CHEST

Natural Course of the Diffusing Capacity of the Lungs for Carbon Monoxide in COPD

Importance of Sex

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BACKGROUND: The value of the single-breath diffusing capacity of the lungs for carbon monoxide (D_{LCO}) relates to outcomes for patients with COPD. However, little is known about the natural course of D_{LCO} over time, intersubject variability, and factors that may influence D_{LCO} progression.

RESEARCH QUESTION: What is the natural course of D_{LCO} in patients with COPD over time, and which other factors, including sex differences, could influence this progression?

STUDY DESIGN AND METHODS: We phenotyped 602 smokers (women, 33%), of whom 506 (84%) had COPD and 96 (16%) had no airflow limitation. Lung function, including D_{LCO}, was monitored annually over 5 years. A random coefficients model was used to evaluate D_{LCO} changes over time.

RESULTS: The mean (± SE) yearly decline in D_{LCO} % in patients with COPD was 1.34% ± 0.015%/y. This was steeper compared with non-COPD control subjects (0.04% ± 0.032%/y; $P = .004$). Sixteen percent of the patients with COPD, vs 4.3% of the control subjects, had a statistically significant D_{LCO} % slope annual decline (4.14%/y). At baseline, women with COPD had lower D_{LCO} values (11.37% ± 2.27%; $P < .001$) in spite of a higher FEV_1 % than men. Compared with men, women with COPD had a steeper D_{LCO} annual decline of 0.89% ± 0.42%/y ($P = .039$).

INTERPRETATION: Patients with COPD have an accelerated decline in D_{LCO} compared with smokers without the disease. However, the decline is slow, and a testing interval of 3 to 4 years may be clinically informative. The lower and more rapid decline in D_{LCO} values in women, compared with men, suggests a differential impact of sex in gas exchange function.

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KEY WORDS: COPD; diffusing capacity of the lungs for carbon monoxide; lung function decline; sex

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ABBREVIATIONS: ATS = American Thoracic Society; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; D_{LCO} = diffusing capacity of the lungs for carbon monoxide; ERS = European Respiratory Society

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Take-home Points

Study Question: Is a low value of diffusing capacity of the lungs for carbon monoxide (DLCO) associated with poor outcomes in patients with COPD? What is the natural course of DLCO in these patients over time, and which other factors, including sex differences could influence this progression?

Results: Patients with COPD have an accelerated decline in DLCO compared with smokers without the disease. Sixteen percent of the patients with COPD, vs 4.3% of the control subjects, had a statistically significant DLCO % slope annual decline (4.14%/y). Women with COPD have a lower DLCO than men even though they have less airflow limitation. Women also appear to have a greater DLCO decline over time compared with men.

Interpretation: These results provide information about the testing frequency (3-4 years) needed to use of DLCO as a marker of COPD progression in clinical practice, as well as in trials of therapies aimed at improving emphysema. Women seem to have a different susceptibility to cigarette smoke in the alveolar or pulmonary vascular domains.

COPD is now the third leading cause of death worldwide and a major public health problem.[1] COPD is a complex and heterogeneous disease, and although there have been advances in the knowledge of its natural history, they have focused mostly on changes in FEV_1 over time.[2-5] Information about the natural course of other important phenotypic domains continues to be significantly limited because of the lack of prospective longitudinal studies.[2,6,7] One such important domain is that of the gas transfer properties of the lungs.

It was more than 100 years ago that Marie Krogh first studied the use of carbon monoxide (CO) to measure the diffusing capacity of gases in the lungs of humans.[8] However, its introduction into clinical practice became possible only after a single breath-holding technique (DLCO) was standardized 50 years later.[9] Since then, this variable, which at first was of interest only to physiologists, has been shown to provide important practical clinical information and has been identified as a surrogate marker of outcomes in diverse lung diseases.[10] In patients with COPD, cross-sectionally obtained low values of DLCO are associated with decreased exercise capacity[11,12] and worse health status.[13] In addition, low DLCO values help preclude surgical lung resection in patients with cancer[14] and relates to mortality independent of other clinical variables.[15] Also, a low DLCO value, as a marker of emphysema in smokers without airflow limitation, signals an increased risk for developing COPD over time.[16] Recently, the first longitudinal study completed in a small cohort (n = 155) of patients from Korea[17] provided information about the slow time course of DLCO progression; however, it did not use a control group of smokers without COPD and included only nine women. Importantly, it reported the change only as the annual median decline for the group and not as individual decline, providing no information about individual variability.

We hypothesized that, just as it has been shown for FEV_1, the gas transfer domain, as measured by the DLCO, indicates a heterogeneous progression of COPD in individuals with the disease. We also hypothesized that other factors, including sex differences, could influence this progression. To test this hypothesis, we analyzed the long-term evolution of patients with COPD and smoker control subjects, in a well-characterized cohort using DLCO measurements prospectively obtained. This information should help define the implementation and frequency of this pulmonary test in the longitudinal assessment of patients with COPD, a practice gap that remains unfilled.

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Methods

Subject Study Cohort

The COPD History Assessment in Spain (CHAIN) is an ongoing observational study of patients with COPD that began enrollment in January 2010 at 24 university hospitals in Spain.[18] COPD was defined by a smoking history of ≥ 10 pack-years and a postbronchodilator $FEV_1/FVC < 0.7$ after administration of 400 μg of albuterol. Patients were stable for at least 6 weeks and received guideline-directed optimal medical therapy.[1] Exclusion criteria included alpha-1 antitrypsin deficiency or uncontrolled comorbidities such as malignancy or other confounding diseases that could interfere with the study. Data analyzed in the present study were taken at baseline recruitment and then annually over 5 years; the last visit for patients occurred on May 31, 2020. Patient data were anonymized with hierarchical access control to guarantee that information was secured. All participants signed the informed consent form approved by the ethics committee (Comité de Etica de Investigación, Hospital Universitario Nuestra Señora la Candelaria, Tenerife, IRB No. 258/2009).

Clinical and Physiologic Measurements

The methodologic aspects of the CHAIN study have been published previously.[18] In summary, trained staff recorded information on age, sex, and BMI at baseline and at subsequent yearly visits. Smoking status was determined by history and confirmed by CO-oximetry (piCO Smokerlyzer; Bedfont Scientific) during each visit, performed at the same time as the lung function tests. All tests were performed in the early morning. A questionnaire helped determine current or former smoker status and pack-years. Pulmonary function tests were performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[19] Diffusing capacity of the lungs for carbon monoxide was determined by the single-breath technique, in accordance with the ERS/ATS guidelines,[20] corrected by the hemoglobin value. Reference values were those of the European Community for Steel and Coal[21] and, for a group of patients (n = 201), we also tested the correlation of DLCO % predicted with the Global Lung Function Initiative (GLI) (e-Fig 1).[22,23] Arterial blood gases were measured with participants in the sitting position while breathing room air. The 6-min walk distance was measured according to the ATS guideline.[24] Dyspnea was evaluated with the modified Medical Research Council dyspnea scale. FEV_1, BMI, 6-min walk distance, and modified Medical Research Council values were integrated into the BODE (BMI, airflow obstruction, dyspnea, and exercise capacity) index.[25] The associated comorbidity load was determined with the Charlson index.[26] Hospitalizations and all-cause mortality were recorded, using information obtained from the family, and then confirmed by reviewing medical records as published previously.[18]

Statistical Analysis

Data are summarized as relative frequencies for categorical variables, mean (SD) for normally distributed variables, and median (10th-90th percentile) for nonnormal data. Comparisons were made between groups using Pearson χ^2 test, the Kruskal-Wallis H test, or the Mann-Whitney U test and one-way analysis of variance or Student t-test as appropriate. Correlations were estimated using Spearman or Pearson linear coefficients. Using all the patients in the study population, a random coefficients model (mixed-effects linear model) with random intercept and slope was applied to annual DLCO %, including COPD, sex, age, current smoker, pack-years, and FEV_1 % as covariates. Evaluation of the interactions of these variables over time allowed us to calculate the DLCO decline rate. In addition, models for patients with COPD and smokers without COPD were derived, using those covariates that had been significant. We performed a mortality Cox regression test including the main variables related to DLCO longitudinal analysis. We also performed a survival analysis, using a multivariate Cox proportional hazards regression model including the main variables related to DLCO longitudinal analysis, to evaluate the effect of DLCO on adjusted overall survival on relevant covariates such as sex.[27] A repeated-measures analysis of variance was applied to analyze the evolution of DLCO over the study period, including the time-by-sex interaction. In an effort to smooth the series and increase the number of individuals available throughout the study period, the definition of three periods of time (initial, intermediate, and final) was considered to be the moving average of two measurements in 2 years. In addition, the difference in FEV_1 % between the initial and final periods was included as a covariate to study the effect on the evolution of the DLCO %. Trend analysis was performed to estimate the individual slope of variables over time. A linear regression model with year as the explanatory variable was used to estimate the slope of the DLCO decline when at least three measurements were available. A significance level was established as a two-tailed P value < .05. Calculations were made with SPSS 25.0 (IBM).

Results

Characteristics of the Participants

The study population included 602 individuals (women, 33%). There were 506 (84%) with COPD, and 96 (16%) were smokers without COPD (control subjects). The classification of COPD vs control subject, using the lower limit of normal vs the FEV_1/FVC, would keep more than 95% of subjects in the same group and not influence the results. The baseline characteristics of the participants are shown in Table 1. The group of patients with COPD included more men; they were slightly older, had a greater pack-year history, but a lower proportion of current smokers. As expected, they had worse lung function, less exercise capacity, higher dyspnea and BODE index scores, more comorbidities, and higher hospitalizations and mortality. However, the two groups had similar hemoglobin levels and BMI values.

Longitudinal Changes in DLCO

The mean (± SE) rate of change in DLCO % over the 5 years in patients with COPD indicated a decline of 1.34% ± 0.015%/y and was higher compared with control subjects (0.04% ± 0.032%/y), that is, smokers without COPD ($P = .004$) (Fig 1). The rate of change was associated with the number of DLCO measurements for the COPD population ($P = .013$) but not for smokers without COPD ($P = .73$). These differences in the mean rate of decline were observed only for the group with one or two measurements

TABLE 1] Baseline Characteristics of Subjects Included in Study, Stratified by Presence of COPD and Number of D_{LCO} Assessments

Characteristic	COPD				Smokers Without COPD				
	Total (N = 506)	1-2 Period[a] (n = 201)	3-6 Period[a] (n = 305)	*P* Value	Total (N = 96)	1-2 Period (n = 27)	3-6 Period (n = 69)	*P* Value	*P* Value[b]
Sex (male)[c]	406 (80%)	149 (74%)	257 (84%)	.004	58 (60%)	19 (70%)	39 (56%)	.155	< .001
Age, y[d]	64 (8.9)	65 (9.0)	64 (8.8)	.542	55 (10.1)	56 (11.0)	55 (9.8)	.683	< .001
Pack-years[d]	59 (27)	60 (27)	58 (27)	.442	45 (24)	48 (23)	43 (24)	.337	< .001
Smokers active[c]	192 (38%)	87 (43%)	105 (34%)	.055	61 (64%)	19 (73%)	42 (61%)	.194	< .001
BMI, kg/m^2 [d]	27.4 (5.0)	27.6 (5.5)	27.3 (4.7)	.441	28.4 (4.9)	28.4 (5.7)	28.4 (4.6)	.954	.087
Hemoglobin, g/dL[d]	14.8 (1.32)	14.4 (1.41)	14.9 (1.25)	.003	15.3 (1.25)	15.8 (0.72)	15.1 (1.38)	.173	.065
CO-oximetry, ppm[e]	5.0 (2-19)	4.0 (2-17.4)	5.0 (2-20)	.103	10.0 (3-33)	12 (3-32.9)	10 (3-37)	.637	< .001
D_{LCO}, mmol/mL/kPa[d]	5.18 (1.98)	4.46 (2.02)	5.35 (1.94)	.016	7.86 (2.35)	7.46 (2.43)	7.95 (2.29)	.154	< .001
D_{LCO}, %[d]	65.0 (23.6)	62.8 (25.4)	66.3 (22.4)	.118	84.6 (19.3)	81.1 (17.9)	85.9 (19.7)	.291	< .001
K_{CO}, %[d]	73.4 (25.1)	70.8 (25.2)	75.2 (24.9)	.062	92.4 (20.6)	88.4 (18.2)	94.2 (21.5)	.226	< .001
FEV_1, L[d]	1.61 (0.63)	1.50 (0.60)	1.69 (0.64)	.001	2.88 (0.75)	2.90 (0.93)	2.87 (0.68)	.856	< .001
FEV_1, %[d]	57.7 (20.3)	56.0 (20.9)	58.7 (19.8)	.147	95.9 (13.8)	91.9 (18.3)	97.5 (11.3)	.147	< .001
FVC, L[d]	3.14 (0.90)	2.93 (0.85)	3.28 (0.91)	< .001	3.77 (1.00)	3.81 (1.21)	3.75 (0.92)	.816	< .001
FVC, %[d]	86.0 (21.1)	84.3 (21.5)	87.2 (20.8)	.128	100.1 (15.2)	96.4 (19.7)	101.6 (12.9)	.216	< .001
FVC_1/FVC, %[d]	51.2 (12.1)	50.9 (12.4)	51.4 (11.9)	.695	77.8 (6.0)	78.0 (6.8)	77.7 (5.6)	.794	< .001
6MWD, m[d]	471 (96)	445 (108)	488 (83)	< .001	534 (89)	538 (102)	533 (85)	.808	< .001
Charlson index[e]	0 (0-3)	0 (0-3)	0 (0-2.4)	.105	0 (0-1)	0 (0-3.9)	0 (0-0)	.055	.007
Dyspnea (mMRC)[e]	1 (0-3)	1 (0-3)	1 (0-2)	.248	0 (0-1.4)	0 (0-2)	0 (0-1)	.969	< .001
Pa_{O_2}, mm Hg[d]	70.0 (10.8)	69.1 (11.9)	70.8 (9.9)	.191	75.8 (13.1)	74.6 (14.1)	76.0 (13.1)	.795	.004
BODE index[e]	1 (0-4)	2 (0-6)	1 (0-4)	.005	0 (0-1)	0 (0-2.4)	0 (0-1)	.178	< .001
Hospitalization (at least one during the study period)[c]	137 (27%)	47 (23%)	90 (30%)	.078	13 (14%)	2 (8%)	11 (16%)	.247	.003
Hospitalization per patient-year[e]	0 (0-0.7)	0 (0-2)	0 (0-0.4)	.939	0 (0-0.3)	0 (0-1.5)	0 (0-0.3)	.628	.013
Respiratory mortality[c]	54 (11%)	30 (15%)	24 (8%)	.009	1 (1.0%)	1 (3.7%)	…	.281	.001
Global mortality[c]	130 (26%)	83 (41%)	47 (15%)	< .001	3 (3.1%)	3 (11.1%)	…	.020	< .001

6MWD = 6-minute walk distance; BODE = BMI, airflow obstruction, dyspnea, and exercise; D_{LCO} = diffusing capacity of the lungs for carbon monoxide; K_{CO} = CO transfer coefficient; mMRC = modified Medical Research Council.

[a]Subjects with fewer than three measurements (1-2 period) vs three or more measurements (3-6 period).

[b]Comparison between subjects with COPD and smokers without COPD.

[c]Data presented as number (percentage).

[d]Data presented as mean (SD).

[e]Data presented as median (10th percentile-90th percentile).

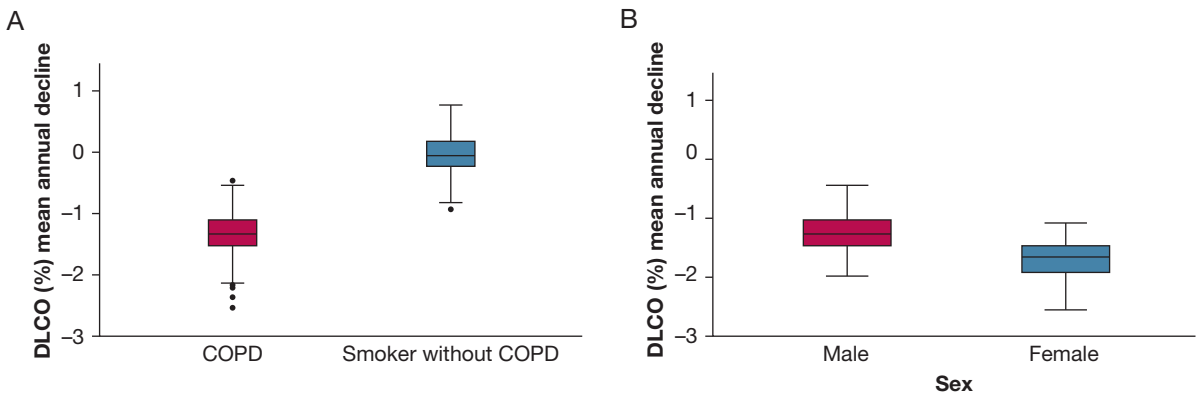

Figure 1 – *Values of DLCO (%) over 5 years. A, Values for all patients with COPD and smokers without COPD. B, Comparison of changes in DLCO (%) in men and women with COPD. DLCO = diffusing capacity of the lungs for carbon monoxide.*

(1.40% ± 0.027%/y; $P = .006$), and there were no differences between those with three (1.33% ± 0.037%/y) vs four to six measurements (1.31% ± 0.019%/y). Although 26% of the patients with COPD died during the study, the mean rates of change did not differ significantly from those who completed the study compared with those who did not (1.31% ± 0.026%/y vs 1.36% ± 0.018%/y; $P = .118$). Age, BMI, FEV_1 %, and presence of active smoking were not associated with differences in the longitudinal change in DLCO values in patients with COPD.

Being a woman was the only factor that related to the annual rate of change in DLCO (Table 2). Women with COPD had lower baseline DLCO values (–11.37% ± 2.27%; $P < .001$) than men with the disease in spite of a higher FEV_1 % than men (64.8% vs 55.9%; $P < .001$). Women exceeded the annual rate of DLCO decline by

TABLE 2] Effects of Patient Characteristics on Baseline DLCO and on Annual Rate of Change in DLCO

	Baseline DLCO		Annual Rate of Change in DLCO	
Characteristic	Effect on Baseline DLCO	*P* Value	Effect on Annual Rate of Change in DLCO	*P* Value
Total model				
COPD, yes vs no	−1.41 ± 2.50	.573	−1.19 ± 0.41	.004
Age, per y	−0.20 ± 0.09	.031	−0.01 ± 0.01	.647
Sex, female vs male	−10.40 ± 2.04	< .001	−0.59 ± 0.34	.096
BMI, per kg/cm^2	1.45 ± 0.16	< .001	−0.05 ± 0.03	.074
Smoking status				
Current smoker, yes vs no	−2.32 ± 1.70	.172	0.01 ± 0.30	.976
Pack-years, per pack-year	0.04 ± 0.03	.363	0.002 ± 0.005	.633
FEV_1 (%) baseline, per %	0.47 ± 0.04	< .001	0.01 ± 0.01	.207
COPD model				
Age, per y	−0.31 ± 0.10	.002	−0.01 ± 0.01	.401
Sex, female vs male	−11.37 ± 2.27	< .001	−0.89 ± 0.42	.039
BMI, per kg/cm^2	1.54 ± 0.17	< .001	−0.04 ± 0.03	.121
FEV_1 (%) baseline, per %	0.48 ± 0.04	< .001	0.004 ± 0.007	.558
Smoker without COPD model				
Age, per y	0.41 ± 0.16	.014	−0.01 ± 0.02	.514
Sex, female vs male	−10.67 ± 3.50	.003	−0.27 ± 0.50	.596
BMI, per kg/cm^2	1.40 ± 0.34	< .001	−0.10 ± 0.05	.065
FEV_1 (%) baseline, per %	0.46 ± 0.12	< .001	−0.01 ± 0.02	.459

Data are presented as mean ± SE. DLCO = diffusing capacity of the lungs for carbon monoxide.

TABLE 3] Evolution of D_{LCO} and Other Functional Variables in Patients With COPD and Smokers Without COPD Over Time: Patients With Three or More Measures of D_{LCO}

	COPD (n = 305)				Smokers Without COPD (n = 69)			
Variable	Initial	Intermediate	Final	*P* Value	Initial	Intermediate	Final	*P* Value
BMI, kg/m^2[a]	27.7 (4.4)	27.7 (4.5)	27.7 (4.7)	.898	28.6 (4.5)	28.7 (4.5)	28.9 (4.4)	.341
D_{LCO}, %[a]	64.2 (20.8)	59.9 (20.7)	57.4 (21.3)	< .001	83.1 (20.9)	80.6 (20.9)	80.8 (20.6)	.032
K_{CO}, %[a]	75.2 (24.7)	74.3 (24.4)	69.3 (25.3)	< .001	94.0 (20.9)	93.2 (20.9)	90.7 (21.6)	.019
Alveolar volume, L[a]	5.26 (1.07)	5.15 (1.11)	5.10 (1.14)	< .001	5.21 (0.96)	5.19 (0.90)	5.13 (0.99)	.406
FEV_1, L[a]	1.67 (0.63)	1.61 (0.62)	1.52 (0.64)	< .001	2.86 (0.75)	2.79 (0.74)	2.66 (0.78)	.007
FEV_1, %[a]	58.2 (19.0)	57.1 (19.0)	55.7 (18.9)	< .001	97.0 (11.7)	97.2 (12.3)	96.4 (13.6)	.519
FVC, L[a]	3.26 (0.90)	3.21 (0.89)	3.10 (0.90)	< .001	3.78 (0.95)	3.74 (1.00)	3.67 (1.02)	.005
FVC, %[a]	86.0 (19.9)	86.3 (20.4)	84.4 (21.4)	.023	102.1 (12.7)	101.3 (13.0)	101.2 (13.1)	.700
FVC_1/FVC, %[a]	51.6 (11.9)	50.3 (12.4)	50.0 (11.6)	< .001	76.6 (5.2)	74.9 (5.2)	74.6 (6.2)	.019
BODE index[b]	1.5 (0-4)	2 (0-4.5)	2 (0-5)	< .001	0 (0-1)	0 (0-1)	0 (0-1)	.206
Smokers active[c]	37.7%	34.1%	28.2%	.034	65.2%	58.8%	47.1%	.033

BODE = BMI, airflow obstruction, dyspnea, and exercise; D_{LCO} = diffusing capacity of the lungs for carbon monoxide; K_{CO} = CO transfer coefficient.
[a]Data are presented as mean (SD).
[b]Data are presented as median (10th percentile-90th percentile).
[c]Data are presented as number (percentage).

0.89% ± 0.42%/y ($P = .039$), compared with men. These differences were not explained by smoking habit (Table 2, e-Tables 1 and 2). There was no influence of center location on rate of DLCO decline (analysis not shown).

Analysis of Subgroups

We identified 305 patients with COPD and 69 smokers without COPD with at least three DLCO measurements over the 5 years (e-Fig 2). The patients with COPD with at least three DLCO measurements were similar to those with fewer than three DLCO measurements in terms of baseline DLCO, BMI, FEV_1 %, and Pao_2. However, they walked a greater distance in the 6-min walk test, had a lower BODE index, and lower mortality. There were no significant differences in the smokers without COPD (Table 1). Table 3 shows that in those patients with COPD, the DLCO %, FEV_1 %, and proportion of active smokers decreased over the 5 years of observation.

On the basis of the individual slope change, 50 patients with COPD (16.4%) (Fig 2) and three smokers without COPD (4.3%) showed a statistically significant yearly loss of DLCO %: –4.139 (95% CI, –4.622 to –3.622) and –4.440 (95% CI, –9.903 to 1.023), respectively (Table 4). In patients with COPD, more women (26%) than men (14%) were in the DLCO decliners group ($P = .005$).

Forty-seven patients with three DLCO measurements died during the follow-up period, and there was no significant difference in mortality between patients with COPD with and without slope DLCO decline ($P = .763$; e-Table 3). There were also no significant differences in hospitalization per patient-year ($P = .447$).

Discussion

This prospective observational study of patients with COPD attending pulmonary clinics has several important findings: First, over 5 years of observation, a proportion of patients with COPD (16%) had a statistically significant annual decline in DLCO. This proportion is four times higher than that of smokers without airflow limitation. Second, with better spirometric values at baseline and throughout the study, smoking women with and without COPD had a lower DLCO than men. Importantly, they also had a greater DLCO decline over the 5 years of observation. These results provide information about the testing frequency needed to use DLCO as a marker of COPD progression in clinical practice, as well as in trials of therapies aimed at improving emphysema. The results also suggest that compared with men, women have a different susceptibility to cigarette smoke in the alveolar or pulmonary vascular domains.

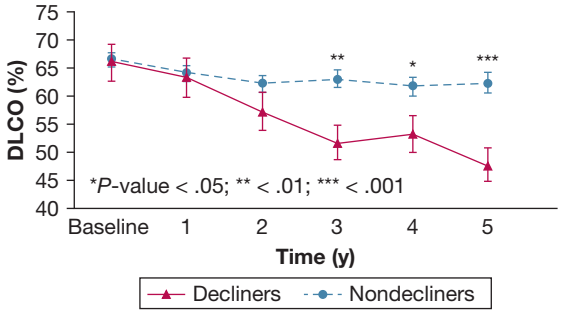

Figure 2 – *Evolution of the mean annual DLCO (%) for patients with COPD depending on its decline was statistically significant negative (decliners) vs the rest of the group (nondecliners).*

DLCO Over Time

Longitudinal studies with repeated measures of DLCO in respiratory diseases have been reported primarily in interstitial lung disease, with a decrease ≥ 15% over 6 to 12 months shown to be associated with increased mortality risk independent of other cross-sectional measures.[28] This has positioned the DLCO as an interstitial lung disease activity biomarker that could guide progression or response to treatment. In COPD, the prognostic information on DLCO has only been reported using single cross-sectional measurements.

To our knowledge, the current report represents the first observational study in patients with COPD compared with smokers without COPD, who served as control subjects. Our data on the mean annual decrease in DLCO in the patients with COPD were similar to those recently published in the multicenter observational study by Kang et al,[17] completed in a smaller number of patients with COPD (n = 155). That study had only nine women and, thus, they could not examine the influence of sex on DLCO progression.

The observed decline in DLCO confirms that COPD progresses relatively slowly, with 16% of the patients showing a statistically significant annual decline over the 5 years of observation. However, this proportion was four times higher than that of the group of smokers without COPD. To place these findings in a practical clinical context we have to relate our findings with those reported in the literature in two cross-sectional COPD studies.[13,29] Analysis of the COPDGene cohort[13] has shown that a 10% lower value of DLCO is associated with a significant impairment in exercise capacity and an increased risk of hospitalizations independent of FEV_1. In another study of a smaller cohort, a lower DLCO value was associated with a lower 6-min walking distance.[12] In our study, there was a numerical difference in the

TABLE 4] Slope Values of DLCO Change in Patients With Three or More Measurements

Slope	COPD (n = 305)					Smokers Without COPD (n = 69)				
	No.	Mean	95% CI		Mean	95% CI	No.	Mean	95% CI		Mean	95% CI
Significantly negative	50	−4.139	−4.622 to −3.657	]			3	−4.440	−9.903 to 1.023	]		
Nonsignificantly negative	180	−3.017	−3.418 to −2.616	}			49	−2.026	−2.579 to −1.474	}		
Nonsignificantly positive	71	1.552	1.221 to 1.882	]	−1.647	−2.044 to −1.251	17	1.548	0.950 to 2.146	]	−1.106	−1.684 to −0.527
Significantly positive	4	3.207	1.356 to 5.058				…	…	…			

Slope values provided according to their direction (positive for increase, negative for a decrease) and statistical significance. DLCO = diffusing capacity of the lungs for carbon monoxide.

number of hospitalizations in the DLCO decliners group, but it failed to reach statistical significance. Our findings, and those of the Korean study, suggest that patients with COPD do not need an annual follow-up measurement of DLCO and that perhaps this test can be performed every 3 to 4 years, even in the highest risk group such as women, as we discuss below.

DLCO in Women

The DLCO at baseline in our study was lower in women than in men with COPD, even though they had higher spirometric values at baseline. This has been reported previously, but has not been adequately discussed and has never been prospectively followed.[29,30] We show that women have a tendency to a more pronounced decrease in DLCO over time despite having a better FEV_1 than men, both at baseline and at the end of 5 years. This difference in DLCO needs to be added to other characteristics described for women with COPD. It is known that women report more dyspnea and worse health status than men,[31] and they have a marked tendency to develop some comorbidities such as anxiety, depression, malnutrition, lung adenocarcinoma, and osteoporosis.[32] Importantly, in studies using CT imaging, women with COPD show smaller emphysematous lesions than men.[33] We can only speculate about some potential reasons to explain the contradictory findings of our study (lower DLCO) and that of less emphysema by CT imaging in other studies.[33] One reasonable explanation is that women have a pulmonary vascular phenotype that may be related to the smoking habit. There may be a loss of the distal arterial capillaries (pruning) with relative preservation of the airways and alveoli.[34] It could also depend on the way smoke is inhaled in women[35] or on other hormonal (estrogenic) factors.[33] These pathophysiologic aspects were outside the scope of this study. However, some support for the potential vascular susceptibility to cigarette smoke in women is provided by the higher prevalence of pulmonary vascular hypertension in this sex.[36]

This study has some limitations. First, not all patients initially enrolled had all the annual measurements of their DLCO over the 5 years. Although the dropout of some subjects can affect the measurement of DLCO decline, we used a random coefficients model (mixed-effects linear model) to minimize this effect. In fact, the differences observed in patients with COPD with fewer measurements compared with those with more measurements were clinically irrelevant. Second, there

may be intrinsic variability in the instruments used to measure DLCO, an area that remains poorly studied. However, daily calibration and biological control subjects minimized this variability. Further, the observed differences in the proportion of rapid DLCO decliners in subjects with COPD vs smokers without obstruction, in a multicenter study, support its practical clinical use in different centers. Third, the current study does not include CT imaging of the chest, a test that would have provided insight into the contribution of factors, such as the behavior of the vascular compartment (vascular pruning), to the pathophysiologic explanation of our observations. This is an area that warrants further study in patients with COPD, but does not negate the importance of our findings. Finally, our results should be replicated in other populations and ethnic groups.

Interpretation

In summary, this longitudinal observational study shows that the decline in DLCO is on average more rapid in patients with COPD than in smoker control subjects. On average, 3 to 4 years is needed to observe a significant decline in DLCO. This information is relevant to help implement the use of this test in clinical practice and therapeutic trials. Importantly, we found that women with COPD have a lower DLCO than men, independent of airflow limitation, and appear to have a greater decline over time. This suggests a differential impact of sex among those factors influencing lung gas diffusion. Further studies in other populations should validate our results.

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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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