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Review

Autoantibodies in chronic obstructive pulmonary disease: A systematic review

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of death worldwide in which the involvement of autoimmunity has been widely investigated and debated. The role of autoantibodies in COPD has been extensively researched in recent years. The aim of this systematic review is to assess the association between autoantibodies and COPD and analyse whether autoantibody levels correlate with disease severity and/or phenotype. PubMed, Embase, OpenGrey and the reference lists of articles were searched. The strongest evidence for an association between autoantibodies and COPD lies with anti-endothelial/epithelial cell autoantibodies (7 studies, all positive), rheumatoid factor autoantibodies (4 studies, all positive), anti-cytokeratin autoantibodies (3 studies, all positive), anti-nuclear autoantibodies (8 studies, 7 positive) and anti-collagen autoantibodies (10 studies, 6 positive). This review also identifies several other autoantibodies which had both positive and negative associations with COPD, however the evidence for these was not as strong and/or the number of studies is low, and further research is required. In particular, a clear case can be made for the potential importance of autoantibodies to carbonylated proteins. The relationship between autoantibody levels and disease severity requires further research with only 17/43 studies investigating this; however, 12 of the studies did show a positive association, making it a promising area for future research. There was also not enough evidence available on the relationship between autoantibody levels and disease phenotype to draw any conclusions, with only 2 studies investigating it (1 positive and 1 negative). This review has shown very promising evidence for the association of several autoantibodies in COPD and has identified those autoantibodies which require further research.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide [1]. The main symptoms of COPD are dyspnoea, sputum production and a chronic cough resulting from emphysema, chronic bronchitis and bronchiolitis. Fifty percent of lifelong smokers develop COPD and it is widely accepted that smoking is the most common cause of COPD worldwide [2].

The immunopathology of COPD is a complex and intensively researched topic; however, there are still significant gaps in the understanding of COPD and its immunological aspects. There are two main pathological processes that occur in COPD, the first being the remodelling and narrowing of the smaller airways and the other being the destruction of the lung parenchyma, both of which contribute to the typical increase in airflow resistance and hyperinflation which give rise to the symptoms of dyspnoea, and coughing [3,4]. COPD has several

Abbreviations: AAbs, autoantibodies; AAg, autoantigen; AATD, alpha-1 antitrypsin deficiency; AECA, anti-endothelial cell autoantibodies; ANA, antinuclear autoantibodies; ANCA, anti-nuclear cytoplasmic autoantibodies; Anti-CCP, anti-cyclic citrullinated peptide; Anti-CK, anti-cytokeratin; Anti-GRP78, glucose regulated protein 78; Anti-HSP, anti-heat shock protein; Anti-MCV, anti-modified citrullinated vimentin; APC, antigen presenting cell; ASMA, anti-smooth muscle autoantibodies; AT, anti-tissue; ATS, American Thoracic Society; BAL, bronchoalveolar lavage; BMI, Body Mass Index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CPFE, chronic pulmonary fibrosis and emphysema; CXCLI and CXCL8, chemokine ligand 1 and 8; DC, dendritic cell; ECM, extra-cellular matrix; ELISA, enzyme linked immunoassay; ELISPOT, enzyme linked immunospot assay; ERS, European Respiratory Society; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; HBEC, human bronchial epithelial cells; HUVEC, human umbilical vein endothelial cells; IFA, immunofluorescence assay; IHC, immunohistochemistry assay; IPF, idiopathic pulmonary fibrosis; LF, lymphoid follicle; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic autoantibodies; MRC, Medical Research Council; NIH, National Institutes of Health; PCR, polymerase chain reaction; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; TNF-α, tumour necrosis factor alpha; WHO, World Health Organisation; β2-AAbs, β2-adrenergic receptor autoantibodies

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characteristics which point towards the involvement of autoimmunity: e.g. the fact that COPD is a self-perpetuating disease following smoking cessation [5], the interaction between environmental and genetic susceptibility factors [6], the fact that not all smokers develop COPD [7] as well as the cellular components of COPD. Mechanisms such as oxidation, nitrosylation, citrullination, polymerisation and carbonylisation of peptides along with mutations due to environmental exposure and the adverse effects of bacterial/viral infection are all known to render host molecules vulnerable to becoming antigenic [8,9]. Processes such as 'molecular mimicry' and 'epitope spreading' have also been suggested as possible mechanisms for the generation of autoantibodies (AAbs) in COPD [10].

An increasing number of studies have investigated the occurrence of autoantibodies in COPD. The aim of this review is to systematically analyse the literature available to gauge the strength of evidence for the association between autoantibodies and COPD and determine whether the presence of autoantibodies relates to the phenotype and/or severity of COPD. In particular, the review considers the corroborative evidence of multiple studies to establish the autoantibodies that can be confidently associated with COPD in terms of their autoantigenic specificities. This may help to determine the clinical utility of detecting autoantibodies in COPD patients.

Details of the literature search methodology are given in the Online Supplement. This is summarised in the PRISMA 2009 Flow Diagram (Fig. 1), which shows that 42 papers were identified for inclusion. The review firstly considers autoantibodies that were identified in 3 or more studies; then autoantibodies reported in less than 3 studies; thirdly, studies are considered that investigated a wide range of autoantibodies. The division between autoantibodies reported in ≥ 3 and < 3 studies does not imply that the latter are necessarily any less important, but simply that generalisations can be drawn more confidently from multiple related studies. Tables in the Online Supplement summarise details of each individual study in relation to the autoantigens recognised. The order of the consideration of autoantibodies correlates with the strength of evidence based on the number of independent studies that draw similar conclusions.

2. Autoantibodies identified in three or more studies

2.1. Anti-endothelial and anti-epithelial cell autoantibodies (Online Supplement, Table S1)

Anti-endothelial cell antibodies (AECA) and/or anti-epithelial cell autoantibodies were investigated in 7 studies all of which saw a positive association between these AAbs and COPD compared to controls [10–16].

Labib et al. [15] investigated AECA in the sera of COPD patients with and without corpulmonale (right ventricular heart failure due to increased vascular resistance) using a commercial assay. They showed significantly higher levels of AECA in COPD patients compared to the controls and also showed that those with corpulmonale had significantly higher levels than those without. As well as this, the study showed a significant negative correlation between AECA levels and SapO2, FEV1 and PaO2 in the COPD patients which was not seen in the controls. The smoking prevalence was much higher in the patient group compared to the control groups however, which may have introduced bias. Karayama et al. [12] showed significantly higher levels of IgG class AECA in the sera of COPD patients compared to controls, but found no correlation of AECA with clinical features or GOLD score. Kirkham et al. [13] showed significantly higher levels of IgG class AECA

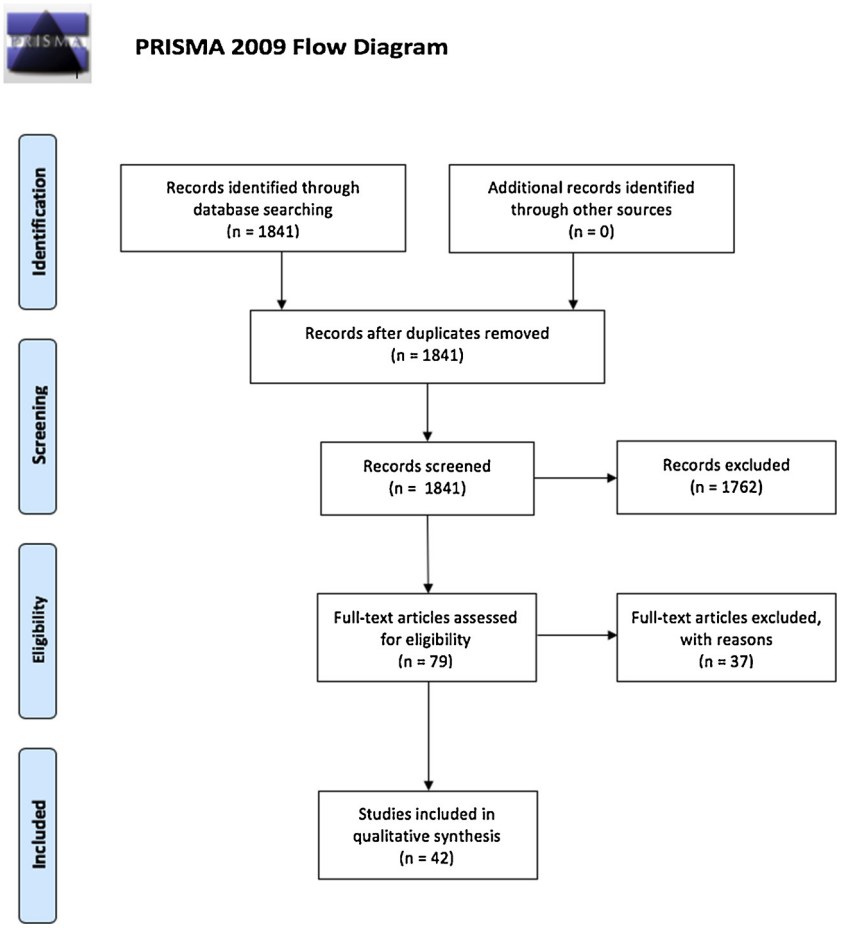

Fig. 1. PRYSMA 2009 diagram.

in the sera of COPD patients than the healthy non-smokers. Kratzer et al. [14] also reported AECA in a proportion of a small number of COPD patients. Taraseviciene-Stewart et al. [16] investigated IgG class AECA in the sera of rats that had been injected with human umbilical vein endothelial cells (HUVEC). This induced enlargement of alveolar spaces and emphysematous changes.

Feghali-Bostwick et al. [10] investigated anti-epithelial cell autoantibodies. They found that 68% of the plasma of COPD patients contained IgG class anti-epithelial antibodies compared to 13% of the smoking controls and 10% of the non-smoking controls. They did not see any association with GOLD stages in the COPD patients. Cheng et al. [11] also investigated anti-human bronchial epithelial cells (HBEC) antibodies in the plasma of COPD patients and found that the percentage of patients with IgG and IgA autoantibodies was signifcantly higher than controls. There was a correlation between FEV1 and FEV1/FVC reduction and positivity for IgG anti-HBEC.

2.2. Rheumatoid factor (RF) autoantibodies (Online Supplement, Table S2)

Four studies investigated RF all of which showed a positive association between COPD and RF compared to controls [17–20].

Newkirk et al. [17] reported that AKR/J mice who were chronically exposed to cigarette smoke showed 100% serum positivity for IgM RF while 83% were IgA RF positive (the induction of RF was specific to this mouse strain). In the same report, they found that COPD patients' sera showed 100% IgA RF positivity and that RF levels remained high after smoking cessation.

Yang et al. [18] also showed by nephelometry that 47% of the COPD patients were positive for RF; as expected, there were higher levels of RF in the RA group than in the COPD group. Tzouvelekis et al. [19] reported that 7.5% of CPFE patients and 10% of IPL patients were 'marginally' positive for RF, and Tamai et al. [20] showed by turbidity immunoassay that 10% of COPD patients and 11% of asthma patients were positive for RF. None of these last three studies included a healthy control group.

2.3. Anti-cytokeratin autoantibodies(anti-CK) (Online Supplement, Table S3)

3 studies investigated anti-CK AAbs all of which found a positive association with COPD [21–23].

Kuo et al. [22] reported that there was a higher proportion of anti-CK18 in the COPD patients (76%) compared to the controls (23.8%) using western blot, immuno-precipitation and mass spectrometry to detect the reactive autoantigen in alveolar epithelial cell extracts followed by screening for reactivity with recombinant human CK18. They also showed that there were higher titres of anti-CK18 in the COPD patients compared to the controls. Daffa et al. [21] also reported that individual COPD smokers and non-COPD smokers showed positive results for serum IgG anti-CK18, although the number of subjects was very small. Xiong et al. [23] found that COPD patients had higher overall plasma levels of IgG, IgA, and IgM against CK18 and CK19 compared to controls. They also reported that levels of IgM anti-CK18 and anti-CK19 increased with disease severity. A similar trend was seen for IgG against CK18 and IgA against CK19. A similar positive result was seen in cigarette smoke exposed mice.

2.4. Anti-nuclear autoantibodies (ANAs) (Online Supplement, Table S4)

Eight studies investigated anti-nuclear autoantibodies in COPD. Seven saw a positive association between COPD and ANA levels [19,24–29] whereas one did not [20].

The earliest study, by Hodson et al. [27], reported that 18% of patients with chronic bronchitis were positive for serum ANAs compared to 4% of the control group; ANAs were more prevalent in patients with more severe bronchitis. More recently, Greene et al. [26] reported 4/6 COPD patients to be positive for IgG ANAs in plasma, Bonarius et al. [24] reported serum ANA positivity in 44% of COPD patients compared to 22% of controls, and Núñez et al. [29] found 34% of COPD patients to be serum ANA-positive compared to just 3% of controls. Tzouvelekis et al. [19] also saw a significant difference in the number of patients with chronic pulmonary fibrosis and emphysema (CPFE) who had increased titres of ANA (42.5%) compared to idiopathic pulmonary fibrosis (26.6%).

Morissette et al. [28] showed, in a small group of COPD patients, that ANA levels in sputum were higher in COPD stages II, III and IV than stages 0 and I. Gouda et al. [25] also reported that serum IgG ANA levels in COPD stages III/IV were higher than in stages I/II; they also showed a negative correlation between ANA levels in the COPD group and their FEV1 readings.

In contrast to the above studies, Tamai et al. [20] found that no COPD patients had clinically significant blood titres of ANAs compared to asthma patients, of whom 10% were ANA-positive; however, they did not include a healthy control group in this study.

2.5. Anti-collagen autoantibodies (Online Supplement, Table S5)

Ten studies investigated autoantibodies to various types of collagen in COPD. Six [21,30–34] found a positive association between anti-collagen and COPD and four [26,35–37] found no association.

The first study identified was by Michaeli et al. [31] who reported that 70% of the emphysema patients were positive for serum IgG antibodies against denatured collagen and 16.5% were positive for antibodies against native collagen. These levels compare to 9% and 1% respectively in the normal population. In a study published in 2010, Brandsma et al. [30] showed an increase in IgM anti-collagen levels in mice after 3 or 6 months of smoke exposure. However, in a subsequent study [35], Brandsma et al. found no significant difference in serum anti-collagen IgG antibody levels between COPD patients and the controls. Several other studies also failed to show an association of anti-collagen antibodies with COPD: Lee et al. [36] found no increase in plasma IgG antibody levels against collagen compared to controls, and ELISPOT analysis also failed to show lung B cells secreting IgG antibodies against collagen. Greene et al. [26] investigated IgG antibodies against proline-glycine-proline (which is a collagen derived peptide) and found no significant difference in plasma titres between COPD patients and controls, or patients with other inflammatory lung diseases. Rinaldi et al. [37] also found no significant difference in IgG anti-collagen levels between the COPD patients and controls. Yadava et al. [34] showed an increase in IgG and IgA anti-collagen levels in BAL and serum in a mouse model of emphysema induced by treatment with LPS plus elastase, but once the mice had been treated with antibiotics the IgA and IgG responses were reduced.

Several other studies examined collagen as part of a wider investigation into an array of autoantigens and autoantibodies in COPD. The details of these studies can be found in the section on investigations of a broad range of autoantibodies, and Supplementary Table S11. Shindi et al. [33] showed that there was no significant increase in IgG antibodies against collagen II but 19/54 patients had raised levels of antibodies against collagen V. Daffa et al. [21] showed that COPD smokers had lower levels of anti-collagen-1 IgG than non-smoking controls and smoking controls; however they did show individual patients who had significantly higher IgG anti-collagen-V and anti-collagen-IV levels than the controls. Finally, Packard et al. [32] reported that there was an increase in anti-collagen antibodies associated with the emphysema phenotype; there was no significant difference in anti-collagen-I or anti-collagen-II between the emphysema and control groups, but a significant difference was seen for anti-collagen-V between these two groups. It thus appears to be important to precisely define the type of collagen being investigated as an autoantigen in the context of autoantibodies in COPD, with the strongest evidence for AAbs to collagen V.

2.6. Anti-cyclic citrullinated peptide autoantibodies (anti-CCP) (Online Supplement, Table S6)

Nine studies investigated anti-CCP autoantibodies of which 4 found a positive association with COPD [38–41] and 5 found no association [17–20,42].

Anti-CCP autoantibodies are mainly associated with rheumatoid arthritis (RA): Gerardi et al. [39] showed that 14% of the COPD patients in their study had a positive result for antibodies to modified citrullinated vimentin (anti-MCV), although levels were significantly higher in RA patients (a healthy control group was not included). Yang et al. [18] also showed that IgG anti-CCP titres were higher in patients with RA than COPD.

Fischer et al. [38] investigated anti-CCP antibodies in a series of patients suffering from a range of different pulmonary conditions. Anti-CCP were detected in a small group of CPFE patients but there was no significant difference in anti-CCP levels between the various disease phenotypes, and no healthy controls were included. Ruiz-Esquide et al. [40] investigated both serum IgG anti-CCP and anti–chimeric fibrin/filaggrin citrullinated synthetic peptides and found that COPD patients who had been heavy smokers had a higher positivity than either non-COPD heavy smokers or non-smoking controls; however these levels were not significant.

Sigari et al. [41] reported that serum IgG anti-CCP levels were significantly higher in a group with wood-smoke induced COPD than either tobacco smoke induced COPD or healthy controls. They did not, however, find a significant difference in anti-CCP titres between the healthy control group and the tobacco induced COPD group. Several other studies also failed to find convincing evidence for an association of anti-CCP with COPD: Wood et al. [42] showed higher levels of anti-CCP in COPD patients compared to AATD patients, but no significant difference from non-smoking controls. A study by Tzouvelekis et al. [19] showed a lower frequency of anti-CCP in the CPFE patients compared to idiopathic pulmonary fibrosis (IPF) patients (5% versus 6.6% respectively) but they were not significantly different; this study also did not include a healthy control group. Tamai et al. [20] reported very low levels of anti-CCP in the serum of COPD patients with only 3% having a positive response; again, a healthy control group was not included. Newkirk et al. [17] showed no increase in serum IgG anti-CCP levels in smoke exposed mice; they also reported that none of a Caucasian group of COPD patients were IgG anti-CCP AAb positive.

2.7. Anti-elastin autoantibodies (Online Supplement, Table S7)

Eleven studies focused on anti-elastin autoantibodies, only 4 of which reported a positive association between COPD and anti-elastin levels compared to controls [30,34,36,43], whereas 7 did not [21,26,32,35,37,42,44].

Plasma IgG anti-elastin was first identified as an AAb associated with emphysema by Lee et al. [36]; they also reported the detection of IgG anti-elastin autoantibody-secreting B cells in the emphysema patients by ELISPOT. Low et al. [43] reported a trend towards higher anti-elastin AAb levels in the bronco-alveolar lavage fluid (BALF) of subjects with alpha-1 antitrypsin deficiency (AATD) or COPD compared to controls, although the differences were not statistically significant. Using a mouse model Brandsma et al. [30] investigated the inflammatory response mediated by smoke inhalation and how it may be augmented when mice are immunized with extra cellular matrix (ECM) proteins, including elastin. Six month smoke exposure plus ECM immunization induced a significant increase in IgM anti-elastin levels compared to sham smoke exposed mice without ECM immnization. Six month exposure to smoke alone also showed an increase in anti-elastin IgM levels compared to the sham smoke control. Yadava et al. [34] reported an increase in anti-elastin IgA, IgG1 and IgM in the BAL of mice with induced emphysematous changes to lung parenchyma. However, treating the mice with antibiotics caused a fall in IgA anti-elastin, suggesting the increase in anti-elastin levels may have been in response to infection.

In contrast to the above reports, Cottin et al. [44] investigated 42 patients with chronic pulmonary fibrosis and emphysema (CPFE) compared to 44 patients with other pulmonary conditions: in each group, serum IgG anti-elastin AAbs were detected in only 3 subjects. Greene et al. [26] also investigated several autoantigens including elastin; there was no significant difference between the COPD and control groups. Indeed, the mean plasma IgG anti-elastin AAb titre was *lower* in the COPD group than the controls. However, this is the same group who reported a trend towards raised levels of anti-elastin in BALF [43], raising the possibility of antibody sequestration to the lung. Wood et al. [42] investigated the presence of AAbs, including IgG anti-elastin, in serum and plasma of subjects with alpha-1 antitrypsin deficiency (AATD) and in subjects with COPD. The healthy controls and the AATD subjects showed a significantly *higher* anti-elastin level than those with COPD. Similarly, Rinaldi et al. [37] reported that plasma IgG anti-elastin levels were *lower* in COPD patients than smoking controls and no relationship between antibody titre and severity was found, with higher levels in the controls compared to GOLD stages III and IV. In contrast to their earlier studies in mice [30], Brandsma et al. [35] also failed to find a significant difference between COPD patients and healthy controls for serum IgG antibodies against elastin.

Several other studies investigated anti-elastin as a part of a wider investigation of autoantibodies in COPD. These studies are considered in more detail below, and the study details are given in the Online Supplement, Table S11. Packard et al. [32] analysed an array of 70 autoantigens including elastin and noted the presence of anti-elastin but did not find any significant increase over baseline in the emphysema or overall COPD groups. Another study which included elastin was carried out by Daffa et al. [21], which found very low levels of IgG to elastin in sera in general and similarly saw no significant difference between COPD smokers, healthy smokers and never smokers for levels of IgG to elastin in lung tissue homogenates.

2.8. Anti-smooth muscle autoantibodies (ASMA) (Online Supplement, Table S8)

ASMA were investigated in 4 studies, 2 indicated a positive association between COPD and ASMA levels compared to controls [25,29] and 2 did not [24,27].

Gouda et al. [25] found that the titre for ASMA was higher in the COPD stages III and IV than in stages I and II. They also showed a negative correlation between FEV1 in the COPD group and ASMA titres. Higher levels of ASMA in the COPD group were seen compared to the control group; however, there were higher levels in the smoking controls compared to COPD stages I/II and the non-smoking control. Also, the precise definition of ASMA in this study was not clearly stated. Núñez et al. [29] carried out a study investigating anti-tissue (AT) antibodies including liver/kidney microsomal anti-smooth muscle antibodies. Results showed that 26% of patients were positive for serum AT antibodies, which was 4.5 times higher than the controls, and most of these patients were also positive for ASMAs.

By contrast, Hodson et al. [27] found no significant difference in titre of serum ASMAs between controls and chronic bronchitis patients. They also failed to show any difference in ASMA levels between the severe and less severe groups. Bonarius et al. [24] also failed to detect serum ASMAs in a small cohort of 12 COPD patients.

2.9. Anti-neutrophil cytoplasmic autoantibodies (ANCA) (Online Supplement, Table S9)

Four studies investigated ANCA of which three [20,24,45] found no association between COPD and ANCAs and one [19] found a positive association.

Tzouvelekis et al. [19] reported on serum myeloperoxidase-ANCA

(MPO-ANCA), and Proteinase 3-ANCA. They noted that there was a higher proportion of CPFE patients with elevated MPO-ANCA levels (17.5%) compared to IPF patients (0%). They also showed that a higher proportion of ANA-positive patients with CPFE were positive for MPO-ANCA compared to the IPF group.

Sugiyama et al. [45] reported that only 4/30 patients with pan-bronchiolitis were positive for serum MPO-ANCA and all of the other patients in the study, including those with COPD, were negative for MPO-ANCA; the study did not include a healthy control group. ANCAs were also investigated in a study by Bonarius et al. [24] who investigated 46 COPD patients and 8 non-COPD subjects, all of whom had a negative result for serum IgG MPO-ANCAs. Tamai et al. [20] also detected no ANCA in the blood of patients with asthma or COPD.

3. Autoantibodies identified in less than three studies (Online Supplement, Table S10)

Autoantibodies to carbonyl-modified proteins (as a consequence of **oxidative stress**) were investigated in COPD by Kirkham et al. [13]. They reported that there was a significant increase in serum IgG AAb levels in GOLD stage III patients compared to non-smoking controls. They also noted that IgG1 AAbs were significantly increased in the COPD and smoking group when compared to non-smokers and that these levels tended to increase with disease severity. This has given rise to a plausible model for the role of oxidative stress-induced modification (carbonylation) of lung proteins inducing autoreactivity in the pathogenesis of COPD; a combination of endogenous factors (e.g. mitochondrial respiration) and exogenous factors (particularly cigarette smoke) could induce the reactive oxygen species that cause these biochemical modifications [9]. This has led to a strategy of measuring AAbs to carbonylated vimentin as a method for determining COPD progression [9].

Anti-heat-shock protein (anti-HSP) AAb were examined in two studies [17,46]. Newkirk et al. [17] found that 85% of a Caucasian cohort of COPD patients were positive for serum IgM anti-HSP70. The same cohort showed a lower frequency of IgA and IgG against this antigen; there were very few or no anti-HSP70 AAbs in the non-COPD controls. In a murine study they saw that 33% of AKR/J strain were positive for serum IgM and IgA anti-HSP70 and 83% were positive for IgG1 after 6 months chronic smoke exposure. Cherneva et al. [46] reported a significant difference in serum IgG anti-αB-crystalline levels between COPD patients and non-COPD smokers, but no difference in AAb titres was observed between the COPD stages.

Glucose regulated protein 78 (anti-GRP78) was investigated by Bon et al. [47] who reported that plasma IgG anti-GRP78 levels were higher in smokers than non-smoking controls, but there was no difference between smokers with or without COPD. There was a significant association between AAb levels and increased severity of emphysema.

Anti-P53 antibodies were examined by Trivers et al. [48] with the intention of determining when these antibodies became detectable in COPD cancer patients compared to non-cancer COPD patients. The study revealed that 22% of the COPD cancer patients were positive for anti-P53 in the serum of which 80% had detectable levels before the diagnosis of their cancer. The group of 44 COPD patients without cancer and the healthy controls were not positive for these autoantibodies.

Autoantibodies against CD80 were investigated by Luo et al. [49] and it was found that the COPD patients had higher serum levels of IgG anti-CD80 than the controls. The study also showed a trend towards higher autoantibody levels in the more severely diseased patients, with a significant difference in titres between COPD GOLD IV and GOLD II.

β2-adrenergic receptor AAbs (β2-AAbs) in COPD were analysed by Hu et al. [50]. They found that after 8 weeks of smoke exposure the serum level of IgG β2-AAbs in rats was increased significantly. In human smoking subjects, they showed that levels of plasma IgG β2-AAbs were negatively correlated with FEV1/FVC, with the majority of the subjects with COPD having higher titres of β2-AAbs.

Anti-double stranded DNA AAbs were analysed in two publications, neither of which [17,19] saw a positive result for any COPD patient.

Autoantibodies against decorin were investigated in two studies by Brandsma et al. In one study [35], they found no significant difference in serum IgG anti-decorin levels between COPD patients and the controls. However, a significant difference was seen in IgG AAbs against decorin between COPD ex-smokers and COPD smokers in favour of the ex-smokers. In another study, Brandsma et al. [30] showed that mice which had been immunized with ECM had an increased levels of anti-decorin after smoke exposure (although this was also seen in the ECM-immunized sham smoke exposed group). AAb to decorin, primarily of IgG class (rather than IgM class) were also detected in COPD patients by Shindi et al. [33] (Online Supplement, Table S11).

Autoantibodies against reticulin were analysed by Hodson et al. [27], who found no difference in serum titres between the bronchitis patients and the controls.

4. Studies investigating multiple autoantibodies (Online Supplement, Table S11)

Leidinger et al. [51] screened the sera of COPD and control subjects against a library of immunogenic clones. A number of the clones that reacted with patients' sera showed homology to various proteins identified as antigens in different conditions e.g. MCM3 in colon cancer and CENPB in systemic lupus erythematosus (SLE). Examples of other antigens examined are given in Supplementary Table S11.

Anti-tissue (AT) AAbs were studied by Nunez et al. [29], who showed positivity in 26% of COPD patients which was 4.5 times higher than in the control group. Anti-smooth muscle antibodies were the most prevalent with 80/328 patients showing positivity. Six patients were positive for gastric parietal cell AAb, 3 were positive for reticulin-like patterns and 1 was positive for both endomysial and mitochondrial AAb. ANA positivity and AT positivity were both seen in 20% of the cases. There was a significant association between increasing AT titres and increasing airflow and gas transfer limitations. AT positivity was also associated with a lower FEV1.

Bonarius et al. [24] examined an array of AAbs including anti-mitochondrial, anti-parietal cell and anti-liver-kidney microsomal antibodies, but none of the 12 COPD patients investigated were positive for these. ANA, anti-SMA and ANCA were also investigated in this study: the findings are described in the relevant preceding sections.

Packard et al. [32] examined an array of 70 autoantigens and found that, in the sera of COPD patients compared to the controls, there was a significant increase in AAb reactivity to 24 antigens. They also reported that emphysema patients had increased reactivity to the antigens compared to patients with bronchitis. 30/70 of the autoantigens were significantly increased in those with emphysema. Overall, emphysema was characterised by more autoreactivity than RA and less than SLE. The autoantigens recognised by emphysema patients are shown in Supplementary Table S11.

Tzouvelekis et al. [19] investigated several antigens: the results for ANA, anti-dsDNA, RF, anti-CCPs and ANCA are discussed in the preceding sections. One CPFE patient had a positive (ENA) panel, including anti-scl70, anti-Ro, anti-La, anti-Sm and anti-RNP.

Daffa et al. [21] investigated both natural and disease specific serum autoantibodies in COPD. The results for collagen, CK-18 and elastin are discussed in the preceding sections. They also reported that no significant difference was seen in levels of anti-vimentin, anti-fibronectin and anti-vitronectin between COPD patients and controls.

Shindi et al. [33] investigated a range of autoantigens which can be seen in Supplementary Table S11. They also examined collagen, the results for which can be found in a preceding section. One aim of this study was to investigate if antibody reactivities were different between IgG and IgM AAbs. IgG had significant reactions to between 1 and 8

Table 1
Summary of AAbs analysed in 3 or more studies in terms of a positive association with COPD.

AAb	All Studies (Positive/Total)	Human studies (Positive/Total)	Animal studies (Positive/Total)	References
Anti-endothelial or anti-epithelial	7/7 2[a]	6/6	3/3	[10,11,12,13,14,15,16]
Rheumatoid factor	4/4 1[a]	4/4	1/1	[17,18,19,20]
Anti-cytokeratin	3/3 1[a]	3/3	1/1	[21,22,23]
Anti-nuclear	7 / 8 1[a]	6 / 8	1 / 1	[19,20,24,25,26,27,28,29]
Anti-collagen	6/10 0[a]	4/8	2/2	[21,26,30,31,32,33,34,35,36,37]
Anti-CCP	4/9 1[a]	4/9	0/1	[17,18,19,20,38,39,40,41,42]
Anti-elastin	4/11 0[a]	2/9	2/2	[21,26,30,32,34,35,36,37,42,43,44]
Anti-smooth muscle	2/4 0[a]	2/4	none	[24,25,27,29]
Anti-neutrophil cytoplasmic	1/4 0[a]	1/4	none	[19,20,24,45]

[a] Number of studies included that investigated the AAb in both humans and rodents.

autoantigens in 89% of COPD patients versus IgM reactivity to between 1 and 11 autoantigens in 93% of COPD patients. IgG reactivities were prevalent to collagen V, histone and scl-70 whereas IgM reactivities were prevalent to CENP-B and La/ssB.

5. Occurrence of AAbs in COPD

This review shows varying findings for the many different AAb/AAgs that have been investigated in COPD. The most confident conclusions can be drawn for those AAb/AAgs which had results available from at least 3 independent studies. Those AAbs which were investigated in only one or two studies will benefit from further independent evidence to determine with confidence whether they do or do not have a positive association with COPD. As shown in Table 1, the strongest evidence for an association between AAbs and COPD lies with AECA, RF, anti-CK and ANA. There is also good evidence for anti-collagen with much of the reactivity directed at Collagen V rather than collagens I-IV. Overall, there is insufficient evidence to determine an association with anti-CCP, anti-elastin, anti-SMA and ANCA.

Although there is insufficient evidence available for those AAbs which were analysed in less than 3 studies, oxidative stress induced AAbs, anti-HSP AAbs, GRP78 AAbs, AAbs against CD80, and β2-AAbs were all shown to have a positive association with COPD while anti-p53, anti dsDNA and anti-reticulin were all negative. Anti-decorin AAbs had one positive study and one negative study. In particular, a strong case has been made for the importance of AAb to oxidative stress-induced (carbonylated) lung proteins, e.g. carbonylated vimentin [9].

Several studies looked at a broad range of AAbs, and it appears that analysis of a range of AAbs/AAgs gives a clearer and more comprehensive view of their role in COPD. This review has shown that few, if any, AAbs/AAgs are positive in *every* COPD patient but, instead, AAbs and their concentrations vary from patient to patient with no two patients having the same autoantibody profile. This is also consistent with the findings of studies examining individual antigens (Supplementary Tables S1-S10), which mainly reported antibodies specific to a particular autoantigen to be present in only a proportion of COPD patients. When a collection of 1827 antigenic clones were analysed, an overall positive association between AAb levels and COPD was seen [51]. Similarly, a study of 70 AAgs showed a positive association [32]. One study showed that some of the positive AAbs in COPD groups were actually higher in the circulation of controls, and suggested that these may be natural AAbs (as opposed to disease-specific AAbs) that are sequestered to the inflamed lung tissues in COPD [21]. Another study showed differences in autoantigenic reactivities between IgG and IgM autoantibodies, and that detecting autoantibodies of both immunoglobulin classes specific for as range of autoantigens distinguished all the COPD patients from smokers without COPD [33].

6. Association of AAbs with severity of COPD

For those AAbs/AAgs that have been examined in more than three studies, Table 2 shows that in 14 cases the relationship between AAbs and severity of COPD was investigated; 6/14 of these concluded that there is a positive correlation between AAbs and disease severity. Several of the reports concerning AAbs investigated in less than 3 studies also examined their relationship with severity: increasing titres were associated with increasing severity for oxidative stress induced AAbs, Anti-GRP78, β2-adrenergic receptor AAbs and anti-CD80 AAbs, while no association was seen for anti-HSP. Two of the studies which investigated a range of AAbs investigated severity, both of which showed a positive association between AAb titres and severity. Overall, in 21 cases the relationship between AAb titres and severity of COPD was investigated, of which 12 reported a correlation. Although there is not yet enough evidence available to reach a firm conclusion, this is a promising area for further research. The details of the studies showing the associations are given in the Online Supplementary Tables.

7. Association of AAbs with phenotype of COPD

The relationship between AAb titres and particular COPD phenotypes was not conclusively explored since most of the included studies focussed on a particular phenotype. However, one study [38] showed

Table 2
Summary of AAbs and their relation to severity of COPD.

AAb	Number of studies investigating severity/total number of studies	Number of studies showing positive association with severity
Anti-nuclear	5/8	3
Anti-endothelial/anti-epithelial	3/7	1
Anti-Cytokeratin	2/3	1
Anti-smooth muscle	1/4	1
Anti-Elastin	1/11	0
Anti-CCP	1/9	0
Anti-Collagen	0/10	0
Anti-RF	1/4	0
Anti-nuclear cytoplasmic	0/4	0

that there was no difference in anti-CCP AAb levels with varying disease phenotypes. In contrast, another study [32] showed higher levels of anti-collagen AAbs in the emphysema phenotype compared to bronchitis.

A perspective by Duncan in 2012 [52] points out that simply because an AAb is seen in abnormal levels in a disease does not necessarily mean it is pathogenic and that in order to truly understand the role of autoimmunity in COPD we must analyse not only the presence or absence of AAbs, but also the ways in which they contribute to pathogenesis. Investigations into AAb titres and the severity or phenotype is a step in the right direction but only a proportion of the studies in this review attempted to answer these questions. Duncan [53] also reminds us of how ANAs have been known about in SLE for more than 50 years, but we still do not fully understand their pathogenic effects; therefore, simply because we are not yet aware of the pathogenic properties of the AAbs considered in this review, we cannot dismiss their potential involvement in the pathogenesis COPD.

8. Overall implications

Since the patient groups, controls, disease phenotypes and methods of laboratory analysis differ between the studies reviewed here, the generalisability of the combined findings to the overall COPD population is limited. As indicated in the Online Supplementary Tables, there is also a great deal of heterogeneity between studies in the extent of cigarette smoke exposure of patients and controls in terms of pack-years and smoking status (current or former smokers): this is also likely to affect the observed outcomes in terms of AAb status. Furthermore, although the majority of the studies cited involved human COPD patients and controls, a few studies additionally or exclusively involved animal models of COPD; findings in the latter cannot be directly extrapolated to the human disease.

Current treatment for COPD consists mostly of bronchodilators and steroid use which, in combination, can help to alleviate symptoms and reduce the ongoing inflammation. If AAbs which are relevant to the progression of COPD can be definitively identified and defined, there is hope that these AAbs could be targeted with the potential to improve treatment of the disease. In addition, even AAbs which do not contribute to the pathogenesis directly may be useful biomarkers of the disease. This review brings us a step closer to identifying AAbs which may have a role in COPD as well as identifying those which need more research to truly understand their role, or lack thereof. It is therefore imperative that future research not only identifies AAbs and determines if their levels are abnormal in COPD, but must also try to investigate the role of such AAbs in the pathogenic process of the disease.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.imlet.2019.08.007.

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