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The clinical significance of symmetric dimethylarginine in laboratory animals

Tahir Ozalp[1]*, Hasan Erdogan[1], Songul Erdogan[1], Kerem Ural[1]

[1]Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Department of Internal Medicine, Aydın, Türkiye

*Corresponding: tozalp@adu.edu.tr

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Abstract
Symmetric dimethylarginine (SDMA) has emerged as an important biomarker for assessing kidney function, offering higher sensitivity and specificity compared to traditional biomarkers such as creatinine and blood urea nitrogen (BUN). This review explores the clinical significance of SDMA in laboratory animals, its role in preclinical research, and its translational applications. A byproduct of protein turnover, SDMA is primarily excreted via the kidneys and serves as a reliable indicator of glomerular filtration rate (GFR). Unlike traditional biomarkers, SDMA is minimally affected by extrarenal factors such as muscle mass or systemic conditions, allowing for more accurate kidney function assessment. In preclinical models, particularly in rodents, SDMA has proven effective in detecting early kidney dysfunction and monitoring nephrotoxicity during drug development. Its stability, ease of measurement via enzyme-linked immunosorbent assays (ELISA), and scalability for high-throughput analyses enhance its utility. Comparative studies have consistently shown that SDMA outperforms creatinine and cystatin C, especially in detecting early-stage kidney disease and experimental nephropathy. Furthermore, SDMA's ability to differentiate between acute and chronic kidney damage strengthens its potential in multi-biomarker panels. Given its translational potential, SDMA serves as a critical bridge between preclinical findings and clinical applications. This review underscores the importance of SDMA in advancing kidney research and improving patient outcomes. The advances in analytical techniques and SDMA's consistent performance across species position it as a key tool for both preclinical studies and clinical nephrology, enhancing diagnostic accuracy and monitoring kidney health.

Keywords: *Laboratory animals, symmetric dimethylarginine, renal biomarkers, preclinical research*

1. Introduction

Kidney injury, characterized by a reduction in glomerular filtration rate (GFR) and the accumulation of nitrogenous waste products, is a severe clinical condition. Acute kidney injury (AKI) is particularly associated with high morbidity and mortality rates, occurring in 20% of hospital admissions and more than 50% of intensive care unit patients.[1-3] AKI has been recognized not only as a short-term complication but also as a significant factor increasing the risk of progression to chronic kidney disease (CKD).[4-6] While the severity of kidney injury plays a crucial role in this transition, the underlying pathophysiological mechanisms remain poorly understood. The irreversible outcomes of CKD and the lack of effective therapeutic strategies highlight the importance of developing sensitive biomarkers capable of detecting kidney function loss at earlier stages. In recent years, symmetric dimethylarginine (SDMA) has emerged as a promising biomarker for the early detection of kidney diseases. SDMA is a byproduct of intranuclear arginine methylation, produced consistently by all nucleated cells and primarily (>90%) excreted via renal clearance.[7] Serum SDMA has been identified as a robust indicator of glomerular filtration rate (GFR) and has demonstrated greater sensitivity compared to traditional biomarkers such as creatinine and blood urea nitrogen (BUN).[7-10] In veterinary clinical settings, SDMA has been shown to detect chronic kidney disease (CKD) in dogs and cats with as little as a 25% loss of renal function.[7,10] Given the sensitivity and specificity limitations of traditional biomarkers, SDMA has become a vital tool not only for clinical diagnosis and monitoring but also for assessing renal function in laboratory animal models.

In this context, studies focusing on the application of SDMA in laboratory animals are critical for evaluating renal health in preclinical research and for modeling human disease processes. This review aims to highlight the importance of SDMA in monitoring and assessing kidney function in laboratory animals.

2. Clinic biomerkers

The term "biomarker," a shortened form of "biological marker," was first introduced in the late 1960s and has undergone several refinements to clarify its role in medical and scientific research.[11,12] A biomarker is broadly defined as a measurable characteristic that serves as an indicator of normal biological processes, pathological states, or responses to therapeutic interventions. In 1999, the NIH Definitions Working Group (NIH DWG) provided a formal definition of a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[13] More recently, the FDA-NIH Biomarker

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Working Group further refined this definition to encompass responses to environmental exposures and medical interventions, including dietary supplements, vaccines, and devices.[14] Biomarkers can be classified based on their intended applications, providing a framework for their use in both research and clinical practice. The most recent classification by the FDA-NIH Biomarker Working Group (2016) identifies seven primary categories:[14]

Susceptibility/Risk Biomarkers: Indicate predisposition to a disease or sensitivity to exposure.

Diagnostic Biomarkers: Identify the presence or subtype of a disease.

Monitoring Biomarkers: Measure changes in disease progression or response to treatment.

Predictive Biomarkers: Determine the likelihood of a favorable or unfavorable outcome from a specific intervention.

Prognostic Biomarkers: Predict the risk of clinical events, disease recurrence, or progression.

Pharmacodynamic/Response Biomarkers: Reflect biological responses to a therapeutic intervention.

Safety Biomarkers: Indicate toxicity or adverse effects of an intervention.

3. Renal biomarkers: Importance and applications

Renal biomarkers are a critical subset, essential for diagnosing, monitoring, and predicting kidney function and injury. Traditional renal biomarkers such as creatinine and blood urea nitrogen (BUN) have long been used to estimate glomerular filtration rate (GFR).[15] However, their limitations, including susceptibility to nonrenal factors like muscle mass and dietary protein intake, have driven the search for more sensitive and specific alternatives. Emerging renal biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and symmetric dimethylarginine (SDMA), have shown promise in addressing these limitations.[16,17] Among these, SDMA has emerged as a particularly reliable marker for assessing renal function.

4. SDMA biochemical properties and excretion

Symmetric dimethylarginine (SDMA) is a byproduct of protein turnover, formed through the methylation of arginine residues in nucleated cells. Following proteolysis, SDMA is released into the bloodstream and excreted primarily through the kidneys without undergoing significant metabolism (<10%).[18,19] This near-complete dependence on glomerular filtration makes SDMA a highly specific indicator of renal function, with its serum levels directly correlating to GFR.[20] Unlike asymmetric dimethylarginine (ADMA), which is extensively metabolized and protein-bound, SDMA's clearance is not influenced by factors such as lean body mass, diet, or systemic conditions like inflammation or diabetes. This independence from confounding variables enhances its reliability compared to traditional biomarkers like creatinine and cystatin C.[21,22]

5. SDMA clinical utility in renal dysfunction

Symmetric dimethylarginine (SDMA) has emerged as an exceptional biomarker for detecting early renal dysfunction in both humans and animals. Compared to traditional biomarkers such as creatinine and blood urea nitrogen (BUN), SDMA exhibits higher sensitivity and specificity, particularly in identifying early declines in kidney function. SDMA levels increase progressively with renal function loss, providing a more accurate reflection of nephron damage and glomerular filtration rate (GFR) than creatinine.[23,24] SDMA is a stable by-product of intranuclear arginine methylation, consistently produced by all nucleated cells, and released into the serum during intracellular protein processing. Its elimination relies predominantly (>90%) on renal clearance.[7] Studies in humans, dogs, cats, and rats have demonstrated that serum SDMA levels are highly correlated with GFR, as measured by indirect markers such as inulin clearance or creatinine clearance.[7-10] Despite the widespread use of traditional biomarkers, indicators like creatinine and BUN have notable limitations. Creatinine levels are influenced by muscle mass, reducing its reliability in patients with muscle wasting. Similarly, BUN levels can be affected by non-renal factors, such as gastrointestinal pathologies. Consequently, interest in biomarkers like SDMA and cystatin C has grown for a more accurate assessment of renal function.

In veterinary medicine, SDMA has been widely used for over a decade to monitor chronic kidney disease (CKD) in companion animals such as dogs and cats. This biomarker has also been applied in conditions such as Lyme nephritis, renal dysplasia, and familial amyloidosis.[24,25] Furthermore, the ability to measure SDMA in plasma or serum eliminates the need for urine collection, facilitating its clinical applications. SDMA's sensitivity is particularly noteworthy, as it can detect functional declines with as little as a 25% reduction in renal capacity. In this context, SDMA is recognized as a superior biomarker to serum creatinine in both humans and animals.[7,10]

In pediatric patients, SDMA has demonstrated higher diagnostic efficiency than cystatin C in detecting CKD.[26] These findings highlight SDMA's potential in preclinical studies for understanding renal function in various species, including rats and dogs. While substantial evidence supports the diagnostic utility of SDMA in naturally occurring kidney diseases, its application as a renal safety biomarker in preclinical models remains underexplored. However, the recent validation of a high-throughput immunoassay for measuring serum SDMA in rats offers new opportunities to investigate its role in safety assessments.[27] This advancement enables the evaluation of SDMA in experimental glomerulopathy models such as passive Heymann nephritis (PHN) in rats.

In addition to SDMA, the inclusion of other biomarkers such as serum creatinine, serum cystatin C, creatinine clearance, and urinary injury biomarkers (e.g., µALB, CLU, KIM-1, NGAL, OPN) facilitates understanding of how SDMA complements existing biomarkers in preclinical toxicity studies. Moreover, correlating biomarker data with histopathological findings enhances SDMA's reliability as a tool for monitoring renal injury in experimental designs.

6. SDMA in preclinical research

Preclinical research has provided significant insights

into the utility of symmetric dimethylarginine (SDMA) as a renal biomarker. In rodent models, particularly in nephrectomy studies, SDMA levels have been shown to increase proportionally to reductions in renal mass, demonstrating its robust correlation with glomerular filtration rate (GFR).[28,29] Unlike traditional biomarkers such as creatinine, SDMA is less influenced by nonrenal factors such as muscle mass, which is particularly relevant in rodent studies where body composition can vary significantly across experimental groups.

Additionally, SDMA has demonstrated its utility in detecting subclinical kidney damage before significant changes in GFR occur. For example, in toxicology studies evaluating nephrotoxic agents like cisplatin, SDMA has outperformed conventional biomarkers by detecting renal impairment earlier and with greater sensitivity.[30] These findings suggest that SDMA could be a valuable tool in assessing nephrotoxicity during drug development, where early detection of renal damage is critical for evaluating compound safety profiles.

Another advantage of SDMA in preclinical research is its stability and ease of measurement. Specialized techniques such as liquid chromatography-mass spectrometry (LC-MS) and high-performance liquid chromatography (HPLC) have traditionally been used to measure SDMA levels with high precision.[29,30] However, the development of ELISA-based assays has simplified its application in larger studies, allowing for high-throughput analysis with minimal serum volumes. This is particularly advantageous in rodent studies, where sample availability may be limited.

SDMA's specificity for renal function also makes it a reliable comparator for evaluating other emerging renal biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and osteopontin (OPN). While these biomarkers are useful for detecting acute kidney injury (AKI), they often show diminishing responses over time or are influenced by extrarenal factors. In contrast, SDMA levels remain stable and reflective of renal function throughout the course of chronic kidney disease (CKD) progression, making it a preferred marker for long-term studies.[31]

Moreover, the application of SDMA in translational research bridges the gap between preclinical findings and clinical practice. Studies have shown that SDMA levels in rodents mirror trends observed in companion animals and humans, reinforcing its validity as a translational biomarker.[28,32] This consistency across species supports its use not only in drug safety studies but also in exploring therapeutic interventions for renal diseases.

Future preclinical studies could further investigate the role of SDMA in diverse experimental contexts, such as models of diabetic nephropathy, ischemia-reperfusion injury, and polycystic kidney disease. Expanding the scope of research may also include evaluating SDMA alongside other biomarkers in multiplex panels to enhance diagnostic accuracy and provide a more comprehensive assessment of kidney health.

7. Comparative studies and analytical advances

In recent years, comparative studies have further solidified the role of SDMA as a superior biomarker for renal function, particularly in comparison to traditional markers such as creatinine and cystatin C. Unlike creatinine, which is heavily influenced by factors such as muscle mass and dietary intake, SDMA reflects renal function more accurately and independently of extrarenal variables.[33,34] Cystatin C, while useful in some scenarios, is affected by inflammatory conditions and thyroid dysfunction, limiting its reliability in both preclinical and clinical settings.[19] Comparative evaluations have consistently shown that SDMA outperforms these markers, particularly in detecting early declines in glomerular filtration rate (GFR), making it an essential tool for renal diagnostics.[7,10]

Rodent studies have also demonstrated SDMA's ability to align closely with measured GFR (mGFR), further validating its reliability across species. For example, in nephrectomy models, SDMA levels increase proportionally to the loss of renal mass, mirroring trends observed in companion animals and humans.[28,29] These findings emphasize the translational potential of SDMA, bridging the gap between preclinical research and clinical applications.

Advancements in analytical techniques have played a pivotal role in enhancing the utility of SDMA as a biomarker. Liquid chromatography–mass spectrometry (LC-MS) remains the gold standard for SDMA measurement due to its precision and specificity.[19,33] However, the high cost and technical expertise required for LC-MS have limited its widespread application, particularly in high-throughput settings such as drug development and toxicology studies.

To address these limitations, novel enzyme-linked immunosorbent assays (ELISA) have been developed, offering a more accessible and scalable alternative. Proprietary ELISA platforms, for instance, have demonstrated improved sensitivity and specificity compared to earlier methods such as the DLD ELISA.[25,30] These advancements enable the analysis of SDMA in small sample volumes, making it suitable for large-scale studies involving rodents and other small animals.[32,35]

The ability to use SDMA in conjunction with other biomarkers has also been explored to improve diagnostic accuracy and provide a more comprehensive assessment of renal health. For example, multiplex assays combining SDMA with biomarkers such as NGAL, KIM-1, and OPN have shown promise in differentiating between acute and chronic kidney injury.[10] Such approaches are particularly valuable in preclinical studies, where early and precise detection of nephrotoxicity is critical for evaluating drug safety. Future research could focus on further optimizing SDMA assays for broader accessibility and exploring its integration into multi-biomarker panels. Additionally, comparative studies across different species and disease models will enhance our understanding of SDMA's diagnostic and prognostic potential in both clinical and research settings.

The combination of comparative studies and analytical advancements has firmly established SDMA as a cornerstone in renal biomarker research. Its superior performance relative to traditional markers and the ongoing development of innovative measurement techniques ensure its continued relevance in the field

of nephrology and toxicology. SDMA's integration into routine diagnostic workflows and research underscores its potential for bridging the gap between preclinical findings and clinical practice. Its ability to provide early and reliable insights into renal health makes it an invaluable tool for improving patient outcomes and advancing translational research.

8. Conclusion

Symmetric dimethylarginine (SDMA) has emerged as a sensitive and reliable biomarker for evaluating renal dysfunction in laboratory animals, particularly in rodent models. Its strong correlation with glomerular filtration rate (GFR), ability to detect early renal function loss, and stable production-elimination mechanism make it superior to traditional biomarkers like creatinine and blood urea nitrogen (BUN). Given the limitations of traditional biomarkers, such as their susceptibility to extrarenal factors like muscle mass loss, SDMA provides significant advantages in the assessment of renal function. The development of immunoassay techniques enabling SDMA measurement in rodents has expanded its application in preclinical research. Studies using models such as passive Heymann nephritis (PHN) in rats have demonstrated that SDMA is a sensitive biomarker for detecting early renal damage. Furthermore, the combined use of SDMA with other biomarkers, including serum creatinine, cystatin C, and urinary renal injury markers, allows for a more comprehensive evaluation of renal dysfunction. In conclusion, SDMA represents an effective tool for diagnosing renal dysfunction and conducting preclinical safety assessments in laboratory animals. Future research will further clarify its potential and support its integration into clinical and preclinical applications.

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Ethical approval

This study does not require approval from the Ethics Committee for Animal Experiments.

Conflict of interest

There is no conflict of interest between the authors

Author contribution

All authors contributed equally and were involved in all stages of the manuscript.

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