Anti-Tissue Antibodies Are Related to Lung Function in Chronic Obstructive Pulmonary Disease

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***Rationale*: Chronic obstructive pulmonary disease (COPD) is a multicomponent disease. Autoimmunity can contribute to the pathogenesis of COPD.**

***Objectives*: This study investigates the prevalence of circulating antinuclear antibodies (ANA) and anti-tissue (AT) antibodies, two common markers of autoimmunity, in COPD and their relationship with several components of the disease.**

***Methods*: We determined lung function, the serum titers of ANA and AT by immunofluorescence, and the serum levels of C-reactive protein (CRP) by high sensitivity nephelometry in 328 patients with clinically stable COPD and in 67 healthy controls recruited in the PAC-COPD study. Multiple linear and logistic regression analysis was used to analyze results.**

***Measurements and Main Results*: The prevalence of abnormal ANA and AT titers was 34% and 26% in patients and 3% and 6% in controls, respectively. Levels of AT greater than or equal to 1:320 were seen in 21% of patients with COPD and were independently associated with the severity of airflow limitation and gas transfer impairment ($P < 0.05$). Neither ANA or AT titers was related to body mass index, current smoking status, use of inhaled steroids, the Charlson index, or serum C-reactive protein values.**

***Conclusions*: Between a quarter and a third of patients with clinically stable COPD present abnormal titers of circulating ANA and AT. The observed relationship between AT and lung function supports a role for autoimmunity in the pathogenesis of COPD.**

Keywords: autoimmunity; bronchitis; emphysema; immune system; tobacco

AT A GLANCE CLINICAL COMMENTARY

Scientific Knowledge on the Subject

Autoimmunity can contribute to the pathogenesis of chronic obstructive pulmonary disease (COPD). The prevalence of circulating antinuclear and anti-tissue antibodies in COPD, and their potential relationship with other domains of the disease, is unknown.

What This Study Adds to the Field

Our results show that between a third and a quarter of patients with clinically stable COPD present abnormal levels of circulating antinuclear and anti-tissue antibodies, the latter being related to lung function impairment. These observations provide further support to the hypothesis that the pathogenesis of COPD involves an autoimmune component.

An enhanced and persistent inflammatory response to the inhalation of particles and gases, mostly tobacco smoking, is considered a key pathogenic mechanism of chronic obstructive pulmonary disease (COPD). Recent evidence indicates that autoimmunity can play a significant role in this response (1). In this context, circulating antibodies against elastin (2), a key component of the matrix of the lung, and the pulmonary epithelium (3) have been recently identified in patients with COPD, and an animal model of autoimmune emphysema has been described (4).

Antinuclear antibodies (ANA) and anti-tissue (AT) antibodies are two markers of autoimmunity commonly used in clinical practice (5) that have not been specifically investigated in patients with COPD. Our study sought to further explore the participation of an abnormal immune response in COPD by determining the distribution of circulating ANA and AT titers in a large and well characterized sample of patients with COPD (6) and healthy controls, and by exploring their relationship with relevant disease domains, such as smoking history, degree of airflow obstruction, nutritional status, the body-mass index (B), degree of airflow obstruction (O), functional dyspnea (D) and exercise capacity (E) (BODE), presence of emphysema, comorbidities or systemic inflammation, or the use of inhaled steroid therapy. Preliminary results of this investigation have been previously reported in abstract form (7).

METHODS

Study Design

This is a prespecified, cross-sectional analysis of the baseline data of the PAC-COPD study, whose design and methodologic details have been described in detail elsewhere (6). Briefly, patients were recruited during their first hospitalization episode caused by an exacerbation of COPD, and they were studied, when clinically stable, 3 months after discharge.

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Population and Ethics

From January 2004 to March 2006, all subjects hospitalized for the first time because of an exacerbation of COPD in the nine participating hospitals in Spain were approached by the investigators. The criteria of first admission was based on the exclusion of patients with previous admissions as assessed by a questionnaire and information contained in the clinical records of the patient in the hospital, if available. The diagnosis of COPD was established when clinically stable according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations (8). Patients younger than 45 years of age, with cancer, residual extensive tuberculous lesions of more than one third of the pulmonary parenchyma, pneumonectomy, or pneumoconiosis did not enter the study. A total of 342 individuals were originally included in the cohort (6). We report here results of the 328 patients with blood samples available for the measurement of ANA and AT (96%). As a control population we studied 67 healthy volunteers (31 smokers and 36 nonsmokers) recruited from primary care clinics, blood donors, and hospital workers.

All subjects signed the informed consent, which had been previously approved by the ethics committees of all participating institutions.

Clinical Characterization

Anthropometric data and information regarding relevant clinical aspects of the medical history of the patient were obtained using structured questionnaires (6). Particular attention was given to the cumulative dose of tobacco smoked before recruitment (pack-years); current or former smoking habits; presence of comorbidities (Charlson index) (9); and therapy prescribed at the time of recruitment. Nutritional status was assessed by the body mass index (BMI). Dyspnea was assessed using the modified Medical Research Council questionnaire (10). A 6-minute walking test was performed according to international guidelines (11). The BODE index was calculated according to Celli and coworkers (12).

Lung Function

Forced spirometry (before and after bronchodilation) (13) and the carbon monoxide diffusing capacity (D_{LCO}) (14), a surrogate for the presence of emphysema (15), were measured according to international guidelines. Reference values where those of a Mediterranean population (16, 17). COPD severity was categorized according to the ATS/ERS classification (8). Pa_{O2} and Pa_{CO2} were measured in an arterial blood sample according to international standards (18). D_{LCO} and arterial blood gases were not measured in controls.

Blood Sampling

A venous blood sample (10 ml) was obtained by peripheral venipuncture in the early morning after overnight fasting. Active smokers were asked to refrain from smoking 8 hours before. Blood was centrifuged at 2,000 rpm for 10 minutes immediately after sampling, and serum was stored frozen at −80°C until analysis. All analyses were performed in the same center (Hospital Universitari Son Dureta, Palma Mallorca, Spain) by specialized technicians.

Circulating Autoantibodies

The serum titers of ANA were quantified by indirect immunofluorescence on Hep2 lines (INOVA, San Diego, CA). Anti–extractable nuclear antigens antibodies were investigated by semiquantitative ELISA (INOVA). In ANA-positive samples with a homogeneous pattern, we tested the presence of anti–double-stranded DNA (dsDNA) antibodies by indirect immunofluorescence on *Crithidia luciliae* slides.

AT including mitochondrial, liver-kidney microsomal smooth muscle (SMA), and parietal gastric cell (PGC) autoantibodies were determined by immunofluorescence on composite block of rodent liver, kidney, and stomach sections (Inmunofluor ANA-AMA-SMA-APCA; MT Promedt Consulting, St. Ingbert, Germany). In anti–SMA-positive samples (>90% of AT total positive cases), we determined the presence of anti–F-actin, the main SMA reactivity found in Type 1 autoimmune hepatitis (19), by ELISA (Quantalite Actin IgG ELISA; INOVA).

All tests were performed masked by a technician and reviewed by an immunologist (M.R.J.). Both for ANA and AT, titers less than 1:160 were considered negative, whereas those 1:160, 1:320, and greater than 1:320 were considered increasingly positive (20, 21).

C-Reactive Protein

Serum levels of C-reactive protein (CRP) were determined by high sensitivity immunonephelometry (Dade Behring, Murgburg, Germany). Assays were performed in duplicate with a variation coefficient lower than 5%. The lower level of detection was 0.1 mg/L. CRP values below 3 mg/L were considered normal (22, 23).

Statistical Analysis

Results are expressed as mean (SD) for quantitative variables, or as frequencies and percentages for qualitative variables. Sample size calculations showed that, accepting an α risk of 0.05 and a β risk of 0.20 in a two-sided test, 45 control subjects and 45 patients were necessary to recognize as statistically significant a difference greater

TABLE 1. ANTHROPOMETRIC, CLINICAL, AND FUNCTIONAL DATA OF 328 PATIENTS WITH COPD, BY THE ATS/ERS CLASSIFICATION OF DISEASE SEVERITY

	ATS/ERS Stage of Disease Severity*				
	I Mild	II Moderate	III Severe	IV Very severe	*P* Value
N	19	159	124	26	
Age, yr, m (SD)	67.8 (8.5)	68.2 (9)	68.8 (7.7)	64 (8.7)	0.074
Males, n (%)	15 (79)	145 (91)	122 (98)	25 (96)	0.004
BMI, kg/m^2, m (SD)	29.1 (5.2)	29.2 (4.4)	28 (4.3)	23.9 (4.3)	<0.001
Inhaled steroid users, n (%)†	9 (47)	90 (57)	91 (73)	24 (92)	<0.001
Current smokers, n (%)	4 (22)	52 (33)	36 (30)	12 (48)	0.245
Pack-years, m (SD)	67.7 (50)	68.8 (39.2)	69.4 (40.4)	63.6 (28.6)	0.924
Charlson index, m (SD)	2.2 (1.8)	2.1 (1.3)	2.2 (1.5)	2.2 (1.5)	0.931
Post-BD FEV_1, % ref, m (SD)	87.4 (7.4)	61.7 (7.9)	41.5 (5)	24.3 (4.1)	<0.001
Post-BD FEV_1/FVC, %, m (SD)	64.8 (4.3)	59.7 (8.5)	48.2 (10.2)	34.5 (7.2)	<0.001
D_{LCO}, % ref, m (SD)	90.7 (18.4)	70.2 (18.1)	59.9 (18.5)	42.5 (21.2)	<0.001
Pa_{O2}, mm Hg, m (SD)	82.1 (10.9)	76.6 (10.9)	72.1 (9.5)	67.1 (7.7)	<0.001
Pa_{CO2}, mm Hg, m (SD)	39.8 (4.3)	40.5 (4.9)	42.9 (5.2)	46.1 (5.3)	<0.001
BODE index	0.5 (0.9)	1.3 (1.2)	3.4 (1.5)	5.5 (2.1)	<0.001
C-reactive protein, mg/L, m (SD)	3.4 (2.2)	7.3 (15.8)	10.6 (22)	6.8 (10.5)	0.257

Definition of abbreviations: ATS = American Thoracic Society; BMI = body mass index; BD = bronchodilator; BODE = body-mass index (B), degree of airflow obstruction (O), functional dyspnea (D) and exercise capacity (E); COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of carbon monoxide; ERS = European Respiratory Society.

* ATS/ERS stages: I, mild, FEV_1/FVC <0.7 and $FEV_1 \geq$ 80% ref; II, moderate FEV_1/FVC <0.7 and FEV_1 <80% and ≥ 50% ref; III, severe, FEV_1/FVC <0.7 and FEV_1 <50% and ≥ 30% ref; IV, very severe, FEV_1 <50% and ≥ 30% ref.

† Alone or in combination.

Some variables had missing data: 7 in smoking, 7 in pack-years, 1 in Charlson index, 45 in D_{LCO}, 11 in Pa_{O2}, 10 in Pa_{CO2}, and 7 in C-reactive protein.

TABLE 2. ANTHROPOMETRIC AND FUNCTIONAL CHARACTERISTICS (MEAN ± SD) IN CONTROLS AND PATIENTS WITH COPD

	Controls (*n* = 67)	Patients with COPD (*n* = 328)	*P* Value
Males, n (%)	62 (92.5)	307 (93.6)	0.75
Age, yr	66.7 ± 5.9	68 ± 8.5	0.22
Pack-years	40 ± 22.1	65.5 ± 39.5	<0.01
FEV_1, % ref	101.8 ± 18.8	52.6 ± 16.3	<0.01
FEV1/FVC, %	79.3 ± 6.5	53.6 ± 12	<0.01

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

than or equal to 20% units when the proportion of autoantibodies in the control group was estimated in 5% (according to previous literature [20, 24]). Comparisons between patients and controls and across controls were performed by means of Student *t* and chi-square tests. Comparisons across stages of disease severity and variables between patients were performed by means of analysis of variance and chi-square tests for quantitative and qualitative variables, respectively. To identify subjects' characteristics and COPD components (including BODE index) related to ANA and AT levels, analysis of variance and chi-square tests were used in the bivariate approach. Multivariate linear or logistic regression models (depending on the distribution of the outcome variables) were built for each COPD component using ANA or AT as categorical exposures. Other patients' characteristics and COPD components were included as covariates only if they were both related to autoantibodies and each specific outcome variable. As sensitivity analysis, we repeated all calculations excluding women. A *P* value lower than 0.05 was considered significant. Data analysis was conducted using Stata 10.1 (StataCorp, College Station, TX).

RESULTS

Clinical Data

Table 1 presents the main anthropometric, clinical, and lung function characteristics of the 328 patients studied, grouped according to the ATS/ERS classification of disease severity (8). Age was similar between groups. Most patients had moderate (stage 2) or severe (stage 3) COPD and were male. The BMI decreased and the BODE index increased significantly in proportion to disease severity. Cumulative smoking exposure (pack-years) was intense and similar in all groups. The percentage of patients using inhaled steroids increased in proportion to disease severity. As expected, gas exchange deteriorated with increasing airflow limitation severity (Table 1). Mean CRP values tended to be higher than normal (3 mg/L) (22, 23) but they were not significantly different between ATS/ERS stages of disease severity (Table 1). Table 2 shows the main anthropometric and functional characteristics of controls compared with the entire population of patients with COPD. Because we did not find any significant difference in antibody titers according to the smoking status of controls (never, former, or current smokers; data not shown), they were analyzed as a single group.

Prevalence of Positive ANA and AT Titers

Figure 1 presents the frequency distribution of ANA and AT titers in the patients and controls studied. Overall, 34% of patients had an abnormally high ANA titer (≥ 1:160) (20), a prevalence 11 times higher than that seen in our control group (Figure 1A), and seven times higher than that reported in healthy subjects (5%) (20). Eleven percent of patients with COPD had ANA titers greater than or equal to 1:320, a figure that is much higher than that observed in healthy subjects (Figure 1A). Among patients with positive ANA titers, less than 1% of patients had anti–dsDNA- or anti–ENA-positive results. The pattern of ANA positivity was speckled (n = 57); mixed (n = 39); cytoplasmic (n = 8); nucleolar (n = 5); centriolar (n = 1); or homogeneous (n = 1).

We also found that 26% of the patients studied showed AT positivity (≥ 1:160), a prevalence 4.5 times higher than determined in our controls (Figure 1B), and four times higher than that reported in healthy subjects (6%) (24). Of note, 21% of patients had AT titers greater than or equal to 1:320, whereas this was not the case in any single healthy subject (Figure 1B). Most (n = 80) AT-positive patients were SMA-positive, whereas only occasionally we observed individuals with PGC-positive (n = 6), reticuline-like pattern (n = 3), endomysial (n = 1), and mitochondrial (distinct from the M2 primary biliary cirrhosis–associated pattern) (n = 1). Among SMA-positive patients, we detected reactivity against F-actin in only 10% of them, and in these cases, this was always at low or moderate levels. In 20% of cases abnormal AT and ANA titers occurred in the same patient. Results did not change when females were excluded from analysis (data not shown).

Relationship between Circulating Antibodies and Patient Characteristics

ANA positivity was more prevalent in women but their limited number (n = 21) restricts the generalizability of this observation. However, AT-positive patients were younger and more likely to be active smokers (Table 3). As shown in Figure 2, ANA titers were not related to the severity of airflow limitation (Figure 2A) or gas transfer (D_{LCO}) deficit

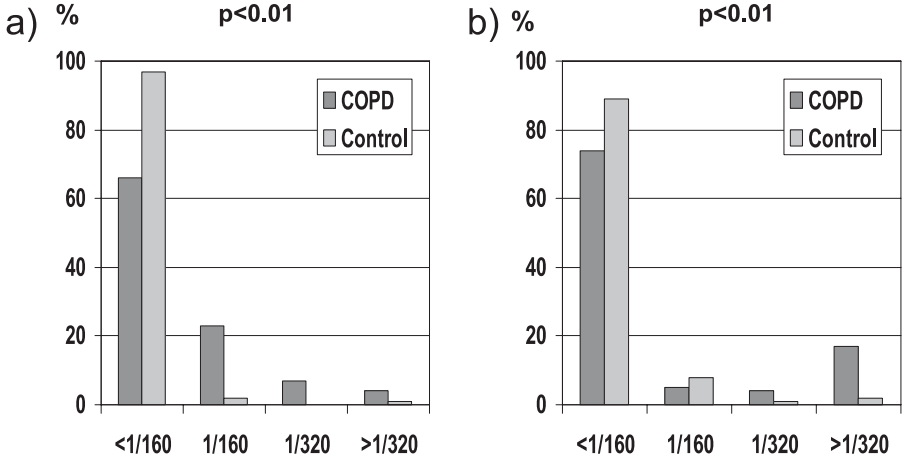

Figure 1. Frequency distribution of (*a*) antinuclear antibody (ANA) titers and (*b*) anti-tissue antibody (AT) titers in patients and controls. COPD = chronic obstructive pulmonary disease.

TABLE 3. PATIENTS CHARACTERISTICS BY AUTOANTIBODIES LEVELS

	ANA					AT				
	<1:160, n = 216 (66%)	1:160, n = 75 (23%)	1:320, n = 25 (7%)	>1:320, n = 12 (4%)	P Value	<1:160, n = 242 (74%)	1:160, n = 16 (5%)	1:320, n = 13 (4%)	>1:320, n = 54 (17%)	P Value
Age, yr, m (SD)	68 (8.6)	67.6 (8.3)	70.5 (7.2)	66.3 (10.8)	0.430	68.8 (8.1)	66.5 (8.8)	64 (8.3)	66.1 (10)	0.042
Males, n (%)	207 (96)	69 (92)	22 (88)	9 (75)	0.016	224 (93)	15 (94)	13 (100)	52 (96)	0.581
BMI, kg/m^2, m (SD)	28.2 (4.8)	28.5 (4.4)	28.1 (3.4)	29.3 (4.4)	0.838	28.1 (4.6)	28.5 (4.8)	29.1 (4.4)	28.8 (5)	0.739
Inhaled steroids users, n (%)	143 (66)	49 (65)	13 (52)	9 (75)	0.471	159 (66)	14 (88)	7 (54)	33 (61)	0.197
Current smokers, n (%)	66 (31)	29 (39)	5 (20)	4 (36)	0.319	65 (27)	5 (31)	6 (46)	27 (52)	0.005
Pack-years, m (SD)	70.8 (41.3)	67.1 (34.9)	58.8 (38.8)	57.2 (32.2)	0.360	67 (40.1)	64.8 (39)	85.6 (33.7)	71 (37.8)	0.377
Charlson index, m (SD)	2.1 (1.4)	2.1 (1.4)	2.6 (1.3)	1.4 (0.7)	0.083	2.1 (1.3)	2.1 (1.5)	2.2 (1.5)	2.3 (1.7)	0.644

Definition of abbreviations: ANA = antinuclear antibodies; AT = anti-tissue antibodies; BMI = body mass index.

(Figure 2B). By contrast, AT titers increased significantly with increasing airflow limitation (Figure 2C) and gas transfer limitation (Figure 2D). Multivariate models adjusted for age and smoking (identified as potential confounders in Table 3) showed that having AT-positive titer (⩾ 1:160) was associated with a reduction of 3.7 percentual units of FEV_1 ($P = 0.142$), and an increased risk (odds ratio = 2; confidence interval, 1.21–3.51) of moderate–severe D_{LCO} impairment (<60%) ($P = 0.016$). There was no relationship between autoantibody titers (ANA and AT) and any other of the COPD variables shown in Table 1. Specifically, the prevalence of positive ANA or AT titers was not related to BODE quartiles (Table 4).

DISCUSSION

Our results show that between a quarter and a third of patients with clinically stable COPD have abnormal titers of circulating ANA (34%) and AT (26%), a prevalence much higher than determined in healthy controls (3% and 6%, respectively) and also higher than that reported in previous studies in the general population (20, 24). AT titers were clearly elevated (⩾ 1:320) among patients with abnormal levels (⩾ 1:160), and AT (but not ANA) titers were related to lung function impairment (airflow limitation and gas transfer defects).

Previous Studies

ANA and AT are two nonspecific markers of autoimmunity (5). In 1976, Hodson and Turner-Warwick (25) reported that 28% of 50 patients with "severe chronic bronchitis," most likely what today would be called COPD, had increased titers of circulating ANA, a figure that was much higher than that determined simultaneously in age and sex-matched "nonbronchitic" controls (4%). This study, however, has gone mostly unnoticed to date. Our results confirm these previous findings in a larger and better characterized cohort by showing a remarkably similar

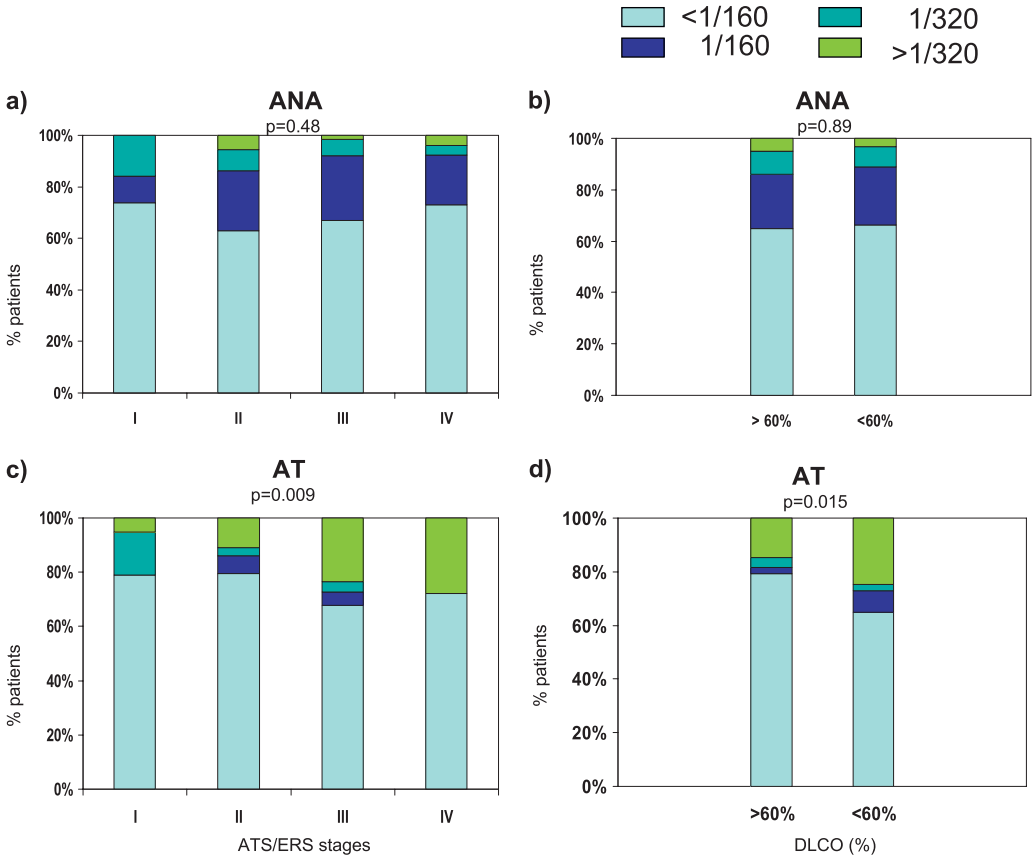

Figure 2. Frequency distribution of antinuclear antibody (ANA) titers and anti-tissue antibody (AT) titers according to the severity of airflow limitation (*a* and *c*) and gas transfer (D_{LCO}) impairment (*b* and *d*). ATS = American Thoracic Society; D_{LCO} = diffusing capacity of carbon monoxide; ERS = European Respiratory Society.

TABLE 4. NUMBER (AND PERCENTAGE) OF PATIENTS WITH DIFFERENT TITERS OF ANTINUCLEAR AND ANTI-TISSUE ANTIBODIES BY BODE QUARTILES

		BODE 0–1, n = 71 (*24%*)	BODE 2, n = 75 (*25%*)	BODE 3, n = 76 (*25%*)	BODE 4–10, n = 79 (*26%*)
ANA ($P = 0.760$)	<1/160	46 (65%)	48 (64%)	50 (66%)	56 (71%)
	1/160	16 (22%)	15 (20%)	21 (28%)	16 (20%)
	1/320	5 (7%)	8 (11%)	4 (5%)	5 (6%)
	>1/320	4 (6%)	4 (5%)	1 (1%)	2 (3%)
AT ($P = 0.167$)	<1/160	56 (80%)	57 (77%)	55 (72%)	52 (67%)
	1/160	3 (4%)	4 (5%)	5 (7%)	2 (3%)
	1/320	5 (7%)	3 (4%)	2 (3%)	2 (3%)
	>1/320	6 (9%)	10 (14%)	14 (18%)	21 (27%)

Definition of abbreviations: ANA = antinuclear antibodies; AT = anti-tissue antibodies; BODE = body-mass index (B), degree of airflow obstruction (O), functional dyspnea (D) and exercise capacity (E).

prevalence of circulating ANA (34%) in patients with COPD. Besides, our study extends these findings by quantifying the prevalence of AT autoantibodies. We found that a relatively high proportion of patients with COPD (26%) also had increased titers of AT and, at variance with ANA, 70% of AT-positive patients have very high levels (>1:320). These observations are in keeping with recent reports of circulating antibodies directed against components of the lung matrix (2) and epithelium (3) in patients with COPD, although it is worth noting that not all studies found such evidence (26–28). Differences in the types of patients studied (COPD, cystic fibrosis, A1AT deficiency, and lung fibrosis), specific antibodies quantified, and in sample size of previous studies can explain this discrepancy. It is also possible, as in fact our results show, that not all patients with COPD have evidence of autoimmunity and that only a subset of them develop it, as previously suggested (1).

Interpretation of Findings

Because this is an observational study, we can only speculate with the mechanisms underlying the observed associations. ANA and AT can either be nonspecific markers of an ongoing autoimmune response (5) or, alternatively, they may be directly involved in the pathogenesis of the disease. That ANA titers were not related to lung function (or current smoking or comorbidity), and that the most frequent antigen specificities of ANA in other autoimmune diseases (ENA, dsDNA) were negative, supports the former possibility (29, 30). By contrast, the fact that AT were inversely related to airflow limitation and D_{LCO} impairment (Figure 2) supports the latter possibility. In this context, it is of interest that more than 90% of AT-positive patients were SMA-positive. This may be relevant for airway remodeling in COPD because airway smooth muscle cells can synthesize extracellular matrix proteins, down-regulate matrix metalloproteinases, and up-regulate their tissue inhibitors (31). In any case, both alternatives are not mutually exclusive and provide further support to the involvement of an abnormal autoimmune response in the pathogenesis of COPD (1, 32).

The BODE index is a multicomponent score with prognostic value in COPD that combines pulmonary and extrapulmonary dimensions of the disease (12). We specifically explored if patients with higher BODE scores (quartiles) present a higher prevalence of positive ANA or AT antibodies titers, but found this not to be the case (Table 4). This observation suggests that the presence of autoantibodies is likely more related to the pulmonary components of the disease.

Systemic inflammation is normally considered an important pathogenic mechanism underlying many of the extrapulmonary effects of COPD (33). Yet, in keeping with the previous discussion on the BODE index, we did not find a clear relationship between ANA or AT titers and CRP values, a marker of systemic inflammation. Similarly, we did not find any relationship between the presence of autoantibodies and the use of inhaled steroids.

Strengths and Limitations

The large sample size of our cohort (one order of magnitude higher than that of previous reports investigating circulating antibodies in patients with COPD [2, 3, 25]), the wide range of COPD severity included in the analysis (Table 1), the careful phenotypic characterization, and the analysis of the relationship between circulating autoantibodies and several important domains of the disease are strengths of our study. However, our study also has some limitations. First, in keeping with previous studies (34), we found that ANA titers were higher in female patients (Table 3) but this was not the case in controls. Yet, because of the relatively low number of female patients studied (6.5%), we cannot be confident that females with COPD have higher ANA titers than male patients. In any case, their inclusion in the study did not influence its results because the results were unchanged when females were excluded from the analysis. Second, AT levels were associated with age and smoking status in patients with COPD in the bivariate analysis. It is well known that autoantibody titers increase with age and with smoking (29, 35). In fact, antielastin antibodies have been considered a marker of aging in animal models (36). Yet, we think that this does not invalidate our results because FEV_1 and D_{LCO} were expressed as percentage of the reference value and were, therefore, age-corrected, and smoking status was included in the multivariate analysis specifically. However, we cannot exclude that increased AT antibodies contribute mechanistically to the accelerated lung aging process that may characterize COPD (37). Finally, it is possible that the exclusion of patients with multiple hospitalizations, which has recently been demonstrated as a stable phenotype (38) before study enrolment, can bias the results against finding an association; conversely, the inclusion of patients with COPD who have not been hospitalized before has the potential to skew the data in the opposite direction. Acknowledging these limitations, however, we found it remarkable that a substantial percentage of the patients studied show abnormal autoantibody titers.

Conclusions

The results of this study show that between a third and a quarter of patients with clinically stable COPD present abnormal levels of circulating ANA and AT, and that the latter are related to impairment of lung function. These

observations provide further support to the hypothesis that the pathogenesis of COPD involves an autoimmune component (1).

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