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Advanced intrauterine growth restriction is associated with reduced excretion of asymmetric dimethylarginine

P.P. Bassareo [a,*,1], V. Fanos [b,1], M. Puddu [b], G. Flore [a], G. Mercuro [a]

[a] Department of Medical Sciences "M. Aresu", University of Cagliari, Cagliari, Italy
[b] Department of Surgery, Section of Neonatal Intensive Care Unit and Puericulture, University of Cagliari, Cagliari, Italy

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ABSTRACT

Background: High blood levels of asymmetric dimethylarginine (ADMA) are associated with future development of adverse cardiovascular events. The ADMA/symmetric dimethylarginine (SDMA) ratio is a marker of ADMA catabolism, with a high ADMA/SDMA ratio being suggestive of reduced ADMA excretion.
Aims: This study aimed a) to verify the presence of a statistically significant difference between ADMA/SDMA ratio levels in a group of young adult subjects who were born preterm with an extremely low birth weight (ex-ELBW) and a group of healthy adults born at term and b) to seek correlations between ADMA/SDMA ratio levels in ex-ELBW and anthropometric and clinical parameters (gender, chronological age, gestational age, birth weight, and length of stay in the Neonatal Intensive Care Unit).
Subjects, study design, outcome measures: Thirty-seven ex-ELBW subjects (11 males [M] and 26 females [F], aged 17–28 years, mean age: 22.2 ± 1.8 years) were compared with 37 controls (11 M and 26 F). ADMA/SDMA ratio levels were assessed for each patient included in the study.
Results: ADMA/SDMA ratio in ex-ELBW subjects was higher compared to controls (1.42 ± 0.31 vs 0.95 ± 0.14, $p < 0.002$) and inversely correlated with birth weight ($r = -0.68$, $p < 0.0001$) and gestational age ($r = -0.54$, $p < 0.0005$).
Conclusions: ADMA catabolism is significantly decreased in ex-ELBW subjects compared to controls, underlining a probable correlation with restriction of intrauterine growth. These results suggest the onset of early circulatory dysfunction predictive of increased cardiovascular risk in ex-ELBW.
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1. Introduction

Asymmetric dimethylarginine (ADMA) is a peptide derived from the continuous protein turnover of all cells in the body. Normally present in blood, ADMA is a strong inhibitor of nitric oxide (NO) synthesis [1,2]. It is an acknowledged fact that high levels of ADMA are associated with multiple morbid conditions which share the endothelial damage and development typical of atherosclerosis: high cholesterol, smoking, diabetes, hypertension, heart failure, chronic renal failure, erectile dysfunction, preeclampsia, and liver failure [3]. Furthermore, the predictive power of ADMA has also been demonstrated. Indeed, initial high blood levels of this substance are associated with the future development of adverse cardiovascular events and cardiac death [4,5].

ADMA is metabolized by the specific enzyme dimethylarginine–dimethylaminohydrolase (DDAH), which, although present mainly in the liver and kidneys, is widely expressed in human tissues [6].

Symmetric dimethylarginine (SDMA) is a structural isomer of ADMA [7]. The ADMA/SDMA ratio is a marker of ADMA catabolism and excretion, an indirect indicator of DDAH activity [8]. A high ADMA/SDMA ratio is suggestive of reduced DDAH activity in the kidneys, and vice versa [7].

The aims of the present study were the following: a) to verify the presence of a statistically significant difference between ADMA/SDMA ratio levels in a group of young adult subjects who were born preterm with an extremely low birth weight (ex-ELBW) and a group of healthy adults born at term and b) to seek correlations between ADMA/SDMA ratio levels in ex-ELBW and anthropometric and clinical parameters, such as gender, chronological age, gestational age, birth weight, and length of stay in the Neonatal Intensive Care Unit (NICU).

2. Methods

2.1. Study population

A comparison of 37 ex-ELBW young adults (11 males and 26 females) ranging from 17 to 28 years (mean age ± SD: 22.2 ± 1.8 years) and a control group (C) of 37 healthy subjects born at term from a healthy mother, matched for sex, age and body mass index (BMI) was carried out. All subjects were contacted in alphabetical

* Corresponding author at: Department of Medical Sciences "M. Aresu", University of Cagliari, Policlinico Universitario, S.S. 554, bivio di Sestu, 09042 Monserrato, Cagliari, Italy. Tel./fax: +39 0706754953.
E-mail address: piercard@inwind.it (P.P. Bassareo).
[1] Contributed equally to the article.

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order from the NICU Records of the University of Cagliari, Italy. All subjects contacted were the first ex-ELBW survivors who had been admitted to the only NICU in Cagliari (Italy). Cagliari is the capital of Sardinia, a region with a relatively small number of inhabitants, the majority of which live in Cagliari and surrounding areas.

Exclusion criteria were as follows: 1) presence of pathological conditions known to interfere with ADMA levels and 2) administration of drugs known to influence ADMA blood concentration [3,9].

All recruited patients or their parents provided informed written consent to take part in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

The authors have previously demonstrated how ex-ELBW displays early signs of impaired renal function, increased ADMA levels, and early cardio-renal involvement [10–13].

2.2. Asymmetric and symmetric dimethylarginine concentrations

ADMA and SDMA levels were obtained by sampling 1 cm^3 of blood from the antecubital vein using a heparin injector. Blood concentrations were assessed by means of high-performance liquid chromatography with highly sensitive laser fluorescent detection, a simple, rapid, specific and sensitive method available worldwide and suitable for use in virtually any laboratory [14].

ADMA/SDMA ratio was calculated for each study subject.

ADMA/SDMA ratios in ex-ELBW subjects were compared to those obtained for C subjects. Subsequently, ADMA/SDMA ratio in ex-ELBW was compared to anthropometric data, age, gestational age, birth weight and length of stay in NICU, obtained from clinical records.

Informed written consent was obtained from all ex-ELBW and C subjects. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.3. Statistical analysis

The results of the study population ($n = 37$) were first analyzed, and the results obtained from adult ex-ELBW subjects were subsequently compared to those from controls born at term ($n = 37$) by means of the parametric Student *t*-test. The relationship between ADMA/SDMA ratio and both gestational age and birth weight was obtained by Pearson's correlation coefficients and by plotting corresponding regression lines. Partial correlation analysis was also performed. Multivariate analysis was not applied due to the small sample size.

Statistical significance was set at $p < 0.05$ throughout the paper. For all analyses, commercially available computer software (SPSS version 20.0, SPSS Inc., Chicago, Illinois, USA) was used.

3. Results

The clinical characteristics of the study population (ex-ELBW vs C) are summarized in Table 1. Statistically significant differences (ELBW vs C) were detected for ADMA/SDMA ratio (1.42 ± 0.31 vs 0.95 ± 0.14, $p < 0.002$).

Table 1
Clinical characteristics of the population in the study.

	Ex ELBW	Control group	p
Age (years)	22.2 ± 1.8	22.0 ± 1.7	ns
Birth weight (g)	940 ± 30.5	3357 ± 51	0.00001
Gestational age (weeks)	22.5 ± 2.0	39.9 ± 0.2	0.00001
Height (cm)	165 ± 14	167 ± 18	ns
Weight (kg)	60 ± 6	58 ± 8	ns
BMI	22 ± 3	21 ± 5	ns
Right kidney longitudinal diameter (cm)	9.4 ± 1.9	10.7 ± 0.6	p < 0.02
Right kidney transverse diameter (cm)	8.3 ± 0.7	9.5 ± 0.5	p < 0.03
Left kidney longitudinal diameter (cm)	9.9 ± 1.6	10.9 ± 0.8	p < 0.05
Left kidney transverse diameter (cm)	8.0 ± 1.1	9.3 ± 0.5	p < 0.02

In ex-ELBW a statistically significant inverse correlation was revealed between ADMA/SDMA ratio and birth weight ($r = -0.68$, $p < 0.0001$; Fig. 1), as well as with gestational age ($r = -0.54$, $p < 0.0005$; Fig. 2). No significant correlations were observed between ADMA/SDMA ratio and anthropometric parameters, age, or length of stay in NICU.

However, partial correlation analysis revealed that the relationship between ADMA/SDMA ratio and intrauterine growth restriction – expressed as birth weight – was unaffected by adjustment for BMI (partial correlation analysis: $r = -0.46$, $p < 0.004$). On the contrary, correlation between gestational age and ADMA/SDMA ratio was no longer significant when controlling for BMI (partial correlation analysis: $r = -0.16$, $p =$ ns).

4. Discussion

The authors had previously demonstrated that blood ADMA levels in a group of former ELBW preterm newborns were higher than in healthy controls born at term [11]. The findings obtained in the present study revealed a reduced ADMA excretion, expressed as ADMA/SDMA ratio, in the population studied. Furthermore, as this ratio correlates more significantly with birth weight than with gestational age, intrauterine growth restriction has been demonstrated to act as the trigger for ADMA reduced catabolism.

It is indeed widely acknowledged that infants born with intrauterine growth retardation and/or preterm, particularly those born prior to 31 or 32 weeks of gestation, present with under-developed kidneys. This incomplete nephrogenesis implies the presence of a reduced number of functional units (nephrons), and consequently reduced glomerular filtration surface, hyperfiltration of each individual nephron, glomerular sclerosis, apoptosis, and early proteinuria [15–17]. At birth, all study subjects weighed less than 1000 g, with 89.2% being delivered at a gestational age of less than 31 weeks.

Increased plasma ADMA levels in kidney disease were initially though to reflect a loss of renal clearance [18]. However, it has been later demonstrated that only a negligible amount of ADMA is excreted unchanged in the urine, with the majority being broken down by the enzyme DDAH.

In the human body 80% of ADMA is metabolized to citrulline by DDAH, while the remainder is excreted by the kidneys [19]. There are 2 isoforms of DDAH: DDAH1 present mainly in the kidneys and brain and DDAH2 found predominantly in the heart and kidneys [20].

High plasma concentrations of ADMA, i.e., the only biologically active endogenous NO inhibitor, have previously been demonstrated even at a very early stage of primary renal disease [21].

A pathophysiological interpretation of our findings should take into account the finding that impaired ADMA degradation by (renal?). DDAH is the cause of increased plasma ADMA concentrations in ex-ELBW patients with early primary renal disease [11]. DDAH is widely present throughout endothelial cells within glomerulus and renal vessels, particularly in renal tubular cells [22]. It regulates intracellular methylarginine levels, thus governing cell-specific L-arginine uptake and NO generation in tubular cells. Destruction of DDAH rich renal tissue may therefore impair renal degradation of ADMA [22].

Inhibition of DDAH activity causes methylarginines to accumulate, blocking NO synthesis, and resulting in vasoconstriction. The critical role of DDAH activity in regulating NO synthesis in vivo has been demonstrated in a transgenic DDAH mouse model; in this animal, DDAH activity is seen to be increased and plasma ADMA levels reduced by 50%. The reduction in plasma ADMA is associated with a significant increase in NO activity, as plasma and urinary nitrate levels are doubled. The increase in NO activity translates into a 15 mm Hg reduction in systolic blood pressure in the transgenic mouse. This study provides insight into the importance of DDAH activity and plasma ADMA levels in regulating NO synthesis [23].

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