Decreased glutathione and low catalase activity contribute to oxidative stress in children with α-1 antitrypsin deficiency

**ABSTRACT**

**Background** Recent investigations in animal models have revealed oxidative stress and oxidative damage in the pathogenesis of α-1 antitrypsin deficiency (AATD). However, no data are available on the oxidative stress status and antioxidant enzymes activity in these patients. This study was aimed to analyse the oxidative stress profile and enzymatic antioxidant defence mechanisms in children with AATD.

**Methods** Oxidative stress parameters and the activity of the main antioxidant enzymes were prospectively measured in serum of fifty-one children diagnosed with AATD and thirty-eight control individuals.

**Results** Oxidative stress was increased in the serum of children with intermediate- (MZ; SZ) and high-risk (ZZ) phenotypes for developing AATD-related emphysema and/or liver disease. When compared with the control group, intermediate- and high-risk groups showed significantly lower total glutathione and reduced glutathione levels, decreased catalase activity and increased glutathione peroxidase activity leading to an accumulation of hydrogen peroxide that would explain the significantly increased levels of oxidative stress biomarkers observed in these patients. No differences were observed between the control (MM) and the low-risk (MS; SS) groups. A gradation in oxidative stress parameters was observed when patients were compared among themselves, in that the expression of the Z allele produces a higher oxidative stress status in homozygous (ZZ) than in heterozygous (MZ;SZ) patients.

**Conclusions** Increased oxidative stress, together with reduced antioxidant defence are involved in the pathophysiology of AATD at early stages, opening up a new rationale for the use of antioxidant therapies in the treatment of the disease.

---

**Table 1 Biomarkers of oxidative stress in AATD and control children**

<table>
<thead>
<tr>
<th>Oxidative stress biomarkers</th>
<th>Control (MM)</th>
<th>Low risk (MS; SS)</th>
<th>Intermediate risk (MZ; SZ)</th>
<th>High risk (ZZ)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSSG/GSH (%)</td>
<td>2.42 (1.97–3.57)</td>
<td>2.62 (1.07–3.77)</td>
<td>4.14 (2.60–6.32)</td>
<td>6.47 (4.56–9.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (μM)</td>
<td>2990 (2592–3687)</td>
<td>2684 (2261–2811)</td>
<td>1818 (1474–2535)</td>
<td>1630 (1292–1800)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GSH (μM)</td>
<td>2864 (2532–3620)</td>
<td>2183 (1947–2622)</td>
<td>1741 (1464–2326)</td>
<td>1713 (1376–1937)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GSSG (μM)</td>
<td>72.98 (63.96–91.81)</td>
<td>85.86 (75.32–108.5)</td>
<td>64.0 (32.11–102.2)</td>
<td>75.60 (68.05–101.6)</td>
<td>0.254</td>
</tr>
<tr>
<td>MDA (pmol/mg)</td>
<td>0.85 (0.75–1.07)</td>
<td>0.72 (0.52–1.85)</td>
<td>1.15 (0.85–1.68)</td>
<td>1.94 (1.44–3.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PC (nmol/mg)</td>
<td>0.15 (0.12–0.20)</td>
<td>0.16 (0.13–0.23)</td>
<td>0.17 (0.16–0.18)</td>
<td>0.25 (0.19–0.26)</td>
<td>0.010</td>
</tr>
<tr>
<td>8-OHdG (ng/mL)</td>
<td>0.61 (0.54–0.71)</td>
<td>0.68 (0.60–0.82)</td>
<td>0.97 (0.68–1.11)</td>
<td>2.00 (1.16–2.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SOD (U/ml)</td>
<td>5.38 (4.56–5.61)</td>
<td>5.90 (4.38–6.30)</td>
<td>6.16 (5.41–7.53)</td>
<td>5.76 (3.78–6.17)</td>
<td>0.080</td>
</tr>
<tr>
<td>CAT (nmol/min/mL)</td>
<td>37.66 (32.05–40.57)</td>
<td>36.95 (31.39–43.01)</td>
<td>26.92 (16.47–38.89)</td>
<td>17.67 (14.05–23.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GPx (nmol/min/mL)</td>
<td>21.52 (18.32–23.18)</td>
<td>22.16 (20.79–24.48)</td>
<td>24.52 (19.37–26.79)</td>
<td>32.35 (29.16–37.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GRd (nmol/min/mL)</td>
<td>3.69 (3.41–4.38)</td>
<td>3.04 (2.79–4.97)</td>
<td>4.46 (2.67–5.22)</td>
<td>4.20 (2.86–4.87)</td>
<td>0.610</td>
</tr>
<tr>
<td>H2O2 (fluorescence units)</td>
<td>198.50 (138.3–333–3)</td>
<td>251.0 (212.0–335.0)</td>
<td>323.0 (258.5–350.0)</td>
<td>584.0 (369.0–601.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

All values are expressed as median (IQR). Statistical significance after application of Kruskal-Wallis test. p Values lower than 0.05 were statistically significant (labelled in bold).

AATD, α-1 antitrypsin deficiency; 8-OHdG, 8-hydroxydeoxyguanosine; CAT, catalase; GPx, glutathione peroxidase; GRd, glutathione reductase; GSH, reduced glutathione; GSSG, oxidised glutathione; MDA, malondialdehyde; PC, protein carbonyl; SOD, superoxide dismutase; TG, total glutathione.
for results and discussion on multiple hypothesis testing).

In conclusion, our study supports the hypothesis that OS is a feature of AATD at early stages, and is associated with the presence of AAT Z protein. An increased chronic oxidative status could contribute to the higher risk of lung and liver damage observed in these patients, suggesting a rationale for the use of antioxidant therapies in the treatment of the disease.5

Amparo Escribano,1,2,3 Mónica Amor,1,2 Sara Pastor,3,4 Silvia Castillo,1,2,3 Francisco Sanz,5 Pilar Codoñer-Franch,1,6 Francisco Dasí1,6
1Department of Paediatrics, Obstetrics and Gynecology, School of Medicine, University of Valencia, Valencia, Spain
2Paediatrics Pneumology Unit, Hospital Clínico Universitario Valencia, Valencia, Spain
3Fundación Investigación Hospital Clínico Universitario de Valencia/Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain
4Department of Physiology, School of Medicine, University of Valencia, Valencia, Spain
5Pulmonology Unit, Consorcio Hospital General Universitario de Valencia, Valencia, Spain
6Paediatrics Unit, Hospital Universitario Dr. Peset Valencia, Valencia, Spain

Correspondence to Dr Francisco Dasí, Fundación Investigación Hospital Clínico Universitario de Valencia/ Instituto de Investigación Sanitaria INCLIVA, c/ Menéndez y Pelayo, 4, Valencia 46010, Spain; Francisco.Dasi@uv.es

Collaborators Maria Mercedes Navarro-García.

Contributors Study design: AE, FS, PC-F and FD. Patient recruitment, anamnesis and physical examination: AE, MA, SC, FS and PC-F. Measurement of oxidative stress parameters: SP and FD. Statistical analysis: SP and FD. Article writing: AE, FS, PC-F and FD.

Funding This work was supported by the 2011 SVN, GVA AP-096/11, 2012 INCLIVA intramural and ISCIII PI11/02884 grants.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was approved by the Clinical Research Ethics Committee of the Hospital Clínico Universitario de Valencia.

Provenance and peer review Not commissioned; externally peer reviewed.

Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2014-205898).


Received 13 June 2014
Revised 20 June 2014
Accepted 23 June 2014
Published Online First 15 July 2014
doi:10.1136/thoraxjnl-2014-205898

REFERENCES