Serum Levels of Asymmetric Dimethylarginine, Malondialdehyde and Paroxonase activity among Asthmatic Children

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Introduction
Asthma is the most frequent chronic inflammatory airway disease in children (Scott et al., 2011).

The prevalence and mortality rate have been increased in the last four decades, affecting more than one third of children from the general population (Masoli et al., 2009).

Although the exact mechanism of the pathogenesis of asthma is unknown, asthma is characterized by imbalance of oxidant –antioxidant defense systems with generation of oxidative stress related mediators (Dut et al., 2008).
The lung is a major source of **Asymmetric Dimethylarginine (ADMA)**. Little is known about the role of (ADMA) in the pathogenesis of airways inflammation in asthmatic children (Grasemann et al., 2010).

It can promote oxidative stress by uncoupling NO synthase activity leading to oxidative cell damage, and exacerbation of airways inflammation (Klein et al., 2011).
ADMA can modify lung function, increase airways hyperreactivity and promote lung collagen production and deposition (Holguin et al., 2013).

ADMA has been linked to endothelial dysfunction which is one of the early abnormalities observed in the pathogenesis of atherosclerosis, hyperlipidemia, hypertension and cardiovascular risk (Gruber et al., 2008).
- **Malondialdehyde (MDA)** is an oxidant marker of pulmonary oxidative stress, and lipid peroxidation in atopic asthmatic children *(Klein et al., 2010)*.

- **Paraoxonase as** an antioxidant enzyme involved in atherosclerosis may play a protective role in asthma.

- Increase in oxidative stress and a decrease in paraoxonase activity may be important contributors to the progression of atherosclerosis in asthmatic patients *(Schanen et al., 2005)*.
Objectives
Aim of our present study

- To evaluate the role of ADMA, MDA, and paroxonase activity in asthma pathogenesis comparing their serum levels with healthy non-asthmatic children.

- To determine the relationship to the underlying etiology, the clinical severity and lung function among asthmatic children in Egypt.
Subjects and Methods
This cross sectional case control study was conducted on sixty asthmatic children aged between 4 to 16 years, compared with sixty healthy children from public schools of matched age and sex with no history of atopic dermatitis, allergic rhinitis/conjunctivitis, asthma, or other respiratory diseases.

The studied patients were divided into three subgroups according to the severity in asthma; mild, moderate and severe persistent asthma, each group include 20 patients.
All the children involved in the study had not had any symptoms of lower or upper respiratory tract infections or asthma exacerbation within the previous four weeks.
The inclusion criteria included
- All known asthmatic patients who had been regularly attending the Pediatric Chest and Allergy clinic, Abo El-Rish Children’s Hospital, Cairo University, Egypt.

Exclusion criteria included
- Obese children,
- Children with chronic inflammatory diseases as infections and autoimmune disorders,
- Immuno-compromised patients,
- Diabetes Mellitus, familial hypercholesterolemia, liver and kidney diseases,
- Children taking antioxidant drugs, and vitamins.
Methods

- The diagnosis was established on the basis of medical history, and physical examination.

- Questionnaire from parents include information on age, sex, family history of bronchial asthma, duration of illness and treatment modalities.

- Each child was subjected to anthropometric measures, dynamic spirometry, and high resolution Computed Tomography (HRCT) scan.
Laboratory investigations

- Serum levels of ADMA, MDA and paroxonase activity were measured by ELISA.
- Serum levels of IgE, CRP and ESR.
Results
Results

- Positive family history of asthma was present in 15 patients (25%).
- Positive history of recurrent hospitalization was present in 18 patients (30%).
- Positive history of hypertension was present in 3 patients (5%).
Anthropometric findings (Cont.)

- The mean BMI and weight for age percentile of all studied patients are within normal range for age compared to controls.

- The height for age percentile of our studied patients were highly significantly lower compared to controls ($13.98 \pm 15.72$ versus $39.05 \pm 5.18$) respectively, ($P<0.001$).
Table (1): Comparison of the anthropometric measures of the studied patients' groups (ANOVA).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mild (group I) N=20</th>
<th>Moderate (group II) N=20</th>
<th>Severe (group II) N=20</th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>19.48±2.72</td>
<td>19.26±3.78</td>
<td>119.14±2.79</td>
<td>0.036</td>
<td>0.965</td>
</tr>
<tr>
<td>Height / age percentile</td>
<td>21.05± 18.8</td>
<td>13.91±9</td>
<td>10.64 ±8.75</td>
<td>3.35</td>
<td><strong>0.038</strong></td>
</tr>
<tr>
<td>Weight / age percentile</td>
<td>29.36± 22.8</td>
<td>22.44±16.5</td>
<td>36.29± 29.08</td>
<td>1.22</td>
<td>0.306</td>
</tr>
</tbody>
</table>
Laboratory findings (Cont.)

Serum levels of ADMA, MDA, and IgE were significantly increased (P<0.001), while serum paraoxonase activity was significantly decreased (P<0.05) among our studied patients compared to healthy controls.
Table (2): Comparison of the laboratory findings of the studied patients' groups (ANOVA).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mild (group I) N=20</th>
<th>Moderate (group II) N=20</th>
<th>Severe (group II) N=20</th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum MDA (IU/L)</td>
<td>1.07±0.15</td>
<td>2.44±0.46</td>
<td>4.07±0.7</td>
<td>12.59</td>
<td>0.000**</td>
</tr>
<tr>
<td>Serum ADMA (mg/dL)</td>
<td>1.37±2.5</td>
<td>2.36±1.43</td>
<td>3.28±1.28</td>
<td>6.96</td>
<td>0.003**</td>
</tr>
<tr>
<td>Serum paroxonase (ng/mL)</td>
<td>149.79±19.96</td>
<td>142.52±13.85</td>
<td>135.49±18.21</td>
<td>2.31</td>
<td>0.039*</td>
</tr>
</tbody>
</table>
Table (3): Correlations between parameters of the pulmonary function with biomarkers of the oxidative status in the asthmatic patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>FVC</th>
<th>FEV1</th>
<th>FEV1/FVC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum paroxonase (ng/mL)</td>
<td>0.142</td>
<td>0.38*</td>
<td>0.35*</td>
</tr>
<tr>
<td>Serum MDA (IU/L)</td>
<td>0.188</td>
<td>-0.32*</td>
<td>-0.33*</td>
</tr>
<tr>
<td>Serum ADMA (mg/dL)</td>
<td>-0.491**</td>
<td>-0.007</td>
<td>0.28</td>
</tr>
</tbody>
</table>
It means that, serum levels of ADMA, and MDA were significantly increased with increasing severity of asthmatic attack \( (P<0.001) \), while serum paraoxonase activity was significantly decreased with increasing severity of asthmatic attacks \( (P<0.05) \).
Table (4): Correlations between serum biomarkers in the studied patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum MDA</th>
<th>Serum ADMA</th>
<th>Serum IgE</th>
<th>ESR</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum paroxonase (ng/mL)</td>
<td>-0.7**</td>
<td>-0.4**</td>
<td>-0.737**</td>
<td>-0.783**</td>
<td>-0.761**</td>
</tr>
</tbody>
</table>
Decreased paraoxonase activity was associated with increased serum levels of oxidative stress mediators.
Conclusions
Conclusion & Recommendation

- Our study revealed imbalance between oxidant and antioxidant defense systems in asthmatic children.

- Increased serum levels of oxidative stress mediators as ADMA and MDA were associated with decreased paraoxonase activity in asthmatic children, supporting role for these mediators in asthma pathogenesis.

- Stunting in our results could be due to chronic disease condition, and the effect of long term use of corticosteroid therapy on bone.

- As elevated ADMA and MDA levels could be associated with atherosclerosis, and cardiovascular disease risk in asthmatic children, further studies must be conducted.
Thank You