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Symmetric dimethylarginine (SDMA) as endogenous marker of renal function—a meta-analysis

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Abstract

Background. Dosing of most drugs must be adapted in renal insufficiency, making accurate assessment of renal function essential in clinical medicine. Furthermore, even modest impairment of renal function has been recognized as a cardiovascular risk factor. The purpose of this analysis was to identify the role of symmetric dimethylarginine (SDMA), the structural isomer of the cardiovascular risk marker asymmetric dimethylarginine, as an endogenous marker of renal function.

Methods. Comprehensive searches of Medline and the Cochrane Library from 1970 to February 2006 were performed to identify studies that evaluated the correlation between SDMA and renal function. The search was augmented by scanning references of identified articles and reviews. The correlation coefficients (R) were recorded from each study for the values of 1/SDMA and clearance estimates and for SDMA and creatinine levels. The summary correlation coefficients with 95% confidence intervals (CIs) were pooled using the random-effects method.

Results. In 18 studies involving 2136 patients systemic SDMA concentrations correlated highly with inulin clearance [$R = 0.85$ (CI 0.76–0.91, $P < 0.0001$)], as well as with various clearance estimates combined [$R = 0.77$ (CI 0.65–0.85, $P < 0.0001$)] and serum creatinine [$R = 0.75$ (CI 0.46–089, $P < 0.0001$)].

Conclusions. SDMA exhibits some properties of a reliable marker of renal function. Future studies have to clarify whether SDMA is indeed suited to improve diagnosis and eventually optimize care of patients.

Keywords: creatinine; glomerular filtration rate; MDRD fromula; renal function; SDMA

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Symmetric dimethylarginine (SDMA)—a novel endogenous marker for renal dysfunction

The dosing of most drugs must be adapted in renal insufficiency, making accurate assessment of renal function a prerequisite in clinical medicine, especially in the elderly. Furthermore, even a modest decline in renal function has been recognized as a cardio-vascular risk factor [1]. However, the diagnosis of kidney impairment is hampered by the lack of reliable markers of glomerular filtration rate (GFR). The gold standard, inulin clearance, is cumbersome and expensive, reducing its utility in clinical practice. This is also true for estimations using the clearance of radioisotopes. Therefore, in clinical practice, serum creatinine alone or in conjunction with a timed urine collection for creatinine clearance is typically used to assess renal function. Despite practical applicability and affordability, creatinine clearance estimates show considerable inter-individual variability associated with muscle mass, protein intake, age and sex. Moreover, obtaining accurate 24-h timed urine collections are labour-intensive and fraught with difficulties for individual patients such as infants, the very elderly and those with urologic abnormalities. Consequently, there is an ongoing search for suitable alternative endogenous markers of renal function.

Dimethylarginines had been known to biochemists for decades [2,3]. In the last decade scientists focused mainly on asymmetric dimethylarginine (ADMA), which had been shown to correlate with traditional and non-traditional cardiovascular risk factors as reviewed by Cooke [4]. Moreover, ADMA is a strong predictor of cardiovascular events and death in selected patient populations [5] and a marker of progression of various chronic renal diseases [6,7]. Until recently, little attention has been paid to the role of the structural isomer of ADMA—symmetric dimethylarginine (SDMA).

Search strategy, selection criteria and statistical analysis

We comprehensively searched Medline and the Cochrane Library from 1970 through February 2006 using the following medical subject headings: renal function, creatinine, GFR, SDMA and symmetric dimethylarginine. We supplemented the search by scanning the references of selected articles identified by this strategy and review articles. We did not restrict the language of publication. Furthermore, abstracts from the Meetings of the International Society of Nephrology, European Dialysis and Transplant Organization and the American Society of Nephrology were evaluated. We included studies that evaluated SDMA and provided correlation coefficients (Pearson or Spearman) to any measure of renal function [GFR estimates by inulin clearance, radio-isotope methods, Cockroft–Gault equation, Modification of Diet in Renal Disease (MDRD) formula or measurement of serum creatinine]. The correlation coefficient for one study [8] was obtained by personal communication. Measurements of ADMA and SDMA were determined using high-performance liquid chromatography (HPLC) or liquid chromatography–mass spectrometry.

We excluded studies that reported data on SDMA and renal function without analysing the correlation [9–12]. In addition, we excluded studies of patients with advanced, stage 5 chronic kidney disease, because creatinine and SDMA rise exponentially with decreasing renal function [13].

The Pearson or Spearman correlation coefficients were recorded from each study for the values of 1/SDMA and clearance estimates and for SDMA and creatinine levels. The summary correlation coefficients with 95% confidence intervals (CI) were obtained by pooling the logarithmic z-values derived from the individual trial correlation coefficients. The results were pooled using the random-effects methods because of the potential for inter-study heterogeneity [14]. In the identified studies the correlation coefficient between ADMA and parameters of renal function was also obtained, if available, and is reported in Table 1. Additionally, we performed a subgroup analysis evaluating the influence of gender and age on plasma SDMA in two of the original data sets available to us [6,15].

Results

We identified 18 studies involving a total of 2136 patients (Table 1). Uniformly these studies revealed strong and highly significant correlations between SDMA and renal function (Figure 1). The correlation coefficient (R) between SDMA and inulin clearance was 0.85 (CI 0.76–0.91, $P < 0.0001$), and for various GFR estimates it was 0.77 (CI 0.65–0.85, $P < 0.0001$). The correlation coefficient for SDMA and serum creatinine was 0.75 (CI 0.46–0.89, $P < 0.0001$), and for all estimates of renal function combined it was (CI 0.65–0.84, $P < 0.0001$).

A subgroup analysis of data from the study by Bode-Boger et al. [15] did not demonstrate a difference in the creatinine-based estimation of GFR between women ($n = 37$, $R = 0.76$, $P < 0.01$) and men ($n = 81$, $R = 0.72$, $P < 0.01$). This was also true for the iothalamate-based clearance estimation by

Table 1. Summary of studies on SDMA, ADMA and renal function

Author [reference]	Population	n	measure of renal function	SDMA correlation (r, P)	ADMA correlation (r, P)
Clearance methods					
Tarnow et al. [8]	IDDM	394	chrome EDTA clearance	0.898, $P < 0.0001$	0.44, $P < 0.001$
Fliser et al. [6]	CKD	227	iothalamate clearance	0.837, $P < 0.01$	0.591, $P < 0.01$
Bode-Boger [15]	CAD	147	MDRD GFR	0.622, $P < 0.01$	0.217, $P = 0.011$
Wang et al. [36]	CAD	145	Cockroft–Gault	0.45, $P < 0.001$	0.21, $P < 0.01$
Al Banchaabouchi [19]	CKD	135	creatinine clearance	0.714, $P < 0.0001$	0.703, $P < 0.0001$
Marescau et al. [23]	CKD	135	Cockroft–Gault	0.916, $P < 0.0001$	0.861, $P < 0.0001$
Nanayakkara et al. [37]	CKD	93	Cockroft–Gault	0.727, $P < 0.0001$	0.342, $P = 0.023$
Dalton et al. [25]	Children	49	inulin clearance	0.8892, $P < 0.001$	0.1212, NS
Kielstein et al. [24]	CKD	44	inulin clearance	0.78, $P < 0.0001$	0.26, $P = 0.09$
Goonasekera et al. [22]	Children with HTN	38	GFR (Morris)	0.38, $P < 0.02$	0.77, $P < 0.001$
Serum creatinine					
Wanby et al. [38]	CVD	363	serum creatinine	0.26, $P < 0.001$	0.19, $P < 0.01$
Fliser et al. [6]	CKD	227	serum creatinine	0.894, $P < 0.01$	0.595, $P < 0.01$
Fleck et al. [39]	CKD	96	serum creatinine	0.83, $P < 0.01$	–, NS
	renal transplant	40	serum creatinine	0.94, $P < 0.001$	–, NS
Ellis et al. [40]	pregnant women	65	serum creatinine	0.694, $P < 0.001$	–, NS
Nijveldt et al. [41]	CAD	20	serum creatinine	0.607, $P = 0.005$	–, NS
Nijveldt et al. [33]	ICU patients	52	serum creatinine	0.80, $P < 0.001$	0.142, NS
Krzyzanowska et al. [42]	GHD	44	serum creatinine	0.48, $P < 0.005$	–, NS
Siroen et al. [43]	pregnancy	38	serum creatinine	0.40, $P = 0.013$	–, NS
Lluch et al. [44]	HRS	11	serum creatinine	0.765, $P < 0.001$	0.038, $P = 0.564$

CKD, chronic kidney disease; CAD, coronary artery disease; CVD, cerebrovascular disease; GHD, growth hormone deficiency; HTN, hypertension; IDDM, insulin dependent diabetes mellitus; HRS, hepatorenal syndrome; NS, not significant.

Fliser *et al.* [6], in which SDMA correlated with GFR in both women ($n = 73$, $R = 0.69$, $P < 0.01$) and men ($n = 154$, $R = 0.69$, $P < 0.01$). In both studies SDMA was also significantly correlated with age $R = 0.272$ ($P = 0.001$) [15] and $R = 0.28$ ($P < 0.01$) [6], respectively. In contrast to SDMA, ADMA showed a correlation to markers of renal function in only some studies (Table 1).

Discussion

Our meta-analysis included data from over 2100 patients to confirm that SDMA is an endogenous marker of renal function. Plasma SDMA levels correlate highly with GFR as assessed by creatinine or inulin clearance.

The presence of SDMA in human brain tissue was first reported in 1971 by Nakajima *et al.* [16]. Subsequently, it has become clear that SDMA, as well as the other methylarginines such as monomethyl-arginine and ADMA, are produced in every nucleated cell. The methylation of arginine residues appears to be required for RNA processing, protein shuttling and signal transduction. Methylation of arginine

residues is catalysed by a group of enzymes called protein arginine *N*-methyltransferases, leading to the formation of proteins containing mono- or di-methylated arginine derivatives and *S*-adenosyl-L-homocysteine [17]. When the proteins undergo prote-olysis, free methylarginines are released, and SDMA and ADMA are excreted in the urine [2]. McDermott [3] provided evidence that SDMA is mainly eliminated by renal excretion, whereas ADMA is largely metabolized.

Since Vallance and co-workers [18] evaluated ADMA accumulation in renal failure in their land-mark paper and could not show an influence of SDMA on the elaboration of nitric oxide (NO) *in vitro*, little attention was paid to this substance. However, data from several studies have suggested that SDMA correlates well with parameters of renal function, in humans as well as in rodents [19]. Plasma SDMA levels increase in parallel with creatinine and blood urea nitrogen after total nephrectomy [20]. In dogs, SDMA has also been shown to correlate well with serum creatinine [21]. Goonasekera and co-workers [22] were the first to report the correlation between SDMA and GFR in children with hypertension. Marescau *et al.* [23] described the close relationship
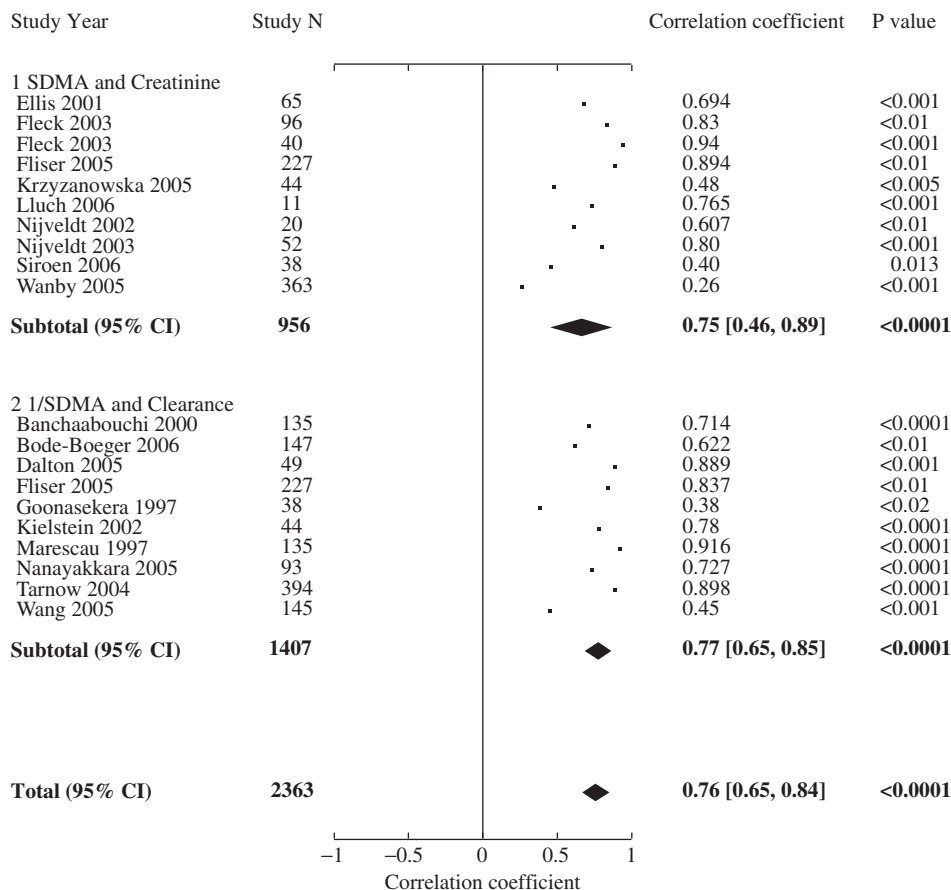
Study Year	Study N		Correlation coefficient	P value
1 SDMA and Creatinine				
Ellis 2001	65		0.694	<0.001
Fleck 2003	96		0.83	<0.01
Fleck 2003	40		0.94	<0.001
Fliser 2005	227		0.894	<0.01
Krzyzanowska 2005	44		0.48	<0.005
Lluch 2006	11		0.765	<0.001
Nijveldt 2002	20		0.607	<0.01
Nijveldt 2003	52		0.80	<0.001
Siroen 2006	38		0.40	0.013
Wanby 2005	363		0.26	<0.001
Subtotal (95% CI)	**956**		**0.75 [0.46, 0.89]**	**<0.0001**
2 1/SDMA and Clearance				
Banchaabouchi 2000	135		0.714	<0.0001
Bode-Boeger 2006	147		0.622	<0.01
Dalton 2005	49		0.889	<0.001
Fliser 2005	227		0.837	<0.01
Goonasekera 1997	38		0.38	<0.02
Kielstein 2002	44		0.78	<0.0001
Marescau 1997	135		0.916	<0.0001
Nanayakkara 2005	93		0.727	<0.0001
Tarnow 2004	394		0.898	<0.0001
Wang 2005	145		0.45	<0.001
Subtotal (95% CI)	**1407**		**0.77 [0.65, 0.85]**	**<0.0001**
Total (95% CI)	**2363**		**0.76 [0.65, 0.84]**	**<0.0001**

Correlation coefficient: $-1 \quad -0.5 \quad 0 \quad 0.5 \quad 1$

Fig. 1. Correlation coefficients for SDMA and renal function. (**A**) SDMA and creatinine. (**B**) 1/SDMA and clearance.

between SDMA and estimated GFR by the Cockroft–Gault equation.

Although there is an excellent correlation between SDMA and established estimates of GFR, it is not known if SDMA fulfils all criteria for an ideal GFR marker, i.e. stable production rate not affected by other diseases, free glomerular filtration and lack of tubular reabsorption. Nevertheless, our analysis of the available information suggests SDMA has promise as such a marker. Each of the 18 studies in our meta-analysis, involving a total of 2136 patients, showed a strong correlation between SDMA and renal function. The largest study was conducted by Tarnow et al. [8], who evaluated 394 type I diabetics using chrome EDTA clearance and observed a very strong correlation between SDMA and renal function. These high correlations are also seen when the gold standard for measurement of GFR, inulin clearance, was used [24] or when children with various degrees of renal function were studied [22,25]

The high correlation of SDMA and renal function is of clinical importance since estimates of GFR from serum creatinine are insensitive even to moderate reductions in GFR and are complicated by considerable inter-individual variability due to muscle mass, protein intake, age and sex [26–28]. Furthermore, obtaining accurate, 24-h timed urine collections is labour intensive and difficult to perform in certain patient populations. Thus, a new stable, convenient and clinically reliable marker of GFR would be desirable. One such potential new marker is cystatin-C, a cationic non-glycosylated low-molecular-weight proteinase [29]. SDMA may have advantages over other novel markers, particularly when measured together with the emerging cardiovascular risk factor ADMA. The technologies of HPLC or coupled gas chromatography–mass spectrometry (GL–MS) for the analysis of ADMA also provide SDMA values with no additional effort. Unfortunately, because SDMA does not directly affect NO synthase activity [18] and because it is not widely appreciated as a sensitive marker of renal function, many investigators have failed to report SDMA values in their studies of ADMA, even when investigating patients with chronic kidney disease [30].

In addition to being an excellent marker of renal function, SDMA may also have an indirect effect on NO synthesis. SDMA inhibits the y+ transporter that mediates the intracellular uptake of L-arginine [31] and inhibits renal tubular arginine absorption [32]. These two mechanisms could indirectly inhibit NO synthesis by interfering with L-arginine uptake. In vitro, SDMA concentration in the physiological range inhibit NO production in endothelial cells [15]. Furthermore, plasma SDMA levels are negatively associated with the plasma L-arginine/ADMA ratio, i.e. an indicator of NO production in vivo, and there is evidence of a significant positive multivariate relationship ($P < 0.001$) between SDMA and cardioembolic infarction [15]. Whether this association of SDMA with cardiovascular disease is due to its indirect effects

on NO synthesis, and/or to its relationship to renal function, is not known. Another study that supports the prognostic value of SDMA was performed in seriously ill patients in the intensive care unit and found that elevated plasma SDMA levels correlated with the total sequential organ failure assessment better than ADMA and indicated both renal and hepatic failure [33].

In contrast to SDMA, ADMA generally did not show a correlation to parameters of renal function. This is not surprising as ADMA is mainly eliminated from the body by enzymatic degradation. As there is a high concentration of the ADMA degrading enzyme (DDAH) in the kidney, it is however conceivable that, depending on the reason for renal impairment, the decline in renal excretory function is paralleled by a reduction of DDAH activity (in the kidney). This might serve as an explanation why ADMA is related to parameters of renal function in some of the studies.

The main limitation of our analysis—the focus on ADMA in all but two of the included studies [15,25]—illustrates vividly the aim of this analysis. Most of the studies were evaluating the role of ADMA in cardiovascular pathology and only secondarily mention SDMA. Therefore, these studies did not provide actual values for SDMA and this GFR estimates. For that reason, we cannot, at this point, make estimates of GFR from SDMA. We hope that the presented high correlation of SDMA with different established parameters of renal function will encourage investigators to include SDMA into their analysis.

Should we stop measuring creatinine and measure SDMA instead? Although the measurement of creatinine as a parameter of renal function has many limitations, it still fulfils requirements for use in everyday clinical practice. It can be reliably and inexpensively measured, and the ease of performance combined with a good sensitivity and specificity describe up the profile of this 'classic' in laboratory medicine, which has been in use for decades. A recent paper by Manolino [34] nicely summarized the dilemma concerning new markers in clinical practice. Although initial reports about novel markers provide exciting clues into the pathophysiology of diseases and enable us to improve diagnostic capabilities, translating these into clinical application requires replication in multiple settings as well as experimental evidence supporting their benefit. Moreover, the high cost of the HPLC- or GC–MS-based methods to measure SDMA is still prohibitive for widespread clinical application. However, SDMA may have a place in a cardiology practice, where it could be measured in combination with the cardiovascular risk marker ADMA. Cardiologists often measure BNP and homocysteine in patients at risk for cardiovascular disease, and have recently become aware of the importance of renal function as another cardiovascular risk factor [35]. Hence, one could imagine that the determination of ADMA and SDMA could be used as a combined marker of classical cardiovascular risk and renal function.

Future studies will be needed to investigate whether SDMA is indeed a stable, convenient and clinically reliable marker of GFR, especially in patient populations in which assessment of the GFR is cumbersome, as is suggested by our analysis. In addition, studies are needed to evaluate the effect of SDMA on NO synthesis and to elucidate its role in mediating the detrimental effects of renal insufficiency on cardiovascular and all cause mortality.

Conflict of interest statement. None declared.

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