Evaluation of ADMA levels in women with pregnancies complicated by severe preeclampsia

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Abstract

Objective: The objective of the study was to determine whether women with pregnancy complicated by preeclampsia have different circulating levels of asymmetric dimethylarginine (ADMA). Patients and methods: The study was carried out on 60 preeclamptic patients (group PRE) and 36 healthy normotensive pregnant women without renal and cardiac diseases. The maternal serum ADMA concentrations were determined using a sandwich ELISA assay. Results: There were no statistically significant differences in gravidity, parity, maternal age and height and BMI in patient profiles between groups. Maternal weight was lower in the control group of patients than in the group of preeclamptic patients. Systolic and diastolic blood pressure and mean arterial blood pressure were significantly higher in the study group of preeclamptic pregnant women than in the control group. Our study revealed the elevated levels of ADMA in serum of women with pregnancy complicated by preeclampsia. The mean values were 0.588 ± 0.179 μmol/l in preeclamptic patients and 0.502 ± 0.107 μmol/l in the healthy controls (p = 0.010097). Conclusions: Preeclampsia is associated with higher maternal levels of circulating ADMA than in normal pregnancy. Our findings may be an important implication for therapy reversing this asymmetric dimethylarginine activity in the serum of preeclamptic women.

Key words: pregnancy, asymmetric dimethylarginine (ADMA), preeclampsia

Preeclampsia is a specific hypertensive disorder in human pregnancy associated with proteinuria. It complicates 5-10% of all pregnancies and is a major cause of maternal and fetal mortality and morbidity and presents a complex problem with management for clinicians [1, 2]. In Western Europe, preeclampsia is the fourth cause of maternal death [3]. Despite recent advances the etiology of preeclampsia remains unclear [4] and there are no specific markers that help to identify pregnant women at risk for developing preeclampsia [3]. Endothelial dysfunction and reduced placental perfusion appear to be crucial for the pathophysiology of this syndrome [5-8].

One of the most important factors and a mediator in healthy endothelium is nitric oxide. Nitric oxide is a potent endogenous vasodilator that plays an important role in the regulation of blood flow and blood pressure and in the maintenance of feto-maternal circulation. Nitric oxide also inhibits platelet aggregation, leukocyte and monocyte adhesion to the vascular endothelium, and proliferation of vascular smooth muscle cells.

Nitric oxide deficiency has been shown to be associated with peripheral, coronary, or cerebral arterial spasms in various experimental models [9, 10]. Decreased endothelial production of nitric oxide results in the increased systemic vascular resistance and blood pressure. It is associated with higher sensitivity to vaso-pressors observed in preeclampsia so it is possible to formulate the hypothesis that preeclampsia might be a “nitric oxide deficiency disease” [11-13].

Nitric oxide production is regulated by asymmetric dimethylarginine (ADMA), which is elevated in cardiovascular disease [3]. It was observed that the infusion of ADMA induced endothelial dysfunction [14, 15] and increased blood pressure secondary to the elevated total peripheral resistance [16] and reduced cardiac output [17].

It was also suggested that ADMA plays an important role in pathogenesis of preeclampsia.

The purpose of this study was to investigate maternal serum concentrations of asymmetric dimethylarginine in the third trimester of pregnancy in preeclamptic women compared with uncomplicated normotensive singleton pregnancies. The study was accepted by the local Ethics Committee.

Patients and methods

The study was carried out on 60 patients in the third trimester of pregnancy complicated by preeclampsia...
sia (the PRE group). The control group consisted of 36 healthy normotensive pregnant women with singleton uncomplicated pregnancies, without any renal, cardiac and vascular diseases and with normal laboratory tests (the C group). Pregnant women with multiple pregnancies were excluded from this study.

Preeclampsia was determined by the increased blood pressure >140 mm Hg systolic and > 90 mm Hg diastolic accompanied by proteinuria defined as the urinary excretion of more than 0.3 g protein in a 24 hour specimen. None of the pregnant patients with preeclampsia was affected by chronic hypertension or renal disorders and/or proteinuria before pregnancy and all were normotensive before the 20th week of pregnancy. All arterial blood pressure measurements in the control group were normal and did not exceed 135/85 mm Hg. None of the patients from the control group suffered from proteinuria. All patients in the study were non-smokers. Informed consent from all studied patients was obtained for peripheral blood sampling.

The soluble ADMA concentrations from maternal serum were evaluated using a sandwich ELISA assay according to the manufacturer’s instructions (human ADMA sandwich ELISA kit Immundiagnostik AG, Stubenwald – Allee Ba, Bensheim).

Data were expressed as a mean ± SD and were statistically analyzed with the computer program “Statistica”. The level of statistical significance was established as p < 0.05.

Results

There were no statistically significant differences in gravidity, parity, maternal age and height and BMI in patient profiles between groups. Creatinine and urea concentrations were normal in all patients. Maternal weight was lower in the control group than in the group of preeclamptic patients. This difference was statistically significant (p = 0.014405). There was no statistically significant difference in maternal BMI although it was higher in preeclamptic women (p = 0.583256).

Systolic and diastolic blood pressure and mean arterial blood pressure were higher in the study group of preeclamptic pregnant women than in the control group. These differences were statistically significant (p < 0.000001). The mean systolic blood pressure values were 165.80 ± 18.06 mm Hg in the group of preeclamptic pregnant patients and 114.12 ± 10.80 mm Hg in the control group. The mean diastolic blood pressure values were 107.69 ± 21.02 mm Hg in women with pregnancy complicated by preeclampsia and 72.33 ± 6.70 mm Hg in the healthy controls. Results of our study are presented in Table 1.

The patients with pregnancy complicated by preeclampsia (the PRE group) revealed higher levels of asymmetric dimethylarginine than the healthy controls. The mean values of ADMA in serum of pregnant women were 0.588 ± 0.179 µmol/l in the group PRE compared with 0.502 ± 0.107 µmol/l in the control group. This difference was statistically significant (p = 0.010097).

Our findings of ADMA levels in maternal serum of studied groups of pregnant women are presented in Figure 1.

Discussion

It has been suggested that deficiency of nitric oxide may explain many of the pathophysiological features of preeclampsia [18]. Asymmetric dimethylarginine as an endogenous nitric oxide synthase inhibitor has been considered as a new risk factor for vascular disease and endothelial dysfunction.

<table>
<thead>
<tr>
<th>Data</th>
<th>Group PRE n = 60</th>
<th>Control group (C) n = 36</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravidity</td>
<td>1.62 ± 1.00</td>
<td>1.33 ± 0.63</td>
<td>0.084288</td>
</tr>
<tr>
<td>Parity</td>
<td>1.48 ± 0.81</td>
<td>1.25 ± 0.48</td>
<td>0.085061</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>28.97 ± 5.18</td>
<td>29.98 ± 3.94</td>
<td>0.310037</td>
</tr>
<tr>
<td>Maternal height (cm)</td>
<td>165.12 ± 5.62</td>
<td>165.35 ± 5.89</td>
<td>0.881775</td>
</tr>
<tr>
<td>Maternal weight (kg)</td>
<td>85.54 ± 17.07</td>
<td>76.48 ± 11.37</td>
<td>0.014405*</td>
</tr>
<tr>
<td>Maternal BMI (kg/m^2)</td>
<td>31.65 ± 5.12</td>
<td>30.28 ± 12.4</td>
<td>0.583256</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>165.80 ± 18.06</td>
<td>114.12 ± 10.8</td>
<td>&lt; 0.000001*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>107.70 ± 21.02</td>
<td>73.33 ± 6.70</td>
<td>&lt; 0.000001*</td>
</tr>
<tr>
<td>ADMA concentrations in maternal serum (µmol/l)</td>
<td>0.588 ± 0.179</td>
<td>0.502 ± 0.107</td>
<td>0.010097*</td>
</tr>
</tbody>
</table>

* statistical significance (p < 0.05)
ADMA levels in preeclamptic women

Chronic renal failure due to arteriosclerosis and chronic heart failure are increased in patients with hypertension and are associated with restrictions in endothelial vasodilatation.

Therefore it was concluded that hypertension, arteriosclerosis and immunological dysfunction in patients with chronic renal failure are connected with a dysfunction of the L-arginin/NO-metabolism and ADMA accumulation. It was observed that the ADMA levels in blood correlate with the degree of arteriosclerosis and cardiovascular morbidity and mortality in dialyzed patients. The correlation between ADMA and the degree of endothelial dysfunction was also observed in humans with isolated hypercholesterolemia. It has been suggested that ADMA may be involved in the development of endothelial dysfunction before the onset of clinical symptoms of atherosclerotic vascular disease [19].

Holden et al. [20] demonstrated that ADMA levels decrease in the course of normal pregnancy parallel with reduced systemic arterial blood pressure.

Abnormal flow patterns in uterine arteries with endothelial dysfunction in the brachial artery and elevated plasma levels of ADMA were observed in pregnant women who later developed preeclampsia [21]. Furthermore Ellis et al. [22] revealed a gradual increase in mean ADMA concentrations that is related to severity of preeclampsia.

Powers et al. [4] observed higher concentrations of maternal ADMA in mid-pregnancy in women who later developed preeclampsia than in controls without complications and than in pregnant women with small-for gestational age fetuses without preeclampsia. They concluded that this NO inhibitor plays a role in the pathophysiology of preeclampsia and plays a crucial role in impairment of angiogenesis and endothelial dysfunction observed in pregnancies complicated by this disorder.

It has been shown in human volunteers that the infusion of ADMA impairs endothelium-dependent vasodilation, increases systemic and renal vascular resistance, and decreases cardiac output. These findings suggest that chronic elevation of ADMA may directly induce vascular disease. On the other hand the supplementation of L-arginine slows the progression of disease and may reverse the atherosclerotic process [23].

Our study has revealed higher levels of ADMA in preeclamptic women than in healthy normotensive pregnant patients. The results seem to suggest that ADMA may be one of the active agents associated with endothelial dysfunction observed in this pregnancy disorder.

Similar findings of higher levels of ADMA in preeclamptic women were presented by Mao et al. [24]. These authors found a highly significant correlation between the plasma concentrations of homocysteine and asymmetric dimethylarginine and concluded that this homocysteine-ADMA-NO pathway may be responsible for the etiology of preeclampsia and could be regarded as a marker for the severity of the disease.

Also Fickling et al. [25] observed significantly higher levels of ADMA in preeclamptic patients, whereas healthy pregnant women had significantly lower ADMA plasma levels. Similar results were presented by Savidou et al. [21], who found the increased levels of ADMA in pregnancies complicated by preeclampsia.

Conclusions

Our results of elevated levels of ADMA in preeclamptic pregnancies as compared with healthy normotensive patients with uncomplicated pregnancies suggest its significant role in the pathogenesis of preeclampsia.

It seems that the increased levels of ADMA may contribute to the endothelial disturbances, renal and vascular dysfunction, increased vasoconstriction, which results in hypertension and proteinuria, the features of preeclampsia.

Our results might also suggest a novel therapeutic strategy for improving the management for patients with preeclamptic pregnancies.

Further studies are needed to clarify these aspects and evaluate role of ADMA in preeclamptic pregnancies in order to improve the management and therapeutic strategies.
This work was supported by a research grant from the Polish State Committee for Scientific Research (KBN grant Nr PBZ-MeiN-8/2/2006 – K140/P01/2007/1.3.2.5).

References


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