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Natural Course of the Diffusion Capacity for Carbon Monoxide in COPD: Importance of Sex.

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ABSTRACT

Background: The value of the single breath diffusion capacity for carbon monoxide (DLco) relates to outcomes in COPD patients. However, little is known about the natural course of DLco over time, the intersubject variability and the factors that may influence DLco progression.

Research Question: What is the natural course of DLco in COPD patients over time, and which other factors, including sex differences could influence this progression?

*Study Design and Methods***:** We phenotyped 602 smokers (33% women) of which 506 (84%) had COPD and 96 (16%) had no airflow limitation. Lung function including DLco was monitored annually over five years. A random-coefficient model was used to evaluate DLco changes over time.

Results: The mean (±SE) yearly decline in DLco% in COPD patients was 1.34 ± 0.015%/year. This was steeper compared with non-COPD controls (0.04 ± 0.032%/year, p=0.004). Sixteen percent of the COPD patients vs 4.3% of the controls, had a statistically significant DLco% slope annual decline (4.14%/year). At baseline, women with COPD had lower DLco values (11.37 ± 2.27%, p <0.001) in spite of a higher FEV_1% than men. Compared to men, women with COPD had a steeper DLco annual decline of 0.89 ± 0.42 %/year, (p= 0.039).

Interpretation: Patients with COPD have an accelerated decline in DLco compared to 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 of DLco values in women compared to men, suggests a differential impact of sex in gas exchange function.

Chronic obstructive pulmonary disease (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 mostly focused on changes in forced expiratory volume in the first second (FEV_1) over time (2-5). Information about the natural course of other important phenotypic domains continue to have significant limitations due to 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 over 100 years ago, that Marie Krogh first studied the use of carbon monoxide (CO) to measure the diffusion capacity of gases in the lungs in humans (8). However, its introduction into clinical practice became only possible after a single breath holding technique (DLco) was standardized 50 years later (9). Since then, this variable, that at first was only of interest to physiologist, 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 overtime (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, but did not use a control group of smokers without COPD and only included 9 women. Importantly, it only reported the

change as annual median decline for the group and not as individual decline, providing no information about the individual variability.

We hypothesized that just as it has been shown for FEV_1, individuals with COPD have a heterogeneous progression of the disease in the gas transfer domain as measured by the DLco. We also hypothesized that other factors, including sex differences, could influence this progression. To test this hypothesis, we analyzed the long-term evolution of COPD patients and smoker controls, 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 patient with COPD, a practice gap that remains unfilled.

METHODS

Subjects Study cohort

The COPD History Assessment In SpaiN (CHAIN) is an ongoing observational study of COPD patients that began enrollment in January 2010 at 24 university hospitals in Spain (18). COPD was defined by a smoking history ≥10 pack-years and a post-bronchodilator FEV1/FVC <0.7 after 400 μg of albuterol. Patients were stable for at least 6 weeks and received guideline directed optimal medical therapy (1). Exclusion criteria were alpha-1-antitrypsin deficiency or uncontrolled co-morbidities such as malignancy or other confounding diseases that could interfere with the study. Data analyzed in the present study were taken from the baseline recruitment and monitored them annually over five years, the last visit occurring in May 31th, 2020. Patient data were anonymized with hierarchical access control in order to guarantee that information was secured. All participants signed the informed-consent approved by the ethics committee ("Comité de Etica de Investigación, Hospital Universitario la Candelaria, Tenerife, IRB nº: 258/2009").

Clinical and physiological measurements

The methodological aspects of the CHAIN study have been published previously (18). In summary, trained staff recorded information on age, gender, and body mass index (BMI) at baseline and 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 following the American Thoracic Society / European Respiratory Society (ATS / ERS) guidelines (19). Diffusion capacity for carbon monoxide was determined with the single-breath technique following the European Respiratory Society/ATS guidelines (20), corrected by the haemoglobin value. Reference values were those of the European Community for Steel and Coal (ECSC) (21) and for a group of patients (N=201), we also tested the correlation of DLco% predicted with the Global Lung Function Initiative (GLI; Figure S1 supplemental material) (22, 23). Arterial blood gases were measured in the sitting position while breathing room air. The 6-minute walk distance (6MWD) was measured following the ATS guideline (24). Dyspnea was evaluated with the mMRC scale. FEV_1, BMI, 6MWD, and mMRC values were integrated into the BODE index (25). The associated co-morbidity 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 (standard deviation) for normally distributed variables and median (10th–90th percentile) for non-normal data. Comparisons were made between groups using Pearson's chi-squared test, the Kruskal-Wallis H test or the Mann-Whitney U test and one-way Analysis of Variance or Student's *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 on annual DLco% including COPD, sex, age, current smoker, pack-years and FEV_1% as covariates. The evaluation of the interactions of these variables over time allowed us to calculate the DLco decline rate. Additionally, models for COPD patients and smokers without COPD were performed using those covariates that had been significant. We performed a mortality Cox regression test including the main variables related with DLco longitudinal analysis. We also performed a survival analysis using a multivariate Cox proportional hazards regression model including the main variables related with DLco longitudinal analysis to evaluate the effect of DLco on adjusted overall survival on relevant covariates such as gender (27). A repeated measures analysis (RM-ANOVA) was applied to analyze the evolution of the DLco over the study period, including the time-by-sex interaction. Trying 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 as the moving average of two measurements in two years. Additionally, the difference in FEV_1% between the initial and final period 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 < 0.05. Calculations were made with SPSS 25.0 (IBM SPSS, Armonk, NY).

RESULTS

Characteristics of the Participants

The study population included 602 individuals (33% women). There were 506 (84%) with COPD, while 96 (16%) were smokers without COPD (controls). The classification of COPD versus control using the lower limit of normal versus the FEV1/FVC would keep over 95% of subjects in the same group and not influence the results. The baseline characteristics of the participants are shown in the table 1. The group of COPD patients included more men, were slightly older, had a greater pack-year history, but a lower proportion of current smokers; and as expected, 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 year in COPD patients was a decline of 1.34 ± 0.015%/year and was higher compared with controls (0.04 ± 0.032%/year) smokers without COPD (p= 0.004). The rate of change was associated with the number of DLco measurements for the COPD population (p= 0.013) but not in smokers without COPD (p= 0.73). These differences in the mean rate of decline were observed only for the group with one or two measurements (1.40 ± 0.027%/year, p= 0.006)) and there were no differences between those with three (1.33 ± 0.037%/year) vs four to six

measurements (1.31 ± 0.019%/year). 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 to those that did not (1.31 ± 0.026%/year vs 1.36 ± 0.018%/year, p= 0.118). The age, BMI, FEV_1% and the presence of active smoking was 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<0.001) than men with the disease in spite of a higher FEV_1% than men (64.8% vs 55.9%, p <0.001). Women exceeded the annual rate of DLco decline by 0.89 ± 0.42 %/year, (p= 0.039) compared to men. These differences were not explained by smoking habit (Tables 2, S1 and S2). There was no influence of center location on rate of DLco decline (analysis not shown).

Analysis of Subgroups

We identified 305 COPD patients and 69 smokers without COPD with at least 3 DLco measurements over the 5 years (Figure S2). The COPD patients with ≥ 3 DLco measurements were similar to those with < 3 DLco measurements in terms of baseline DLco, BMI, FEV_1% and PaO_2. However, they walked more distance in the 6MWT, had a lower BODE index and lower mortality. There were no-significant differences in the smokers without COPD (Table 1). Table 3 show that in those patients with COPD, the DLco%, FEV_1% and the proportion of active smokers decreased over the 5 years of observation.

Based on the individual slope change, 50 (16.4%) patients with COPD (Figure 2) and 3 (4.3%) smokers without COPD showed a statistical significant yearly loss of DLco %: -4.139 (95% CI: -4.622; -3.622) and -4.440 (95% CI: -9.903; 1.023) respectively (Table

4). In patients with COPD, more women (26%) than men (14%) were in the DLco decliners group (p= 0.005).

Forty-seven patients with 3 DLco measurements died during the follow-up period, and there was no significant difference in mortality between COPD patients with and without slope DLco decline (p=0.763; Table S3). There were also no significant differences in hospitalization per patient-year (p= 0.447).

DISCUSSION

This prospective observational study of patients with COPD attending pulmonary clinics has several important findings: First, over 5 years of observation, a proportion (16%) of patients with COPD have a statistically significant annual decline of the DLco. This proportion is four times higher that of smokers without airflow limitation. Secondly, 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 of 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.

DLco over time

Longitudinal studies with repeated measures of DLco in respiratory diseases have primarily been reported in interstitial lung disease (ILD), with a decrease ≥15% over 6-12 months shown to be associated with increased mortality risk independent of other cross-sectional measures (28). This has positioned the DLco as an ILD activity biomarker that could guide progression or response to treatment. In COPD, the prognostic information of DLco has been only 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 controls. 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 (n=155) COPD patients. That study only had 9 women and thus, they could not examine the influence of sex on DLco progression.

The observed decline of DLco confirms that COPD progresses relatively slow, with 16% of the patients showing a statistically significant annual decline over the 5 years of observation. However, this proportion was four times higher 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 in 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 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 COPD patients 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 shall 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 before, 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 the 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, 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 computerized tomography, 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 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 other hormonal (estrogenic) factors (33). These pathophysiological aspects were outside the scope of this study. However, some support to 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 the DLco decline, we used a random coefficients model (mixed effects linear model) in order to minimize this effect. In fact, the differences observed in COPD patients with few measurements compared with those with more measurements were clinically irrelevant. Secondly, there may be intrinsic variability in the instruments used to measure DLco, an area that remains poorly studied. However, daily calibration and biological controls minimized this variability. Further, the observed differences in the proportion of rapid DLco decliners in subjects with COPD versus smokers without obstruction in a multicenter study, support its practical clinical use in different centers. Thirdly, the current study does not include computerized tomography 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 pathophysiological

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 of DLco is on average more rapid in patients with COPD than in smokers controls. On average, 3 to 4 years are 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 in those factors influencing lung gas diffusion. Further studies in other populations should validate our results.

Take-Home Point:

Study question: Is a low value of diffusion capacity for carbon monoxide (DLco) associated with poor outcomes in patients with chronic obstructive pulmonary disease (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 to smokers without the disease. Sixteen percent of the COPD patients vs 4.3% of the controls, had a statistically significant DLco% slope annual decline (4.14%/year). 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 to men.

Interpretation: These results provide information about the testing frequency (3 to 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.

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Table 1. Baseline characteristics of the subjects included in the study stratified by presence of COPD and nº of DLCO assessments.

	COPD				Smoker without COPD				
	Total (n = 506)	**1-2 period[2] (n = 201)**	**3-6 period[2] (n = 305)**	**P value**	**Total (n = 96)**	**1-2 period (n = 27)**	**3-6 period (n = 69)**	**P value**	**P value[1]**
Gender (male) *	406 (80%)	149 (74%)	257 (84%)	0.004	58 (60%)	19 (70%)	39 (56%)	0.155	<0.001
Age, yr	64 (8.9)	65 (9.0)	64 (8.8)	0.542	55 (10.1)	56 (11.0)	55 (9.8)	0.683	<0.001
Pack-years	59 (27)	60 (27)	58 (27)	0.442	45 (24)	48 (23)	43 (24)	0.337	<0.001
Smokers active*	192 (38%)	87 (43%)	105 (34%)	0.055	61 (64%)	19 (73%)	42 (61%)	0.194	<0.001
Body mass index, kg/m^2	27.4 (5.0)	27.6 (5.5)	27.3 (4.7)	0.441	28.4 (4.9)	28.4 (5.7)	28.4 (4.6)	0.954	0.087
Haemoglobin, g/dL	14.8 (1.32)	14.4 (1.41)	14.9 (1.25)	0.003	15.3 (1.25)	15.8 (0.72)	15.1 (1.38)	0.173	0.065
Cooximetry, ppm**	5.0 (2-19)	4.0 (2-17.4)	5.0 (2-20)	0.103	10.0 (3-33)	12 (3-32.9)	10 (3-37)	0.637	<0.001
DLco, mmol/ml/kPA	5.18 (1.98)	4.46 (2.02)	5.35 (1.94)	0.016	7.86 (2.35)	7.46 (2.43)	7.95 (2.29)	0.154	<0.001
DLco, %	65.0 (23.6)	62.8 (25.4)	66.3 (22.4)	0.118	84.6 (19.3)	81.1 (17.9)	85.9 (19.7)	0.291	<0.001
KCO, %	73.4 (25.1)	70.8 (25.2)	75.2 (24.9)	0.062	92.4 (20.6)	88.4 (18.2)	94.2 (21.5)	0.226	<0.001
FEV_1, L	1.61 (0.63)	1.50 (0.60)	1.69 (0.64)	0.001	2.88 (0.75)	2.90 (0.93)	2.87 (0.68)	0.856	<0.001
FEV_1, %	57.7 (20.3)	56.0 (20.9)	58.7 (19.8)	0.147	95.9 (13.8)	91.9 (18.3)	97.5 (11.3)	0.147	<0.001
FVC, L	3.14 (0.90)	2.93 (0.85)	3.28 (0.91)	<0.001	3.77 (1.00)	3.81 (1.21)	3.75 (0.92)	0.816	<0.001
FVC, %	86.0 (21.1)	84.3 (21.5)	87.2 (20.8)	0.128	100.1 (15.2)	96.4 (19.7)	101.6 (12.9)	0.216	<0.001
FVC_1/FVC, %	51.2 (12.1)	50.9 (12.4)	51.4 (11.9)	0.695	77.8 (6.0)	78.0 (6.8)	77.7 (5.6)	0.794	<0.001
6MWD, m	471 (96)	445 (108)	488 (83)	<0.001	534 (89)	538 (102)	533 (85)	0.808	<0.001
Charlson Index**	0 (0-3)	0 (0-3)	0 (0-2.4)	0.105	0 (0-1)	0 (0-3.9)	0 (0-0)	0.055	0.007
Dyspnea (mMRC)**	1 (0-3)	1 (0-3)	1 (0-2)	0.248	0 (0-1.4)	0 (0-2)	0 (0-1)	0.969	<0.001
PaO_2, mmHg	70.0 (10.8)	69.1 (11.9)	70.8 (9.9)	0.191	75.8 (13.1)	74.6 (14.1)	76.0 (13.1)	0.795	0.004
BODE index**	1 (0-4)	2 (0-6)	1 (0-4)	0.005	0 (0-1)	0 (0-2.4)	0 (0-1)	0.178	<0.001
Hospitalization (at least one during the study period)*	137 (27%)	47 (23%)	90 (30%)	0.078	13 (14%)	2 (8%)	11 (16%)	0.247	0.003
Hospitalization per patient-year**	0 (0-0.7)	0 (0-2)	0 (0-0.4)	0.939	0 (0-0.3)	0 (0-1.5)	0 (0-0.3)	0.628	0.013
Respiratory mortality*	54 (11%)	30 (15%)	24 (8%)	0.009	1 (1.0%)	1 (3.7%)	-	0.281	0.001
Global mortality*	130 (26%)	83 (41%)	47 (15%)	< 0.001	3 (3.1%)	3 (11.1%)	-	0.020	<0.001

Data presented as mean (SD), except: *number (percentage), **Median (P_{10}-P_{90}).

[1] Comparison between subjects with COPD versus smokers without COPD.

[2]. Subjects with <3 measurements (1-2 period) vs ≥3 measurements (3-6 period).

Table 2. Effects of patient characteristics on baseline DLco and on Annual Rate of Change in DLco.

Characteristics	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	0.573	-1.19 ± 0.41	0.004
Age (per yr)	-0.20 ± 0.09	0.031	-0.01 ± 0.01	0.647
Gender (female vs male)	-10.40 ± 2.04	<0.001	-0.59 ± 0.34	0.096
Body mass index (per Kg/cm^2)	1.45 ± 0.16	<0.001	-0.05 ± 0.03	0.074
Smoking status				
Current smoker (yes vs no)	-2.32 ± 1.70	0.172	0.01 ± 0.30	0.976
Pack-years (per pack-yr)	0.04 ± 0.03	0.363	0.002 ± 0.005	0.633
FEV_1 (%) Baseline (per %)	0.47 ± 0.04	<0.001	0.01 ± 0.01	0.207
COPD Model				
Age (per yr)	-0.31 ± 0.10	0.002	-0.01 ± 0.01	0.401
Gender (female vs male)	-11.37 ± 2.27	<0.001	-0.89 ± 0.42	0.039
Body mass index (per Kg/cm^2)	1.54 ± 0.17	<0.001	-0.04 ± 0.03	0.121
FEV_1 (%) Baseline (per %)	0.48 ± 0.04	<0.001	0.004 ± 0.007	0.558
Smoker without COPD Model				
Age (per yr)	0.41 ± 0.16	0.014	-0.01 ± 0.02	0.514
Gender (female vs male)	-10.67 ± 3.50	0.003	-0.27 ± 0.50	0.596
Body mass index (per Kg/cm^2)	1.40 ± 0.34	<0.001	-0.10 ± 0.05	0.065
FEV_1 (%) Baseline (per %)	0.46 ± 0.12	<0.001	-0.01 ± 0.02	0.459

Data presented as mean ± standard error.

Table 3. Evolution of DLco and other functional variables in COPD patients and smokers without COPD over time (patients with ≥ 3 measures of DLco).

	COPD (n = 305)			P value	Smoker without COPD (n = 69)			P value
	Initial	Intermediate	Final		Initial	Intermediate	Final	
Body mass index, kg/m^2	27.7 (4.4)	27.7 (4.5)	27.7 (4.7)	0.898	28.6 (4.5)	28.7 (4.5)	28.9 (4.4)	0.341
DLco, %	64.2 (20.8)	59.9 (20.7)	57.4 (21.3)	<0.001	83.1 (20.9)	80.6 (20.9)	80.8 (20.6)	0.032
KCO, %	75.2 (24.7)	74.3 (24.4)	69.3 (25.3)	<0.001	94.0 (20.9)	93.2 (20.9)	90.7 (21.6)	0.019
Alveolar Volume, L	5.26 (1.07)	5.15 (1.11)	5.10 (1.14)	<0.001	5.21 (0.96)	5.19 (0.90)	5.13 (0.99)	0.406
FEV_1, L	1.67 (0.63)	1.61 (0.62)	1.52 (0.64)	<0.001	2.86 (0.75)	2.79 (0.74)	2.66 (0.78)	0.007
FEV_1, %	58.2 (19.0)	57.1 (19.0)	55.7 (18.9)	<0.001	97.0 (11.7)	97.2 (12.3)	96.4 (13.6)	0.519
FVC, L	3.26 (0.90)	3.21 (0.89)	3.10 (0.90)	<0.001	3.78 (0.95)	3.74 (1.00)	3.67 (1.02)	0.005
FVC, %	86.0 (19.9)	86.3 (20.4)	84.4 (21.4)	0.023	102.1 (12.7)	101.3 (13.0)	101.2 (13.1)	0.700
FVC_1/FVC, %	51.6 (11.9)	50.3 (12.4)	50.0 (11.6)	<0.001	76.6 (5.2)	74.9 (5.2)	74.6 (6.2)	0.019
BODE index**	1.5 (0-4)	2 (0-4.5)	2 (0-5)	<0.001	0 (0-1)	0 (0-1)	0 (0-1)	0.206
Smokers active*	37.7%	34.1%	28.2%	0.034	65.2%	58.8%	47.1%	0.033

Data presented as mean (SD), except: *number (percentage), **Median (P_{10}-P_{90}).

Table 4. Slope values of the DLco change in patients with three or more measurements. Slope values provided according to their direction (positive for increase, negative for a decrease) and statistical significance.

	COPD (n = 305)					**Smoker without COPD (n = 69)**				
Slopes	N	Mean	$CI_{95\%}$	Mean	$CI_{95\%}$	N	Mean	$CI_{95\%}$	Mean	$CI_{95\%}$
Significantly negative	50	-4.139	(-4.622; -3.657)			3	-4.440	(-9.903; 1.023)		
Non-significant Negative	180	-3.017	(-3.418; -2.616)			49	-2.026	(-2.579; -1.474)		
Non-significant Positive	71	1.552	(1.221; 1.882)	-1.647	(-2.044; -1.251)	17	1.548	(0.950; 2.146)	-1.106	(-1.684; -0.527)
Significant Positive	4	3.207	(1.356; 5.058)			-	-	-		

CI: Confidence interval.

Legends.

Figure 1. Values of DLco (%) over 5 years. Panel A shows the values for all COPD patients and smokers without COPD. Panel B compares the changes in men and women with COPD.

Figure 2. Evolution of the mean annual DLco (%) for COPD patients depending on its decline was statistically significant negative (decliners) vs the rest of the group (non-decliners).

Figure 1. Values of DLco (%) mean annual decline (▭ COPD patients and ▭ smoker without COPD). Panel A shows the values for all COPD patients and smokers without COPD (p = 0.004). Panel B compares the changes in men and women with COPD (p = 0.039).

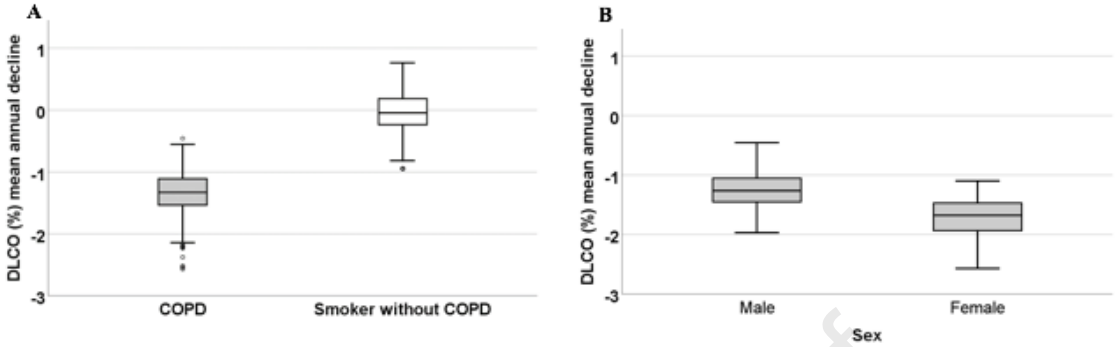
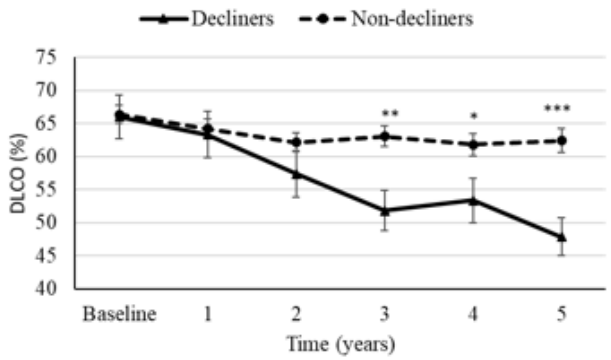


Figure 2. Evolution of the mean annual DLco (%) for COPD patients depending on whether its decline was statistically significant negative (decliners) vs the rest of the group (non-decliners).



*p-value <0.05; ** < 0.01; *** < 0.001