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Serum levels of alpha-1 antitrypsin in the general Spanish population: relationship to respiratory health

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Alpha 1-antitrypsin, a member of the serine proteinase inhibitor or serpin super family(1), is a potent inhibitor of neutrophil elastase and other proteases. Patients with serum deficiency of AAT (alpha-1 antitrypsin deficiency; AATD) due to mutations in the SERPINA1 gene locus have early onset panacinar emphysema that typically has a bibasal predominance. It was this observation that led to the protease-antiprotease hypothesis in COPD. AATD is a clinically relevant phenotype of respiratory disease, with specific treatment available in the form of intravenous augmentation therapy which elevates AAT levels closer to normal and reduces progression of emphysema(2). Case finding for AATD in symptomatic respiratory patients is recommended by the World Health Organisation and by experts in AATD in Europe (3), consequently measurement of AAT level in clinical practice would usually be done to identify and then manage such patients. A number of genetic polymorphisms can cause AATD, with the normal allele known as M and the most common deficiency alleles being S and Z; individuals with 2 abnormal alleles are at higher risk of developing emphysema and COPD, and those who

are MZ heterozygotes have increased risk in the presence of environmental risk factors such as smoking(4). Similar to CRP and fibrinogen, AAT is also a positive acute phase protein where hepatic synthesis of AAT is augmented by interleukin 6 (IL-6) in response to tissue inflammation(5). It is considered a reliable marker of systemic inflammation although it's role in this capacity is less well studied in relation to COPD, where pulmonary inflammation is a definite feature, and systemic inflammation a potential poor prognostic marker (6).

Barrecheguren and Miravitlles(7) conducted a post-hoc analysis of the relationship between serum AAT levels in patients with COPD (defined as post bronchodilator FEV1/FVC ratio <0.7), those with respiratory symptoms and no COPD and healthy participants. Data was collected from the EPI-SCAN study, a multicentre, cross sectional, observational study of the Spanish population with the primary objective of establishing the national prevalence of COPD in individuals between 40 and 80 years old. Of the 3802 patients enrolled, 837 had a plasma AAT level available and were included in the analysis reported in this journal. Those with COPD and respiratory symptoms had higher adjusted serum levels of AAT compared to control (1.55g/L, 1.57g/L and 1.43g/L respectively). Though these results meet the generally accepted level of statistical significance ($p<0.001$), the clinical impact of these findings is less clear. The authors plausibly propose that AAT could serve as a surrogate marker of chronic inflammation and as a biomarker for long-term outcomes in COPD. Given the small actual differences in AAT level between groups it seems logical that it could form one part of a composite score with inclusion of other relevant biomarkers, rather than a standalone test, to risk stratify COPD patients and allow targeted therapy. Certainly, inclusion of an AAT level for all patients with a new COPD diagnosis would simultaneously screen for AATD and is therefore a worthwhile area of further

scientific exploration. The authors add to data collected from the Copenhagen General Population study which characterised the SERPINA1 genotype and AAT level of 13,405 individuals with and without COPD which found increased inflammatory markers including AAT in smokers and patients with COPD compared with control(8).

It is worth mentioning that there is significant overlap in serum AAT levels between genotypes for AATD, and variation in level alone is therefore not adequate to diagnose MZ or other intermediate deficiencies(3), in part due to the impact of inflammation at the time of sampling. Simultaneous measurement of CRP is one proposed strategy to recognise falsely elevated AAT level as a result of an acute phase protein response(9). Further genotyping could be reserved for those with levels lower than 24.4µM/L (1.1g/L) to detect known common deficiencies (SZ, ZZ etc.) or gene sequencing for those suspected to have rarer variants(10). The study by Barrecheguren and Miravitlles(7) reported 57 patients with low levels of AAT which may represent an underlying AAT deficiency. Unfortunately, specific patient genotypes were not available in this study which means that we cannot be certain of either AATD prevalence in Spanish patients who have COPD, or of the degree to which systemic inflammation in COPD is masking underlying AATD. Patients in the study were not checked for symptoms of a pulmonary exacerbation. Since AAT is an acute phase protein, AAT could have been falsely elevated in some cases which would alter the validity of any of the study conclusions.

The authors raise an interesting discussion regarding chronic inflammation associated with COPD. It is commonly observed that patients with COPD are multimorbid with increased incidence of disease with similar inflammatory aetiologies. These include cardiovascular

disease, osteoporosis, diabetes mellitus and skeletal muscle dysfunction(11). A recent systematic review concluded that patients with stable COPD have raised markers of systemic inflammation including CRP, fibrinogen and WCC with associated increased risk of mortality(12).

The observation that AAT levels are higher in patients with COPD supports the presence of chronic systemic inflammation, however it remains unclear whether inflammation is the result of a primary systemic problem (such as might result from a genetic cause, like AATD), spill over of inflammatory cytokines from the lungs or secondary to co-morbidity observed in COPD (such as inflammation associated with ischaemic heart disease(13)). Attempts to manage inflammation as a primary pathology in COPD have had varying degrees of success. Early trials of anti-tumour necrosis factor therapy reported no benefit in symptom outcomes(14) despite its effectiveness in the treatment of other inflammatory disease such as rheumatoid arthritis and inflammatory bowel disease. However monoclonal antibodies targeting eosinophilic inflammation have had greater impact (15). In addition inhaled steroids appear increasingly likely only to benefit patients with relatively high blood eosinophils(16). This may simply indicate that neutrophilic COPD has a more complex underlying inflammatory phenotype with interaction of multiple cytokines that cannot be addressed by targeting individual molecules. Further trials are needed to explore the usefulness of specific therapies against implicated inflammatory cytokines, to delineate the contribution of AATD to inflammatory pathologies and to elucidate whether AAT is a useful biomarker in COPD beyond its role as an indicator of deficiency genotypes.

Conflict of Interest: none to declare

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