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Dimethylarginines as Risk Markers of Atherosclerosis and Chronic Kidney Disease in Children with Nephrotic Syndrome

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Nephrotic syndrome in children is commonly associated with dyslipidemia, which is considered a risk factor for endothelial dysfunction and atherosclerosis. Recently new markers of endothelial dysfunction, such as asymmetric dimethylarginine (ADMA), have gained importance. Another L-arginine derivative – symmetric dimethylarginine (SDMA) – may reflect the glomerular filtration rate (GFR).
Objectives. The main aim of this study was to assess ADMA as a marker of atherosclerosis. Secondly, SDMA was examined for GFR assessment.
Material and Methods. The study involved 32 children with nephrotic syndrome. Several parameters were examined in the remission and relapse phases of nephrotic syndrome, including ADMA, SDMA, cholesterol, triglycerides and GFR.
Results. In the relapse phase there was a negative correlation between ADMA and lipids (cholesterol and triglycerides). In both phases SDMA was negatively correlated with GFR.
Conclusions. The role of ADMA as a marker for endothelial dysfunction is not significant. SDMA may be utilized to monitor GFR in children with nephrotic syndrome (**Adv Clin Exp Med 2015, 24, 2, 307–313**).

Key words: nephrotic syndrome, ADMA, SDMA, endothelial function, GFR, atherosclerosis.

Dimethylarginines (asymmetric dimethylarginine – ADMA – and symmetric dimethylarginine – SDMA) are methylated L-arginine derivatives. Among the known methyloarginines only ADMA, since its discovery by Patrick Vallance in 1992, has gained importance as a marker of endothelial dysfunction and atherosclerosis in cardiovascular diseases. Its positive correlation with hypercholesterolemia is especially interesting, although increases in ADMA concentration are also seen in liver and kidney failure, hyperglycemia, hyperhomocysteinemia and oxidative stress [1–6].

ADMA, SDMA and L-arginine compete for access to cells through cation channels. ADMA blocks the entrance of L-arginine, which results in a decrease of nitric oxide (NO) in the endothelium. That is why ADMA is an endogenous inhibitor of nitric oxide synthase. Increases in ADMA concentration are common in endothelial dysfunction and atherosclerosis [7–10].

It has been shown that SDMA concentration reflects the glomerular filtration rate (GFR) [1, 11–14].

Nephrotic syndrome (NS) results in homeostatic failure, caused mainly by a loss of protein through damaged filtration membranes in the renal glomeruli. This biochemical disorder is often accompanied by dyslipidemia [15, 16]. The exact mechanisms of this correlation are unknown, although it is surely a result of common metabolism. Dyslipidemia causes a malfunction of all glomerular structures, including the endothelium,

mesangium and podocytes. Receptors for lipoproteins are also located in the mesangium and podocytes [17]. In NS there is an uncontrolled increase in the concentration of lipoproteins in these cells, which results in their proliferation [15, 17]. In addition, lipoprotein complexes remain in glomerular capillaries [18]. In the mesangium, lipoproteins are oxidized (oxLDL) and in this form they stimulate the production of antibodies against themselves. The oxLDL antibodies are scavenged by macrophages, causing their transformation into foam cells. Subsequently, the foam cells produce mediators of the inflammation process, which causes collagen synthesis in the glomeruli. Eventually podocyte apoptosis, loss of glomeruli function and chronic kidney disease can be observed [19, 20].

Dyslipidemia is one of the main causes of atherosclerosis [21]. There are several markers of endothelial dysfunction that help in risk assessment for cardiovascular diseases. However, none of them has an established position in clinical practice.

The aim of the current study was to assess ADMA and SDMA as markers of atherosclerosis and kidney function in children with NS.

Material and Methods

Inclusion and Exclusion Criteria

The study was conducted prospectively from 2009 to 2011. The inclusion criteria were age 1–18 years old, NS based on primary glomerulonephritis, normal GFR, and an absence of clinical and biochemical infections. The exclusion criteria were secondary NS, chronic kidney disease I–V, hypertension, diabetes, myocardial and liver diseases and C-reactive protein (CRP) > 3 mg/L.

Ethics

The Medical University of Silesia Ethics Committee approved the study protocol (decision no. 9/2008). Informed consent to participate in the study was received from each patient's guardian or next of kin.

Patients

A total of 36 children between 2 and 17 years of age were enrolled in the study (mean age: 8.3 years); 4 of them were excluded due to a lack of remission of the disease. The study lasted 17 months. Among the 32 children who completed study protocol, 26 had one relapse of the disease, while 6 suffered two recurrences. The total number of relapses taken into account in the statistical analysis was 38.

Methods

The biochemical analysis conducted included ammonium, creatinine, uric acid, protein and CRP concentrations. Additional measurements included the blood cell count, lipid profile, erythrocyte sedimentation rate, concentration of sodium, potassium, calcium, magnesium and phosphorus as well as alanine and asparagine aminotransferase activity (ALT and AST). Finally, ADMA, SDMA and L-arginine concentrations were measured. On the first day of hospitalization, the daily urine protein concentration was analyzed. The blood analysis was conducted twice: before treatment and after clinical and biochemical remission was achieved. ADMA, SDMA and L-arginine serum concentrations were analyzed using high-performance liquid chromatography (HPLC).

Statistical Analysis

All the variables were checked for normality with the Kolmogorov-Smirnov test. For dependant variables without normal distribution, the Wilcoxon test was used for data assessment. All correlations were analyzed using Spearman's R correlation coefficient. P values of less than 5% were considered significant. STATISTICA StatSoft® was used for the statistical analysis.

Results

All the children in the study met the criteria of NS. Mean urine protein concentration was 5.1 g/day; mean total protein concentration was 49 g/L; mean albumin concentration was 22.6 g/L; mean cholesterolemia was 328 mg/dL; mean triglyceridemia was 209 mg/mL; mean CRP concentration was 2.4 g/L.

The characteristics of the study group in the remission and relapse phases are presented in Table 1. As shown, remission was associated with fluctuations in the concentration of lipids, proteins, proteinuria, CRP and AST. There were no significant changes in the concentration of ADMA, SDMA or L-arginine in the two phases.

In the relapse phase (Table 2) the following negative correlations were statistically significant: ADMA with cholesterolemia, triglyceridemia and CRP; urine protein concentration with L-arginine; SDMA with HDL-cholesterol and ALT; and SDMA with GFR. Positive correlations were found between

Table 1. Selected parameters in children with NS in the relapse and remission phases

	Relapse phase, mean (SD)	Remission phase, mean (SD)	P-value
Weight [kg]	34.9 (18.1)	35.2 (17.8)	0.18
Systolic pressure [mm Hg]	106.8 (10.9)	105.7 (9.6)	0.23
Diastolic pressure [mm Hg]	68.5 (8.9)	70.4 (8.0)	0.08
Proteinuria [mg/kg/24 h]	212 (156)	0	< 0.001
Proteinuria [g/24 h]	6.2 (4.0)	0	< 0.001
Protein concentration [g/L]	49.9 (8.9)	69.5 (4.5)	< 0.001
Albumin concentration [g/L]	21.1 (7.2)	38.6 (3.6)	< 0.001
Cholesterolemia [mg/dL]	333 (84)	207 (41)	< 0.001
LDL cholesterol [mg/dL]	189 (64)	102 (33)	< 0.001
HDL cholesterol [mg/dL]	83.1 (27.7)	78 (26)	0.52
Triglyceridemia [mg/dL]	245 (147)	138 (57)	< 0.001
Creatinine concentration [mg/dL]	0.52 (0.16)	0.55 (0.14)	0.14
GFR [mL/min]	139 (29)	130 (20)	0.30
Urea concentration [mg/dL]	16.3 (11.1)	23.7 (8.8)	0.63
CRP concentration [mg/L]	2.65 (1.90)	1.64 (1.19)	0.001
ALT activity [U/L]	19.2 (10.8)	19.0 (8.2)	1.00
ADMA concentration [μmol/L]	0.53 (0.11)	0.54 (0.11)	0.62
SDMA concentration [μmol/L]	0.31 (0.07)	0.30 (0.06)	0.13
Arginine concentration [μmol/L]	50.7 (17.1)	53.3 (11.5)	0.20

SD – standard deviation.

ADMA and L-arginine; and between follow-up time and L-arginine.

In the remission phase (Table 3) the following positive correlations were statistically significant: total protein concentration with ADMA and SDMA; SDMA with albumin concentration; ADMA with L-arginine (similarly to the relapse phase). Negative correlations were found between SDMA and GFR (similarly to the relapse phase); and between L-arginine and CRP.

Discussion

Many negative effects of NO synthase inhibition by ADMA commonly present with hypercholesterolemia and hypertriglyceridemia, which are "traditional" atherosclerosis risk factors. It has been shown that ADMA concentration is positively correlated with other "traditional" risk factors, such as hyperhomocysteinemia [22–25], intima media thickness [26] and flow mediated vasodilatation [27, 28]. Attempts to explain the correlation between ADMA and hypercholesterolemia led to the following hypothesis: a high concentration of low-density lipoproteins (LDL), especially oxLDL, causes an increase in the expression of the protein methylotranferase (PRMT) gene (which has a crucial effect in methyloarginine synthesis) and suppression of dimethylarginine-dimethyloaminohydrolase (DDAH) activity – the enzyme that utilizes ADMA [25, 29, 30].

In light of these facts, in children with NS and hypercholesterolemia, a high concentration of ADMA should be expected. Another significant cause of presumed high ADMA concentrations in these children is endothelial dysfunction due to biochemical disturbances and hypertension, which is commonly found. In children with NS, cardiovascular events, including myocardial infarction, may result from early atherosclerosis due to endothelial dysfunction [31, 32]. The aim of this study was to ascertain whether ADMA may play a role as an early marker for atherosclerosis in children with NS.

In contrast to many studies [1, 11, 32–35], the outcomes of the current study show that in the relapse phase, ADMA was negatively correlated with

Table 2. Spearman's R correlation coefficients between selected parameters in the relapse phase in children with NS

	ADMA	**SDMA**	**L-arginine**
Systolic pressure	R = –0.098 p = 0.55	R = –0.014 p = 0.93	R = 0.286 p = 0.08
Diastolic pressure	R = –0.077 p = 0.64	R = –0.121 p = 0.46	R = 0.137 p = 0.41
Proteinuria [mg/kg/24 h]	R = –0.112 P = 0.50	R = 0.132 p = 0.42	R = –0.417 p = 0.008
Proteinuria [g/24 h]	R = –0.152 P = 0.36	R = 0.057 p = 0.73	**R = –0.276** **p = 0.09**
Protein concentration	R = 0.077 p = 0.64	R = –0.127 P = 0.44	R = 0.204 p = 0.21
Albumin concentration	R = 0.153 P = 0.35	R = –0.223 p = 0.17	R = 0.213 p = 0.19
Cholesterolemia	**R = –0.316** **p = 0.05**	R = –0.002 p = 0.99	R = –0.116 p = 0.48
LDL cholesterol	R = –0.155 p = 0.34	R = 0.146 P = 0.38	R = –0.169 p = 0.31
HDL cholesterol	R = –0.023 p = 0.89	**R = –0.364** **p = 0.02**	R = 0.086 p = 0.60
Triglyceridemia	**R = –0.418** **p = 0.008**	R = –0.009 p = 0.96	R = –0.171 p = 0.30
Creatinine concentration	R = 0.020 p = 0.90	R = 0.233 p = 0.15	R = –0.007 p = 0.97
GFR	R = –0.043 p = 0.79	**R = –0.373** **p = 0.019**	R = 0.288 p = 0.07
Urea concentration	R = –0.118 p = 0.48	R = 0.019 p = 0.91	R = –0.151 p = 0.36
CRP concentration	**R = –0.391** **p = 0.014**	R = –0.117 p = 0.47	R = –0.264 p = 0.10
ALT activity	R = –0.012 p = 0.94	**R = –0.317** **p = 0.05**	R = 0.070 p = 0.67
AST activity	R = 0.084 p = 0.61	R = 0.137 p = 0.41	R = –0.222 p = 0.17
ADMA concentration	–	R = 0.240 p = 0.14	**R = 0.310** **p = 0.05**
SDMA concentration	R = 0.240 p = 0.14	–	R = –0.170 p = 0.30
Arginine concentration	**R = 0.310** **p = 0.05**	R = –0.170 p = 0.30	–

GFR – glomelural filtration rate; CRP – C reactive protein; ALT – alanine aminotransferase; AST – asparagine aminotransferase; ADMA – asymmetric dimethyloarginin; SDMA – symmetric dimethyloarginin.

cholesterolemia and triglyceridemia. There are several explanations for these controversial results. Firstly, the present study involved only children with normal GFR, unlike other studies [36, 37]. Secondly, ADMA is a small molecule compound (202Da), easily filtrated through the glomerular

Table 3. Spearman's R correlation coefficients between selected parameters in the remission phase in children with NS

	ADMA	SDMA	L-arginine
Systolic pressure	R = –0.006 p = 0.97	R = 0.045 p = 0.78	R = –0.181 p = 0.27
Diastolic pressure	R = 0.027 p = 0.87	R = 0.124 p = 0.45	R = –0.160 p = 0.33
Protein concentration	**R = 0.336** **p = 0.037**	**R = 0.354** **p = 0.027**	R = 0.126 p = 0.45
Albumin concentration	R = 0.146 p = 0.37	**R = 0.366** **p = 0.022**	R = –0.073 p = 0.66
Cholesterolemia	R = –0.158 p = 0.34	R = –0.151 p = 0.36	R = –0.068 p = 0.68
LDL cholesterol	R = 0.058 p = 0.73	R = 0.111 p = 0.50	R = –0.018 p = 0.91
HDL cholesterol	R = –0.166 p = 0.31	R = –0.203 p = 0.22	R = –0.204 p = 0.21
Triglyceridemia	R = –0.182 p = 0.27	R = –0.127 p = 0.44	R = 0.279 p = 0.09
Creatinine concentration	R = 0.143 p = 0.39	R = 0.273 p = 0.09	R = 0.022 p = 0.89
GFR	R = –0.218 p = 0.18	**R = –0.478** **p = 0.002**	R = –0.088 p = 0.59
Urea concentration	R = 0.035 p = 0.83	R = –0.121 p = 0.46	R = –0.040 p = 0.81
CRP concentration	R = –0.074 p = 0.65	R = –0.073 p = 0.66	**R = –0.349** **p = 0.029**
ALT activity	R = 0.056 p = 0.74	R = 0.003 p = 0.98	R = 0.029 p = 0.86
AST activity	R = –0.046 p = 0.78	R = 0.235 p = 0.15	R = 0.068 p = 0.68
ADMA concentration	–	–	**R = 0.436** **p = 0.005**
SDMA concentration	R = 0.222 p = 0.18	R = 0.222 p = 0.18	R = –0.063 p = 0.70
Arginine concentration	**R = 0.436** **p = 0.005**	R = –0.063 p = 0.70	–

GFR – glomelural filtration rate; CRP – C-reactive protein; ALT – alanine aminotransferase; AST – asparagine aminotransferase; ADMA – asymmetric dimethyloarginin; SDMA – symmetric dimethyloarginin.

membrane [38]. In physiological conditions ADMA is bound to albumin [2, 11, 39]. The albuminuria that is prevalent in NS causes high concentrations of free ADMA, which is easily excreted with urine; at the same time, complex ADMA (bound to albumin) is also freely eliminated. Thirdly, normal ADMA values in children with NS may result from DDAH activation due to high liver cell activity in this disease. Fourthly, the significant negative correlation between ADMA and lipids may indicate other disturbances (i.e., a loss of ADMA due to high proteinuria or high L-arginine metabolism, which override ADMA synthesis). There are also a few studies that deny any positive correlation between ADMA and cholesterolemia [40, 41]. In summary, it should be emphasized that ADMA is

not a good marker for atherosclerosis in children with NS.

On the other hand, the negative correlation between SDMA and GFR in both the remission and relapse phases supports the outcomes of other authors regarding the utilization of SDMA in quantifying the filtration rate [1, 11, 12, 42].

The results of the present study in the relapse phase of NS showed a negative correlation between urine protein concentration and ADMA, as well as a significant negative correlation between urine protein concentration and L-arginine.

In the remission phase a significant positive correlation was found between total protein concentration and ADMA and SDMA, as well as between SDMA and albumin concentration. Correlations between L-arginine, ADMA and SDMA, in both the remission and relapse phases, are significantly positive. Such outcomes indicate the direct dependence of the product (ADMA, SDMA) and substratum (L-arginine) and therefore confirm the dominating role of protein loss in children with NS.

The correlations outlined above may be explained based on the basis of the relationship between ADMA and protein concentration. Ninety percent of ADMA is bound to albumin. A loss of albumin is the main mechanism in NS [2]. This dependence was confirmed in studies by Silva et al. and Zoccali et al. [30, 42].

The analysis of the results of the current study revealed a significant negative correlation between CRP and ADMA in the relapse phase. This is probably due to the high molecular weight of CRP (25106 Da). In NS the loss of albumin is greater than the loss of high molecular weight proteins. The high degree of L-arginine loss (the substratum for ADMA) with high CRP concentrations in NS may explain this correlation. It cannot be excluded that the correlation may also be the result of an endothelial inflammation process. Similar results were obtained by Zoccali et al., who showed a negative correlation between CRP and ADMA during acute infection [42].

In conclusion, it should be stated that ADMA concentration in children with NS is associated with basic metabolic disturbances, such as negative correlations with hypercholesterolemia and hypertriglyceridemia; it is not significantly correlated with urine protein concentration. The role of ADMA as a marker for endothelial dysfunction is not significant. SDMA may be utilized to monitor GFR in children with NS.

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