Plasma levels of TIMP-1 are higher in 34-year-old individuals with severe α1-antitrypsin deficiency

α1-Antitrypsin (AAT) is one of the major proteins in the circulation eliciting significant protection against activated serine proteases, such as neutrophil elastase and proteinase-3. Moderate and severe AAT deficiency (AATD) is almost entirely caused by the Z (Glu342 to lysine change) and S (Glu264 to valine change) alleles as opposed to the normal wild-type M allele. Severe ZZ deficiency of AAT, characterised by a decrease in serum AAT levels to values <20% of normal, entails a high risk of developing pulmonary emphysema. This fact provides the rationale for the protease–antiprotease imbalance theory of the pathogenesis of emphysema.

We hypothesised that in subjects with AATD, other protease inhibitors may mitigate the deficiency of AAT, and ensure the normal growth and function of the lung from childhood to early adulthood. In a previous report focusing on plasma markers of the serine protease–antiprotease balance, we have shown that 18-year-old ZZ and SZ AATD subjects, identified in the Swedish neonatal AATD screening of 1972–1974, had significantly higher plasma concentrations of α2-macroglobulin and α1-antichymotrypsin, and lower levels of neutrophil lipocalin, a marker of neutrophil activity. Interestingly, at the age of 26 the same ZZ and SZ AATD subjects had significantly higher plasma secretory leucocyte protease inhibitor and, again, lower neutrophil lipocalin levels, compared withagematched controls. At the 30-year check-up, these discrepancies were not confirmed.

In this study we wanted to investigate whether there is any relationship between circulating plasma levels of AAT and tissue inhibitor of metalloproteases-1 (TIMP-1), an important inhibitor of metalloproteases (MMPs) that plays a role in the pathogenesis of emphysema. The study cohort included the above-mentioned 34-year-old AATD subjects (ZZ, n=50; SZ, n=22) and 84agematched controls with normal AAT concentrations. As shown in table 1, plasma levels of AAT in the subjects were ranked MM>SZ>ZZ and were different among the groups (p<0.001). The levels of C-reactive protein, a general marker of inflammation, were normal in all three groups. The mean (95% CI) level of plasma TIMP-1 was 153.5 ng/ml (114.1 to 157.5) in the ZZ group, 99.4 ng/ml (74.97 to 123.5) in the SZ group and 65.5 ng/ml (56.99 to 73.59) in the MM group. Thus, plasma levels of TIMP-1 were higher in the ZZ (52.1%, p<0.001) and SZ (27%, p<0.05) as compared with the controls. Linear regression analysis revealed an inverse relationship between levels of TIMP-1 and AAT (r=−0.459, p<0.001) (figure 1, supplementary data). Notably, the elevated TIMP-1 and its negative correlation with AAT levels were not related to the levels of C-reactive protein.

Previous studies in which TIMP-1 was analysed showed that under normal conditions the TIMP-1 levels outweigh MMPs, tipping the balance in favour of protease inhibitors. We therefore think that higher levels of TIMP-1 in young adults with AATD might provide a compensatory mechanism in maintaining the protease–antiprotease balance and blocking the destructive potential of proteases. We hope this finding opens a new window for further studies on the role of TIMPs/MMPs in the pathogenesis of AATD-related emphysema.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Regional Ethical Review Board of Lund University, Sweden.

Provenance and peer review Not commissioned; externally peer reviewed.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Number</th>
<th>Males/females</th>
<th>AAT (ng/ml) mean (SD)</th>
<th>CRP (mg/ml) mean (SD)</th>
<th>TIMP-1 (ng/ml) mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>MM</td>
<td>84</td>
<td>29/55</td>
<td>1.28 (0.36)</td>
<td>1.22 (0.3)</td>
<td>1.32 (0.3)</td>
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<tr>
<td>SZ</td>
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<td>0.601*** (0.11)</td>
<td>0.58 (0.09)</td>
<td>0.64 (0.13)</td>
</tr>
<tr>
<td>ZZ</td>
<td>50</td>
<td>31/19</td>
<td>0.225** (0.08)</td>
<td>0.23 (0.06)</td>
<td>0.23 (0.11)</td>
</tr>
</tbody>
</table>

*p<0.05 and ***p<0.001 show significant difference between ZZ or SZ AAT deficiency and controls with the normal MM genotype of AAT.

Identifying supportive and palliative care needs in people with a recent diagnosis of thoracic cancer: acceptability of the SPARC questionnaire

National guidelines recommend that physical, psychological, social, spiritual and financial support needs are routinely assessed in people with lung cancer, as a minimum, around the time of diagnosis, on completion of primary treatment, when there is significant deterioration of symptoms and when dying is diagnosed. Self-assessment is considered a useful part of the process and several tools have been highlighted. One of these, the Sheffield Profile for Assessment and Referral to Care (SPARC), contains 45 questions with 56 possible responses covering seven areas of potential need. For most questions, patients rate the degree to which they have been distressed or bothered by a symptom or issue in the past month using the responses: 0 ‘Not at all’, 1 ‘A little bit’, 2 ‘Quite a bit’ and 3 ‘Very much’. However, because there are no reports of its

Table 1 Study groups and plasma concentrations of α1-antitrypsin (AAT), C-reactive protein (CRP) and tissue inhibitor of metalloproteases-1 (TIMP-1)