Arginine dimethylation products in pediatric patients with chronic kidney disease

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HIGHLIGHTS

- The underlying pathogenic mechanisms for pediatric CKD are multiple and interlocking.
- Disturbed serum levels of Arg and its dimethyl derivatives may underlie development and/or progression of CKD.
- Elevated serum SDMA level is strongly correlated with impaired kidney functions.
- Elevated SDMA level can be a predictor for kidney functions deterioration and CKD progression.

ARTICLE INFO

ABSTRACT

Background: arginine and its metabolites have been linked to pediatric chronic kidney disease (CKD). We aimed to estimate serum levels of argninine (Arg), asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) in pediatric CKD patients and its relation to altered kidney function.
Patients and methods: 132 pediatric patients with CKD and 120 healthy age and sex matched controls were compared regarding; serum Arg, ADMA and SDMA levels.
Results: In comparison to their values in control subjects, serum Arg levels were significantly lower; serum ADMA levels were non-significantly higher, but serum SDMA levels were significantly higher in CKD patients (p values: < 0.000; $= 0.054$; <0.000, respectively).
Calculated Arg/ADMA and Arg/SDMA ratios were significantly higher in patients compared to controls (p values: 0.001, and <0.000, respectively). However ADMA/SDMA ratio was significantly lower in patients compared to controls (p = 0.001. Serum Arg levels showed positive significant correlation, while serum ADMA and SDMA levels showed negative significant correlation with eGFR. Moreover, Arg/ADMA ratio showed negative significant correlation, while ADMA/SDMA ratio showed positive significant correlation with eGFR of patients. Regression analysis defined high serum SDMA level as persistently significant predictor for low eGFR.
Conclusion: Disturbed serum levels of arginine and its dimethyl derivatives may underlie development and/or progression of CKD. Elevated serum SDMA level is strongly correlated with impaired kidney functions and could be considered as a predictor for kidney functions deterioration and CKD progression.

1. Introduction

Chronic kidney disease (CKD) is defined as irreversible kidney damage that can progress to end-stage renal disease (ESRD). CKD has 5 stages; stage 1 to 5. Stage 5 is considered ESRD. CKD is a major health problem worldwide and detailed epidemiological studies in the adult population are now accessible. On the contrary, what is known about the epidemiology of CKD in the pediatric age group is less. ESRD is a major disorder associated with high mortality and cardiovascular morbidity, as well as other problems specific to children, such as growth retardation and psychosocial problems, all of which seriously affect the quality of life [1—3].

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The prevalence rate of chronic kidney disease (CKD) among individuals younger than 20 years of age varies from 10 to 100 per million-age-related population. Previous studies have reported that the largest proportions of CKD cases in children are caused by congenital anomalies of the kidney and urinary tract (30—60%), hereditary nephropathies (10%—35%) and glomerulopathies (3%—25%) [4—6].

In the perspective of a lack of national registries and surveys, estimating the causes of CKD, in children in low and middle income countries, is challenging. In Turkey and other countries in the Middle East, CAKUT (congenital anomalies of the kidney and urinary tract) is the leading cause of CKD (47—62%) with an obvious predominance of uropathies over hypodysplasia followed by hereditary nephropathies (17—30%) [7—10]. Neuropathic bladder is still an important cause of CKD in Turkey (15%), while it represented about 4% in Italy and Belgium. These figures might reflect a delay in appropriate urological diagnosis and treatment. In addition, the higher incidence of genetic diseases found in the Middle East than in Europe can be explained by a higher prevalence of consanguineous marriages. Chronic glomerulonephritis is the main reported cause of CKD in various studies from India, Southeast Asia, Latin America and Caribbean area and sub-Saharan Africa, with a prevalence ranging from 30 to almost 60% [11—18]. Such high proportions of glomerulonephritis may be claimed to high prevalence of bacterial, viral, and parasitic infections that commonly affect the kidneys in developing countries, as well as a different age distribution in these reports where patients are referred in the later stages of CKD.

CKD in children can progress to ESRD; however, the time course being influenced by several modifiable factors. Early diagnosis of CKD allows for the institution of renoprotective treatment of modifiable factors and treatment to prevent the development of complications. The two most important modifiable factors that can be treated successfully are hypertension and proteinuria. Early identification and treatment of modifiable risk factors of CKD decreases the burden of disease and delays or prevents the need for renal replacement therapy [19,20].

L-Arginine (Arg) is a cationic amino acid involved in multiple areas of human physiology and metabolism. L-Arg can be broken down by transformation into guanidinoacetate and creatine and by oxidation to L-citrulline and nitric oxide (NO) by endothelial NO synthase. Protein residues of Arg can be methylated and their subsequent proteolysis gives rise to asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and N-monomethyl-L-arginine (NMMA) [21].

Production of NO from Arg is inhibited by endogenously produced NMMA and ADMA. Elevated levels of ADMA, by limiting NO production, may lead to endothelial dysfunction and cardiovascular disease. Symmetric dimethylarginine and the arginine homolog homo-arginine have also been associated with cardiovascular disease. Although NO synthesis, as well as generation of NMMA, ADMA, SDMA and homoarginine, occurs intracellularly, these biomarkers are usually measured in plasma. Despite extensive transmembrane transport, it is not clear whether plasma levels of these biomarkers are a valid proxy for their intracellular levels [22,23].

Endothelial dysfunction does occur in CKD (characterized by blunted release of endothelial NO) and in ESRD, even during early stages of disease [23—27]. Although no clinical evidence is available, animal studies implicate intrarenal NO deficiency in CKD.7—13 Given the persistent oxidative stress induced in early-stage CKD [28], reduced NO synthesis is likely to be widespread in both CKD and ESRD.

Chronic inhibition of NOS in otherwise normal animals produces hypertension and focal segmental glomerulosclerosis, the hallmark of progressive CKD [29]. It therefore seems likely that the NO deficiency associated with CKD contributes to progression of kidney damage and eventual development of ESRD.

It was initially reported that plasma levels of ADMA were markedly increased in patients with chronic renal failure [30]. Because dimethylarginines are excreted in urine [31], impaired renal function may, at least in part, cause an elevation of ADMA levels in patients with CKD. Nevertheless, recent evidence against this belief has accumulated. First, when dimethylarginines such as SDMA and ADMA are injected into rats intravenously, 66% of the injected SDMA is totally recovered in urine, whereas only 5% of the ADMA is excreted in the urine [32]. Second, plasma ADMA levels are elevated even in patients with incipient renal disease with normal renal function [33]. These findings suggest that only a small portion of circulating ADMA is excreted in the urine and that the contribution of the renal clearance of ADMA to its circulating levels may be very small. In support of this, plasma levels of ADMA in patients with endstage renal disease (ESRD) are markedly lower than those of SDMA [34].

We designed our comparative study to estimate serum levels of arginine and its dimethylation products in children with CKD, to correlate these values with altered kidney function, and to evaluate the value of deranged arginine metabolism as a predictor of severity of kidney function alteration and CKD progression.

2. Patients and methods

The current case control study was conducted at the Departments of Pediatrics and Clinical Pathology, Faculty of Medicine, Benha University Hospital, and Benha Specialized Children Hospital, Benha, Egypt during the period from June 2014 to June 2015. After approval of the study protocol by the local research and ethical Committee of Faculty of Medicine, Benha University Hospital and after obtaining parents' written fully informed consent; 132 children with CKD; stage 1 to stage 5; and 120 healthy age and sex matched controls were enrolled in the study. Controls were children attending the outpatient clinics with no known renal disease. It is known that cases of atherosclerosis, hypertension, asthma, cancer, sickle Cell Disease, sepsis and inflammatory bowel disease can cause derangement of arginine metabolism [35,36]. Hence, we selected our control subjects from the healthy children attending outpatient clinics suffering from upper respiratory tract infections and/or mild gastroenteritis to exclude the possibility of them having an abnormal arginine metabolism.

Inclusion criteria were confined to the disease underlying CKD (stage 1—5) including congenital anomalies of the kidney/urinary tract as aplastic/hypoplastic/dysplastic/cystic kidneys and obstructive uropathy; glomerulonephritis, or focal segmental glomerulosclerosis. Cases of CKD due to causes other than intrinsic kidney disease such as lupus nephropathy were excluded from the study.

Baseline data including age, gender, anthropometric measures, CKD-underlying pathology, serum urea and creatinine were recorded. Systolic and diastolic blood pressures and total 24-h protein in urine were also determined and reported.

Venous blood samples were collected under complete aseptic conditions and were allowed to clot for 30 min at room temp; then sample was centrifuged for 20 min at 3000 rpm, then serum was divided into two aliquots the first was used for immediate estimation of serum creatinine and urea, while the second part was collected in clean dry Eppendorf tube and stored at −20 °C till be ELISA assayed.

2.1. Methods

1 Urea and creatinine were estimated using Biosystem A15 Autoanalyzer by appropriate chemical principles using coupled-enzymatic method for urea estimation [37] and modified Jaffe's reaction for creatinine estimation [38].

2 Estimated glomerular filtration rate (eGFR) was calculated by the modified Modification of Diet in Renal Disease equation as follows: eGFR (ml/min/1.73 m^2) = 186.3 × (serum creatinine in mg/dl) $^{-1.154}$ × (age in years)$^{-0.203}$ (×0.742 for females) [39].

3 ELISA estimation of serum Arg, asymmetric dimethylarginine and symmetric dimethylarginine using ELISA kits produced by Eagle Biosciences; Germany according to kit manufacturer's instructions [40].

3. Statistical analysis

Obtained data were presented as mean ± SD, ranges, numbers and ratios. Results were analyzed using the Student t-test and Chi-square test (X^2 test). Possible relationships were investigated using Spearman linear regression. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors. Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value < 0.05 was considered statistically significant.

4. Results

The study included 132 CKD pediatric patients; 84 males and 48 females with mean age of 11.5 ± 2.8; range: 6—15 years and mean BMI of 13.7 ± 1.5; range: 11—18 kg/m^2. Their mean eGFR was 38 ± 9.2; range: 14.9—57.2 ml/min/1.73 m^2. Demographic data of studied subjects are shown in Table 1.

Serum levels of Arginine were significantly lower in patients compared to controls, while serum ADMA levels were non-significantly higher in patients compared to controls. On the contrary, serum SDMA levels were significantly higher in patients compared to controls. Calculated Arg/ADMA and Arg/SDMA ratios were significantly higher in patients compared to controls. However ADMA/SDMA ratio was significantly lower in patients compared to controls. Serum Arg levels showed positive significant correlation, while serum ADMA and SDMA levels showed negative significant correlation with eGFR. Details of measurements and ratios are shown in Table 2.

Serum levels of Arg showed positive significant correlation, while serum ADMA and SDMA levels showed negative significant correlation with eGFR of CKD patients. Moreover, Arg/ADMA ratio showed negative significant correlation, while ADMA/SDMA ratio showed positive significant correlation with eGFR of patients. On

the contrary, Arg/SDMA ratio showed negative non-significant correlation with eGFR of patients (Table 3).

Regression analysis of estimated parameters showed that high serum SDMA level was found to be persistently significant predictor for low eGFR, in three analysis models, while high serum ADMA was significant predictor in two analysis models and ADMA/SDMA ratio in one model (Table 4).

5. Discussion

Vascular endangerment is one of the mechanisms that may underlie the development of CKD or happens as a sequel secondary to CKD. NO, a potent vasodilator, regulates systemic blood pressure and local blood flow. A deficiency of NO can lead to vasoconstriction and cause diseases including hypertension and CKD. Reduced L-Arg bioavailability and ADMA both contribute to NO deficiency with subsequent vasoconstriction and impairment of local blood supply of multiple organs including kidney [41—43].

The current study detected significantly lower serum levels of Arg, significantly higher SDMA, and non-significantly higher ADMA serum levels in CKD patients compared to controls. These findings indicated disturbed Arg metabolism in these patients. Moreover, serum levels of Arg showed positive significant correlation, while serum ADMA and SDMA levels showed negative significant correlation with eGFR; a finding indicating a close relationship between impaired Arg metabolism and deterioration of kidney function of CKD patients.

These findings are supported by the study reported by Wasilewska and coworkers [44] who found that plasma SDMA and serum Cystiene C (CysC), which is a marker for kidney injury, levels were significantly elevated in all CKD children compared to healthy controls with significantly higher levels in patients of CKD stage 3 compared to those of stage 1—2 and statistical analyses showed that plasma SDMA level was a better diagnostic tool than serum CysC for identifying CKD stage among all the examined children and for detecting patients of CKD stage 1—2, so could be considered as useful biomarker for the diagnosis and progression of CKD.

Similarly, Taranta-Janusz and colleagues [45], reported increased plasma osteopontin and SDMA levels in children with solitary functioning kidney and both plasma osteopontin and SDMA levels were correlated with eGFR. Recently, Protas et al. [46] found that SDMA levels were higher in low birth weight children with subclinical kidney injury compared to reference groups with a

Table 1
Demographic data of the studied subjects.

Data		Cases with CKD	Controls	P-value
Age (years)		11.5 ± 2.8	11 ± 2.7	0.151
Gender	Males	84 (63.6%)	75(62.5%)	
	Females	48 (36.4%)	45(37.5%)	
Weight (kg)		28.7 ± 5.4	29.3 ± 3.9	0.317
Height (cm)		143.3 ± 12.6	145.9 ± 10.7	0.080
BMI (kg/m^2)		13.7 ± 1.5	14.1 ± 3.3	0.210
Etiology of CKD	Kidney & urinary tract congenital abnormality	48 (36.3%)	NA	
	Focal and segmental glomerulosclerosis	33 (25%)	NA	
	Polycystic kidney disease	21 (15.9%)	NA	
	Acute injury (sepsis or hemolytic uremic syndrome	15 (11.4%)	NA	
	Undetermined	15 (11.4%)	NA	
Blood urea (mg/dl)		53.3 ± 9.1	10 ± 2.1	0.000
Serum creatinine (mg/dl)		1.64 ± 0.36	0.6 ± 0.24	0.000
Estimated GFR (ml/min/1.73 m^2)		38 ± 9.2	112 ± 6.7	0.000
Blood pressure measures (mmHg)	Systolic	106.8 ± 9	103.3 ± 7	0.001
	Diastolic	68.5 ± 7.7	66.3 ± 5.2	0.009
Proteinuria	mg/kg/24 h	48.2 ± 14.2	NA	
	Total (g/24 h)	6.65 ± 3.2	NA	

Data are presented as numbers & mean ± SD; percentages are in parenthesis.
BMI; body mass index, CKD; chronic kidney disease, eGFR; estimated glomerular filtration rate; p < 0.05: significant.

Table 2
Serum levels of estimated parameters and their ratios to each other in studied patients compared to control levels.

Data		CKD patients (n = 132)	Control (n = 120)	P Value
Serum levels (μmol/L)	Arg	138.3 ± 18.6	111.5 ± 28.3	0.000
	ADMA	62.75 ± 16.5	67.14 ± 19.55	0.054
	SDMA	54.8 ± 10.9	117 ± 35.6	0.000
Ratios of estimated levels	Arg/ADMA	2.312 ± 0.613	1.939 ± 1.015	0.001
	Arg/SDMA	2.622 ± 0.617	1.789 ± 0.85	0.000
	ADMA/SDMA	0.919 ± 0.273	1.095 ± 0.526	0.001

CKD; chronic kidney disease, n; number, Arg; arginine, ADMA; asymmetric dimethylarginine, SDMA; symmetric dimethylarginine.

Table 3
Spearman's rho correlation between eGFR and estimated parameters in studied patients.

Parameters	Spearman's rho	p
Arg	0.306	=0.043
ADMA	−0.537	=0.0009
SDMA	−0.692	=0.0007
Arg/ADMA	−0.570	=0.0009
Arg/SDMA	−0.139	>0.05
ADMA/SDMA	0.599	=0.0008

eGFR; estimated glomerular filtration rate, Arg; arginine, ADMA; asymmetric dimethylarginine, SDMA; symmetric dimethylarginine.

Table 4
Regression analysis of estimated parameters in studied patients as predictors of severity of kidney disease as judged by eGFR.

Models	Parameters	β	t	P
Model 1	Serum SDMA level	−0.320	−2.183	0.035
	Serum ADMA level	−0.330	−3.016	0.004
	ADMA/SDMA	−0.343	−0.404	0.021
Model 2	Serum SDMA level	−0.554	−4.804	0.0008
	Serum ADMA level	−0.309	−2.679	0.011
Model 3	Serum SDMA level	−0.632	−5.284	0.0006

eGFR; estimated glomerular filtration rate, ADMA; asymmetric dimethylarginine, SDMA; symmetric dimethylarginine.

strong correlation between SDMA and Cys C, also SDMA negatively correlated with eGFR and concluded that elevated SDMA concentration may play an important role in pathogenesis of CKD.

In our study the calculated Arg/ADMA ratio was significantly lower, while ADMA/SDMA ratio was significantly higher in patients compared to controls and the Arg/ADMA ratio showed negative significant correlation, while ADMA/SDMA ratio showed positive significant correlation with eGFR of patients. These data go in hand with other authors who reported that ADMA, SDMA/ADMA ratio and SDMA were 38–200% higher in CKD patients and that blood pressure elevations and elevation of SDMA are seen in children and adolescents with stage 2–3 (mild-moderate) CKD and concluded that SDMA is a strong marker for reduced eGFR and serves as a moderate but significant indicator of 24-hr blood pressure variability [47].

Moreover, in our study, Regression analysis defined serum SDMA, as significant predictor for reduced kidney function, manifested as reduced eGFR. In line with this finding, Wang and coworkers [48], found that children with CKD had higher levels of ADMA and SDMA than their healthy siblings. Similarly, Lücke and colleagues [49] detected elevated plasma levels of ADMA in children suffering from sporadic focal and segmental glomerulosclerosis (FSGS) compared to healthy controls with an inverse correlation between ADMA and eGFR and concluded that ADMA synthesis is elevated in sporadic FSGS and is involved in the pathogenesis of this disease in childhood.

Other reports showed that reduced eGFR was associated with higher plasma ADMA and SDMA; however, reduced renal plasma clearance (RPCL) of ADMA was not associated with higher plasma ADMA but reduced eGFR was associated with lower RPCL of SDMA and concluded that RPCL of ADMA is independent, while that of SDMA was dependent on renal function in hypertensive patients with mild to moderate renal insufficiency [50].

More recently, Hyla-Klekot et al. [51] found that the role of ADMA as a marker of endothelial dysfunction is not significant, but SDMA may be utilized to monitor eGFR in children with nephrotic syndrome.

Multiple studies tried to explore the underlying mechanisms for the relationship between serum Arg and dimethylarginine derivatives and kidney diseases where Betz and coworkers [52], using rat kidney ischemia-perfusion model found serum L-Arg increased whereas intracellular L-Arg concentration diminished and renal messenger RNA expression of cationic amino acid transporters which mediate L-Arg uptake, remained unchanged and concluded that the marked increase in serum SDMA, especially when accompanied by a diminished Arg/SDMA ratio might reflect competitive inhibition of cellular L-Arg uptake by SDMA and leading to a pathologic renal L-Arg deficiency inducing acute kidney injury. Thereafter, Hall et al. [53] using animal model found serum SDMA and creatinine concentrations were significantly correlated to eGFR, however, serum SDMA became increased before sCr and had higher sensitivity (100%) compared with sCr (17%), but lower specificity (91% versus 100%) and positive predictive value (86% versus 100%) and concluded that using serum SDMA as a biomarker for CKD allows earlier detection of CKD compared with sCr.

Recently, in 2015; Nabity et al.[54] also, using animal model of CKD, found increased serum SDMA during disease progression, correlating strongly with an increase in sCr and decrease in eGFR, SDMA identified, on average, <20% decrease in eGFR, which was earlier than sCr and concluded that SDMA is useful for both early identification and monitoring of decreased renal function in animal model of CKD.

6. Limitations

There are some limitations of our study. First we relied in our results on single blood sample. Another limitation is that 24 h protein was not measured in the control group. This could help in demonstration of the validity of the control group. However, our selection of controls, with exclusion of cases attending the outpatient clinics suffering from conditions that might cause abnormal arginine metabolism, could make our controls valid for comparison with the cases.

7. Conclusions

Disturbed serum levels of arginine and its dimethyl derivatives are associated with abnormal renal functions. The elevated serum SDMA level is strongly correlated with impaired kidney functions and could be considered as a predictor for kidney functions deterioration and CKD progression.

8. Implications

Chronic kidney disease of children is a devastating health problem. The disturbed arginine metabolism with particularly elevated serum SDMA levels can predict deterioration of kidney function and CKD progression. This would help in detection of patients with CKD at an early stage to take possible measures for preventing further progression of the condition towards ESRD.

Ethical approval

The study was approved by the research and ethical committees of the contributing hospital.

Sources of funding

None.

Author contribution

AE, EB, AA, WA.

- Substantial contributions to the conception and design of the work and acquisition of data.
- Drafting the work.
- Final approval of the version published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NK, MS, EA:

- Statistical analysis, and interpretation of data.
- Drafting the work and revising it critically for important intellectual content.
- Final approval of the version published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interests

There is no conflicts of interests.

Guarantor

Akram E. El-Sadek.

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