Symmetric Dimethylarginine (SDMA) as a Kidney Function Biomarker

ACVIM 2014
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Background

Early indicators of kidney damage include a reduction in glomerular filtration rate (GFR). Later indicators include impaired urine concentrating ability and azotemia [elevated serum creatinine and blood urea nitrogen (BUN) concentrations]. Measurement of GFR is the gold standard method for estimating renal function and staging kidney disease.\(^1\) Because measuring GFR is technically cumbersome and expensive, serum creatinine concentration remains the standard surrogate for GFR.\(^2\) However, serum creatinine has limitations as a marker of kidney function, most notably insensitivity because it remains in the normal reference interval (with a flat slope over much of the GFR range) until GFR is reduced approximately 75%.\(^3\) In addition, other nonrenal factors influence serum creatinine, including endogenous production by muscle such that muscle mass, breed, and sex may influence serum creatinine concentration. Although serial evaluations of serum creatinine within the same animal (if available) increase its sensitivity for detecting progressive changes in GFR,\(^2\) there is need for a better biomarker for earlier detection of CKD.

Serum symmetric dimethylarginine (SDMA) is a byproduct of protein methylation. Although phosphorylation is the best understood post-translational modification of proteins, arginine methylation is gaining prominence.\(^4\) Arginine methylation occurs when the nitrogens of arginine within polypeptides are post translationally modified to contain methyl groups. There are three main species of methylated arginine: monomethylarginine (MMA), asymmetric dimethylarginine (ADMA), and SDMA.\(^4\) The methyl group is transferred from S-adenosylmethionine to a nitrogen of arginine by one of several protein arginine methyltransferases (PRMT).\(^4\) Subsequent protein degradation of methylated proteins by hydrolysis yields individual methylated arginine amino acids, which are biologically active. ADMA functions as an endogenous nitric oxide synthase (NOS) inhibitor,\(^5\) preventing production of nitric oxide from L-arginine. Although SDMA is not a direct inhibitor of NOS, it can compete with arginine for transport across membranes,\(^5\) and thus, indirectly reduces nitric oxide synthesis by limiting L-arginine supply.\(^5,6\) ADMA is primarily degraded to dimethylamine and citrulline (\(\geq 80\%\)) after metabolism by dimethylarginine dimethylaminohydrolase (DDAH), whereas only a small amount of intact ADMA (\(\leq 20\%\)) is eliminated by the kidneys.\(^7,8\) SDMA is excreted primarily (\(\geq 90\%\)) by renal clearance.\(^8,9\) Because SDMA is excreted by the kidneys, plasma concentrations are affected by changes in GFR. ADMA accumulates in patients with renal dysfunction, although it is less abundant than SDMA, and its accumulation may be related to renal parenchymal damage, resulting in reduced DDAH expression and activity, rather than to reduced glomerular filtration of ADMA.\(^8\)

Symmetric dimethylarginine (SDMA) has been shown to be an accurate and precise biomarker for calculating estimated GFR in humans,\(^5\) as well as a more sensitive biomarker than serum creatinine for assessing renal dysfunction.\(^10\) In healthy human subjects from the Framingham offspring cohort, dietary components were not associated with plasma SDMA concentration.\(^11,12\) SDMA concentrations correlated positively to age and serum creatinine concentration, and negatively to body mass index, effective GFR, and diastolic blood pressure.\(^13\) A meta-analysis of 18 studies involving human patients showed that SDMA concentrations correlated highly with inulin clearance (\(r = -0.85\)) and serum creatinine (\(r = 0.75\)).\(^14\) In another study with human subjects, a close correlation among GFR (measured by an iodothalamate clearance technique) and serum creatinine with SDMA was reported (\(r = -0.84\) and 0.89, respectively).\(^15\) Plasma SDMA concentrations have also been shown to be increased in cats with chronic kidney disease and to correlate with plasma Cr concentration (\(r = 0.74\)).\(^7\)
SDMA, Unlike Creatinine, Increases in Geriatric Cats as GFR Declines with Age

A recent study in older cats (n = 32), mean age 14.0 years (range 8.3 to 19.6 years) that were fed complete and balanced foods that met the nutrient requirements for adult cats is summarized. Serum concentrations of renal function markers (serum creatinine and SDMA) and GFR were measured at baseline, and at 1.5, 3, and 6 months. Body composition was determined by dual-energy x-ray absorptiometry. There was no significant change in renal function or total lean bodyweight in individual cats over time of study (6 months). There was, however, a benefit of using serum SDMA vs. serum creatinine to monitor renal function in older cats with less total lean bodyweight. Compared with cats < 12 years of age, cats > 15 years had a lower total lean bodyweight (p < 0.01), lower GFR (p < 0.05), and lower serum creatinine concentration (p < 0.05). However, serum SDMA concentrations were higher in the older cats (p < 0.01). This study shows that serum SDMA concentration is a sensitive indicator of change in renal function in cats, and unlike serum creatinine, which declines with age in cats with muscle wasting, SDMA increases as GFR declines with age.

SDMA Allows Earlier Detection of Chronic Kidney Disease in Cats Compared with Serum Creatinine

In another study in cats with chronic kidney disease (n = 21), SDMA and serum creatinine concentrations were determined retrospectively from historical data or banked serum samples. Both SDMA and serum creatinine concentrations were significantly correlated to GFR. SDMA increased above the upper reference limit of 14 µg/dL before (mean 14.6 months; range 1.5 to 48 months) creatinine increased above the upper limit of the reference interval (2.1 mg/dL). Earlier detection of chronic kidney disease is desirable for initiating renoprotective interventions that may slow progression of disease.

Comparison of Serum SDMA and Creatinine as Kidney Function Biomarkers in Healthy Geriatric Dogs

A recent study in older dogs (n = 81), mean age 10.4 years (range 8 to 14 years), that were fed complete and balanced foods that met the nutrient requirements for adult dogs is summarized. Serum concentrations of renal function markers (serum creatinine and SDMA) and GFR (determined by iohexol clearance) were measured at baseline, and at 1.5, 3, and 6 months. Body composition was determined by dual-energy x-ray absorptiometry. There was no significant change in total lean bodyweight in individual dogs over time of study (6 months). All dogs showed an increase in GFR (p < 0.001), which was correlated to a decrease in SDMA (p < 0.001) and a decrease in serum creatinine (p < 0.001) concentrations over the 6-month feeding period. Of note, older dogs (10.4 to 14.2 years) had significantly lower total lean bodyweight (p < 0.001), lower GFR (p < 0.001), and higher SDMA concentrations (p < 0.001) compared with younger dogs (7.9 to 10.3 years). Serum creatinine concentrations were not influenced by age (p = 0.3), likely because serum creatinine was positively correlated to total lean bodyweight (p < 0.01), such that the decline in total lean bodyweight with age offset any effect of decreasing GFR on serum creatinine. This study shows that serum SDMA concentration is a sensitive indicator of change in renal function in dogs, because it is not affected by change in muscle mass with aging.

SDMA Elevates Earlier Than Serum Creatinine in Dogs with Chronic Kidney Disease

In a retrospective study, 8 dogs with CKD (diagnosis based on > 30% reduction in GFR) and with normal serum creatinine and SDMA at the time of diagnosis, were followed for 3 years. The aim of the study was to determine the point at which these dogs developed elevated serum SDMA and creatinine concentrations, in order to determine if SDMA increases earlier than creatinine. Two of the 8 dogs currently have normal SDMA and creatinine concentrations. In the other 6 dogs, SDMA increased above the upper reference limit of 14 µg/dL before (mean 17 months; range 11 to 26 months) creatinine increased above the upper limit of the reference interval (1.5 mg/dL). These results suggest that serum SDMA is an earlier biomarker than serum creatinine for diagnosing and monitoring CKD in dogs also.

References


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