 66% of kidney function is lost, and creatinine increases above normal when up to 75% of kidney function has been lost. Therefore early in CKD, it is common for the SDMA to be increased and the creatinine to be normal. It is also not unreasonable for animals to still have well-concentrated urine early in the course of their CKD. Therefore, early kidney disease is still possible, and the patient should be rechecked in 4–6 months, sooner if clinical signs or urinary abnormalities are noted. You may wish to discuss with the pet owner renoprotective strategies in husbandry, medication choices, and for any necessary anesthesia, and book the recheck visit to improve compliance. Acquaint them with the signs that might suggest progressive kidney disease, to include PU/PD, nocturia or household accidents, soaking the litter box, or progressive malaise, anorexia, or vomiting.

• What to do in a patient with high SDMA and normal creatinine with urinary findings to support kidney disease

History, physical examination and creatinine are normal, but urinalysis is abnormal with inappropriate concentration (USG less than 1.030 for dogs, USG less than 1.035 for cats), proteinuria, glucosuria, and/or active urinary sediment.

If abnormalities are found on urinalysis in conjunction with high SDMA and normal creatinine, then early kidney disease is likely and the [SDMA algorithm](#) should be followed to investigate, manage, and monitor the patient. Investigate for underlying cause of kidney disease and evaluate for proteinuria and hypertension; manage by treating any identified cause and to delay progression of the disease; and

monitor based on clinical signs with initial recheck in 2 weeks to determine persistence and progression of disease.

• **What to do in patient with high SDMA and high creatinine**

Kidney disease is likely. SDMA increases as kidney function decreases. A complete urinalysis should be performed to evaluate for inappropriate USG, proteinuria, and other evidence of kidney disease. Investigate, manage, and monitor kidney disease appropriately.

39. What if both SDMA and creatinine are normal?

If both SDMA and creatinine are within their reference intervals, then kidney disease is unlikely. If SDMA and/or creatinine is at the upper end of the reference interval, early kidney disease cannot be ruled out. A complete urinalysis should be performed to confirm there is no other evidence of kidney disease.

40. What if the creatinine is increased, but the SDMA is normal?

Consider the possibility that increased muscle mass, such as may be seen with certain heavily muscled breeds like pit bull-type dogs, might be contributing to a higher than expected creatinine. Review patient history, physical examination findings, and urinalysis for any other evidence of kidney disease. Consider retesting in 2–4 weeks.

Next steps: Investigation to consider when SDMA is increased

41. What findings on a urinalysis are consistent with kidney disease?

Urine changes consistent with kidney disease include but are not limited to:

- Inappropriate urine concentration—USG less than 1.030 for dogs, USG less than 1.035 for cats.
- Proteinuria—While small amounts of protein may normally be found in the urine, proteinuria can indicate both renal and nonrenal disease. If significant proteinuria is detected and there is an inactive sediment, a urine protein:creatinine (UPC) ratio should be performed for protein quantification for accurate assessment and monitoring.
- Glucosuria (without hyperglycemia)—Persistent renal glucosuria may suggest tubular injury from renal infection, as with pyelonephritis or leptospirosis, exposure to potential toxins (e.g., jerky treats or heavy metals), or less commonly congenital renal glucosuria.
- Active urine sediment—Presence of pyuria and bacteruria in a sterilely acquired specimen would be suggestive of urinary tract infection, and a urine culture and sensitivity should be performed. The significance of hematuria, crystals, and epithelial cells would depend on the method of urine collection and storage. Significance of casts depends on type of cast and number present.

42. When do you consider testing an asymptomatic canine patient with increased SDMA for leptospirosis? What tests are recommended?

Leptospirosis is a common cause of acute kidney injury and liver disease associated with vasculitis. Less commonly it may contribute to chronic inflammatory disease when patients are

minimally symptomatic. Testing for chronic leptospiral infection will likely have the highest yield in patients that have not been vaccinated regularly for leptospirosis and that have interactions with wildlife or access to infected water sources and may also have a history of febrile illness. Urinalysis findings might include glucosuria, proteinuria, granular casts, hematuria, and pyuria. It is recommended to test for both antigen with the *Leptospira* spp. RealPCR™ Test on whole blood and urine, and antibodies with the SNAP® Lepto Test or *Leptospira* spp. Antibody by ELISA on serum. The potential for zoonosis and disease progression justifies testing for leptospirosis in patients with acute or chronic kidney disease.

43. When do you consider testing a canine patient with increased SDMA for Lyme disease?

Testing for Lyme disease with a SNAP® 4Dx® Plus Test is appropriate for all dogs with proteinuria. Lyme nephritis may present as acute, stable, or progressive protein-losing nephropathy. Acute signs of illness include vomiting, anorexia, and lethargy. Some dogs may display more subtle or chronic signs, progressing slowly over weeks to months. Urinalyses show proteinuria with variable inappropriately concentrated urine, hematuria, pyuria, bilirubinuria, and glucosuria. Early recognition and treatment of Lyme nephritis might allow for successful treatment of this often highly fatal complication of Lyme infection.

44. Why is it important to test my canine patients that have an increased SDMA and proteinuria with a SNAP 4Dx Plus Test?

Testing for common infectious diseases associated with glomerulonephritis using the SNAP 4Dx Plus Test is supported by diagnostic recommendations described in the IRIS Consensus Clinical Practice Guidelines for Glomerular Disease in Dogs. The SNAP 4Dx Plus Test screens for six vector-borne diseases, including Lyme disease, heartworm, *Ehrlichia canis*, *Ehrlichia ewingii*, *Anaplasma phagocytophilum* and *Anaplasma platys*.

45. Why is it important to test my feline patients that have an elevated SDMA with a SNAP® Feline Triple® Test or SNAP® FIV/FelV Combo Test?

Testing for retrovirus infection is recommended by the American Association of Feline Practitioners for all sick cats, irrespective of life style, prior history, or previous viral status. FeLV is a specific risk factor for glomerulonephritis (GN); both FeLV and FIV increase the risk for lymphoma and myeloproliferative disorders that may also contribute to GN. The SNAP Feline Triple Test screens for heartworm in addition to FeLV and FIV. Heartworm infection can also lead to the development of GN.

46. Why is diagnostic imaging recommended in animal with increased SDMA?

Diagnostic imaging is suggested for motivated pet owners especially when urinary calculi, pyelonephritis, renal neoplasia or dysplasia, glomeronephritis, or other structural abnormalities are suspected. Radiography and abdominal sonography offer the most powerful combination to indicate kidney size and

architecture.

47. My clients don't want to pay for a urinalysis. How do I help convince them I need the test?

It may be helpful to point out that a urinalysis is a very inexpensive test, relative to the potential information gained, with a low cost/high benefit ratio. A urinalysis should be part of the minimum database for all routine preventive healthcare screens and in sick dogs and cats. Patients with kidney disease may have few clinical signs, but findings on the urinalysis can provide supportive evidence of the presence of kidney disease and perhaps help determine etiology. Inappropriately concentrated urine is one of the most consistent findings when kidney function is reduced by about 67%, when SDMA would typically be increased, and before azotemia has developed. Identifying proteinuria in absence of inflammation or significant hematuria would lead to measurement of UPC. Presence of pyuria with or without bacteruria would lead to a urine culture and sensitivity being performed. Identifying crystalluria or presence of casts might also lead to additional diagnostics being performed.

Often the challenge can be just collecting the urine. For dogs, you might request that the pet owner drop off a first morning's urine specimen in a clean or sterile container. For cats, the owner might bring a specimen from a clean litter box, or it may be more practical to simply palpate the bladder and isolate it for collection of a urine specimen by cystocentesis; ultrasound guidance should not be necessary.

SDMA impact on management of kidney disease

48. Do medications affect SDMA results?

SDMA correlates very well to GFR. Therefore, if a drug improves GFR, SDMA should decrease. If a drug reduces GFR, then SDMA should increase.

49. What treatments should be given to a patient with a high SDMA?

SDMA is a kidney function test to help identify kidney disease in dogs and cats. Once CKD has been diagnosed, the animal should be staged using the International Renal Interest Society (IRIS) guidelines to help determine appropriate therapy.

50. My patient's SDMA is increased. Should I start a kidney diet?

SDMA is a kidney function test to help identify kidney disease in dogs and cats. Once CKD has been diagnosed, the animal should be staged using the International Renal Interest Society (IRIS) guidelines to help determine appropriate therapy.

Dietary therapy is often a key component for management of CKD in dogs and cats. Renal therapeutic diets are protein restricted, phosphorus restricted, nonacidifying and often supplemented with antioxidants and omega-3 fatty acids.

According to the IRIS treatment guidelines, it is appropriate to start a renal therapeutic diet in dogs and cats with IRIS stage 1 CKD if there is significant proteinuria (UPC greater than 2) or in IRIS stage 2 CKD. Starting a renal therapeutic diet at the earliest appropriate time is ideal because transitioning to a new food will likely be more successful when the patient's appetite is still good. Maintaining body weight and muscle

is essential to successful management of CKD and this is achieved primarily by adequate caloric intake. Another primary goal of feeding a renal diet is to maintain a low-normal serum phosphorus above 2.7 mg/dL and below 4.6mg/dL.

For nonproteinuric, IRIS stage 1 CKD dogs and cats, there is no evidence-based rationale for feeding a renal therapeutic diet; however, there may be some benefit to mild phosphorus restriction, avoiding acidifying diets, and supplementing with omega-3 fatty acids in the form of a kidney-supportive diet while the pet is still eating well. We suggest evaluating the current diet and considering transition to a kidney-supportive diet based on qualities of the current diet, client expectations, and other health concerns.

51. Are there any evidenced-based studies to support that renal diets slow down the progression of CKD or have any impact on survival time?

Yes, there are 2 widely accept published studies in cats where cats with stage 2 or 3 CKD were either fed a maintenance diet or a renal diet. In one study, the cats fed the renal diet survived 2.4 times longer than the cats on the maintenance diet (on average 633 days versus 264 days).⁵ In the other study, cats were followed for 2 years during which none of the cats fed a renal diet had a uremic crisis (severe illness secondary to kidney disease) or died from their kidney disease, whereas for cats fed a maintenance diet, 26% of them had a uremic crisis and 22% of them died of kidney disease.⁶

A similar study in dogs found dogs fed renal diet had a 75% reduced risk for having a uremic crisis, and at the end of the 2-year study, 65% of dogs fed maintenance diet had died from kidney disease, compared with 33% of dogs fed a renal diet. Dogs fed the renal diet lived at least 13 months longer than the dogs fed the maintenance diet.⁷

52. Can diet affect SDMA?

SDMA correlates strongly with GFR. Dogs and cats demonstrate measured alterations in GFR depending on the diet fed, and SDMA will be impacted accordingly. However, unlike BUN, it is not expected that SDMA will be impacted by protein content of the diet or gastrointestinal bleeding independent of GFR.

53. Should NSAIDs be avoided in patients with increased SDMA?

NSAIDs, other potentially nephrotoxic drugs, and drugs primarily eliminated by renal excretion should be used cautiously in animals with altered kidney function. SDMA should be interpreted along with creatinine, urinalysis, and other findings to diagnose kidney disease, but SDMA will often be the earliest indicator of a decrease in kidney function in CKD.

NSAIDs may be needed to sustain quality of life in some patients with CKD and should be used cautiously. NSAIDs should never be used in patients with acute kidney injury. Pet owners should be clearly and specifically educated about NSAIDs that are prescribed.

If using NSAIDs in patients with CKD, ideally:

- Use other pain management strategies first, to include opioids, weight loss, and nutraceuticals.

- Use the least effective dose or use them intermittently.
- Avoid other risk factors when NSAIDs are in use, such as general anesthesia, salt restriction, diuretic use, dehydration, and others.
- Select an NSAID with a low risk of gastrointestinal toxicity to avoid causing dehydration secondary to gastrointestinal disturbance.
- Monitor for changes in liver activity and kidney function after initiating NSAID therapy and before and after each dose adjustment with blood testing and urinalysis
- Discontinue NSAID use if toxicity is suspected or confirmed

Monitoring patients with early kidney disease with SDMA

54. If the SDMA is increased and creatinine is normal, when should I recheck the patient?

See question #38. If no other evidence of kidney disease, then recheck in 4–6 months. Otherwise, recheck should be based on clinical signs with initial recheck in 2 weeks to determine persistence and progression.

55. Is SDMA useful in monitoring and measuring success of therapy/treatment of CKD? Will this be the same or similar to changes in BUN and creatinine?

Because SDMA correlates specifically with GFR, SDMA will decrease if kidney function improves with treatment and will increase if kidney function is worsening in spite of treatment. Generally, similar trends to BUN and creatinine should be expected. However, BUN is more affected by prerenal factors such as diet and hydration, so changes in BUN may be less specific and harder to interpret during treatment. SDMA and creatinine are influenced by diet only if GFR changes but not independent of GFR like BUN. SDMA, in contrast to creatinine, is not affected by changes in lean body mass, so it is a more sensitive indicator of kidney function as patients lose lean muscle mass, a common scenario in patients with advanced CKD. Therefore, SDMA is helpful in monitoring CKD patients, especially those with muscle wasting.

56. Is SDMA useful in monitoring and measuring success of therapy/treatment of CKD? Will this be the same or similar to changes in BUN and creatinine?

SDMA, like creatinine and GFR, has a biologic variability of 15%–20% from measurement to measurement in the same patient over a week or more. Therefore, changes need to be greater than this to indicate a true change. For example, with 20% biologic variability, an initial SDMA result of 14 $\mu\text{g}/\text{dL}$ could recheck anywhere from 11–17 $\mu\text{g}/\text{dL}$ based on biologic variability alone, just like a creatinine of 1.5 mg/dL could vary from 1.2–1.8 mg/dL .

57. What if the creatinine is normal, and the previously increased SDMA is lower on recheck and becoming normal?

If your patient is clinically stable, with no obvious clinical

differences, and no treatments or diet changes have been implemented, but the SDMA is within the reference interval on recheck and the measured change is $<20\%$, then the change is likely due to inherent biologic variability in renal function. SDMA, like creatinine and GFR, can change 15%–20% from measurement to measurement in the same patient over a week or more.

If no urinary abnormalities or other evidence of kidney disease were found previously in the complete workup, then recheck the patient and kidney function in 4–6 months.

If there were urinary abnormalities seen previously or other evidence of kidney disease, then kidney disease is still likely, and it is appropriate to monitor according to the original plan. If no active urinary problem was identified, then the patient likely has stable CKD, and you can continue with conservative monitoring, rechecking in 2–3 months, sooner if progressive signs of illness or urinary abnormality appear.

58. What if the creatinine is normal and stable, and the previously increased SDMA is higher on recheck?

Determine if the patient is losing weight. SDMA is not impacted by changes in lean body mass whereas creatinine is. In an older or underweight animal, SDMA is a more sensitive indicator of kidney function than creatinine. In addition, changes in SDMA up to 20% are potentially consistent with biologic variability; greater changes are more likely to indicate a true progression in kidney disease. A complete physical examination (including determination of body weight and body condition score), careful history (including access to potentially nephrotoxic medications or substances), and a complete urinalysis (if not already performed) are recommended to try to determine if disease is likely to be progressing and cause of progression.

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