ERECTILE DYSFUNCTION IS A COMMON PROBLEM IN INTERSTITIAL LUNG DISEASES

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ABSTRACT. *Introduction:* Erectile dysfunction (ED) is related to chronic diseases, including COPD. The pathogenesis may involve chronic hypoxia, which is common in interstitial lung disease (ILD). We aimed to study the relationship between ILD and ED. *Method:* Male patients with ILD detected by high-resolution computed tomography (HR-CT) and/or histopathological findings in a lung biopsy were prospectively enrolled at two European ILD centers. Participants were asked to fill in the International Index of Erectile Function questionnaire (Danish or Dutch version). Information on type of ILD, lung function tests, 6-minute walking test (6MWT), co-morbidities, medication and smoking history was obtained from patient records. *Results:* Of 82 enrolled patients, 54 patients (65.9%) returned the questionnaire. Mean age was 66.8 years (SD: 9.03). Twenty-six patients (48.1%) had IPF. Overall, 38 (70.4%) had some degree of ED, thirty (56.6%) had moderate to severe ED, and 23 (43.4%) had severe ED. Low diffusion capacity and high body mass index showed a trend of increasing risk of moderate to severe ED. The risk increased with age (OR per 5-year increase=2.63 (1.25; 5.53)) and decreased with 6MWT distance (OR per 50 m increase=0.60 (0.41; 0.89)). Only two patients (6.7%) received specific treatment with phosphodiesterase-5 inhibitors. *Conclusion:* Severe ED is a common problem in men with ILD, and is associated with poor walking distance and high age. Treatment coverage is low, and physicians should address this problem as a part of the routine care. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 356-364)*

KEY WORDS: interstitial lung disease, erectile dysfunction, respiratory diseases

INTRODUCTION

Erectile dysfunction (ED) is common among patients with chronic diseases such as diabetes and atherosclerosis as well as hypertension and hyperlipidemia (1-12). Previous studies have also found an association between chronic obstructive pulmonary disease (COPD) and ED (13, 14). The pathogenesis

of ED is not clearly established although some risk factors for ED may act through an elevated risk of atherosclerosis (15). A significant correlation was demonstrated between chronic hypoxemia and ED in two relatively small studies (16, 17) and in one study, the erectile function improved with prescription of long-term oxygen treatment (LTOT) (16) pointing at an independent an possibly reversible effect of hypoxemia. Still, systemic inflammation (14), hormonal disturbances (16, 17) and endothelial dysfunction (18) are also possible explanations of ED.

ED is easily overlooked by health professionals but has great impact on the quality of life. A simple tool for detection and classification is the *International Index of Erectile Function* (IIEF) (19). Developed for the clinical trials of Sildenafil in the 1990s

(20), this 15-item questionnaire has been thoroughly validated and was previously used in a number of studies of ED in different settings.

Interstitial lung diseases (ILDs) form a heterogeneous group of more than 200 disease entities. The idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis (IPF), are the most frequent. Chronic hypoxemia is a key problem in many patients with ILD. This is caused by impaired gas transfer in the lung alveoli due to fibrosis and inflammation in surrounding tissue. In the majority of patients with IPF co-morbidities are present (21). The most commonly observed comorbidities are cardiovascular diseases, arterial hypertension, pulmonary hypertension, reflux and diabetes (21).

Hypoxemia and comorbidities with elevated risk of ED imply that ED may be common in ILD. Nevertheless, only one single study including eight patients with pulmonary fibrosis has reported on the occurrence of ED (17). We therefore aimed to estimate the prevalence of ED in ILD and to describe risk factors for ED in two European ILD centres.

Methods

Male patients with ILD were recruited from two highly specialized European centers (Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark and Department of Respiratory Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands) between 1 December 2012 and 31 December 2014. Inclusion criteria were ILD diagnosed by a high resolution computed tomography (HRCT) and/or bronchoscopy with bronchoalveolar lavage and/or a surgical lung biopsy. All diagnoses were evaluated and classified according to the recent ATS/ERS statement on ILD (22,23) at a multidisciplinary team conference.

After obtaining informed consent patients were asked to fill in the IIEF, version 2.0 (19, 20, 24, 25). IIEF is a self-administered questionnaire, validated in both Danish and Dutch. IIEF retest reliability is high and sensitivity and specificity for detecting treatment-related changes (22) is well documented. IIEF provides a numerical score and is divided into five categories with lower scores indicating more severe impairment: Severe ED (1-10 points), moderate ED (11-16 points), mild-moderate ED (17-21 points), mild ED (22-25 points) and no ED (26-30 points). IIEF covers five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction.

Patients were given the choice to complete the questionnaire at the clinic or at home and bring it for their next scheduled visit. Body mass index (BMI), tobacco and alcohol abuse history, pulmonary function (diffusion capacity for carbon monoxide (DLCO), total lung capacity (TLC) and forced ventilatory capacity (FVC)), oxygen saturation measured by pulse oximetry or arterial puncture, and 6-minute walking test (6MWT) were obtained from patient records, if available within three months before or after the return of the IIEF questionnaire. Generally, these data were registered at every follow-up visit, and thus obtained at the same day as the questionnaire was handed out. Also, information on prescription of antidepressants, betablockers, thiazide diuretics and sildenafil or any other treatments of ED were registered as well as any comorbid diagnoses (ischaemic heart disease, atherosclerosis, hypertension and diabetes mellitus).

The study was approved by the Central Denmark Region Committee of Biomedical and Research Ethics and by the Research Ethics Committee at Erasmus MC University Medical Center, The Netherlands. Also, data collection and handling was approved by the Danish Data Protection Agency.

Data are reported as means or medians with 95% confidence intervals; normality was assessed visually by histograms and Q-plots. Comparison of means was performed by Student's t-test. Groups were compared for risk of ED by logistic regression, reported as an odds ratio (OR) with 95% confidence interval. All statistical analyses were performed using STATA, version 14 (StataCorp, College Station Tx). A confidence level of 0.05 was applied in all tests.

Results

Participants

A total of 82 male patients gave informed consent for participation; 54 patients (65.9%) returned the questionnaire. Mean age was 66.8 years (SD: 9.03). Twenty-six patients had IPF, seven had fibrotic NSIP and 21 had other ILDs (NSIP with cellular

predominance, n=2; connective tissue disease-related ILD, n=8; desquamative interstitial pneumonitis, n=2; hypersensitivity pneumonitis, n=2; unclassifiable ILD, n=7). One patient was of Asian origin, the others were Caucasian. Table 1 shows demographics including medication and lung function characteristics for the respondents in the three main diagnosis categories.

Six patients were current smokers, 35 former smokers and 12 had never smoked. Current smokers had significantly more pack years (mean: 41.67 (33.20; 50.13)) than former smokers (mean: 24.29 (19.26; 29,31)). Four patients (7.55%) reported excess alcohol intake defined as more than 21 units (1 unit=12 grams ethanol) per week (1 with IPF, 1 with NSIP, 2 with other ILDs).

Diabetes and cardiac disorders were each present in seven patients (13%) and were most common among patients with IPF (Table 3). Hypercholesterolemia was present in 21 patients (38,9%) and hypertension in 18 (33,3%); no significant differences were seen between diagnostic groups. The number of patients with multiple comorbidities is shown in Table 1.

A total of 27.8% of patients were on corticosteroid treatment. The number of patients receiving treatment with betablockers, antidepressants, thiazide diuretics and steroids is included in Table 1.

Patients returning the IIEF questionnaire were significantly older than non-responders (mean age: 66.8 years versus 60.2 years, p=0.017), and had significantly lower DLCO (45.4% versus 55.3% of pre-

Table 1. Demographic data, key lung function parameters and medication

	Total	IPF	NSIP	Others*
N	54	26	7	21
Age, mean (95% CI)	66.8 (64.3; 69.2)	69.3 (66.5; 72.0)	68.7 (64.2; 73.2)	63.0 (58.3;67.8)
Smoking				
Present smokers	6	3	1	2
mean pack years	41.67	50.00	25.00	37.50
Former smokers	35		16	6 13
mean pack years	24.29	21.25	27.17	26.70
Never-smokers	11	7	0	5
Lung function parameters				
FVC , mean (95% CI)	77.7 (72.1; 83.3)	78.7 (70.1; 87.2)	82 (67.2; 96.8)	75.2 (66.5; 83.9)
DLCO, mean (95% CI)	45.7 (41.6; 49.9)	40.1 (35.0; 45.2)	45.0 (32.8; 57.2)	52.9 (46.2; 59.7)
6 minute walking test				
Distance, mean	448.2 (414.0; 482.4)	445.5 (401.3; 489.7)	423.3 (254.4; 592.3)	461.8 (418.1; 505.4)
Desaturation under 92%	36 (66.7%)	21 (80.8%)	5 (71.4%)	10 (47.6%)
Desaturation under 88%	24 (52.2%)	15 (62.5%)	3 (50%)	6 (37.5%)
Medication				
Betablockers	7 (13.0%)	2 (7.7%)	1 (14.3%)	7 (13.0%)
Thiazides	1 (1.9%)	0	0	1 (4.8%)
Antidepressants	2 (3.7%)	0	0	2 (9.5%)
Steorids	15 (27.8%)	3 (11.5%)	3 (42.9%)	9 (42.9%)
Number of comorbidities				
0	25 (46.3%)	12 (46.1%)	2 (28.6%)	11 (52.4%)
1	10 (18.5%)	5 (19.2%)	2 (28.6%)	3 (14.3%)
2	10 (18.5%)	3 (15.4%)	2 (28.6%)	5 (23.1%)
3 or more	9 (16.7%)	6 (23.1%)	1 (14.3%)	2 (9.6%)

CI=confidence interval. FVC=forced vital capacity. DLCO=carbon monoxide lung diffusion capacity.
*Others: NSIP with cellular predominance, n=2; connective tissue disease-related ILD, n=8; desquamative interstitial pneumonitis, n=2; hypersensitivity pneumonitis, n=2; unclassifiable ILD, n=7

dicted, p=0.042). There were no significant differences regarding 6MWT distance, a diagnosis of IPF, presence of comorbidities or use of medication.

Prevalence of erectile dysfunction

Of the 54 men returning the questionnaire, 38 (70.4%) experienced some degree of ED. A total of 56.6% had moderate or severe ED (Table 2), whereof 23 patients (43.4%) reported severe ED. The proportion of patients with mild and moderate to severe ED was not significantly different between diagnostic groups. The median IIEF score of all participants was 12 (IQR 4 to 27). Among the men with ED, the median IIEF score was 8 (IQR 2 to 12). The mean scores in the IIEF domains orgasmic function (OF), sexual desire (SD), intercourse satisfaction (IS) and

overall satisfaction (OS) are included in Table 2; the mean scores were not significantly different between the different diagnostic groups.

Demographics and predictors of ED

Mean age of patients with moderate to severe ED (69.67 years (66.66; 72.68)) was higher than of those with no or mild ED (62.78 years (59.08; 66.48)). Low DLCO and a high BMI were associated with a trend for a higher odds ratio for moderate to severe ED when compared to mild or no ED. However, the correlation remained non-significant also in a multivariate model (Table 3 and Figure 1).

The probability of having moderate to severe ED decreased significantly with increasing 6-minute walking test distance in a univariate model (Table 4)

Table 2. Prevalence of erectile dysfunction and median or mean score on 5 International Index of Erectile Function (IIEF) domains

Category	Erectile function (EF)				Orgasmic function Mean score (95% CI)	Sexual desire Mean score (95% CI)	Intercourse satisfaction Mean score (95% CI)	Overall satisfaction Mean score (95% CI)
	Any ED		Moderate-severe ED					
	n (%)	Median EF score (IQR)	n (%)	Median EF score (IQR)				
All	38 (70.4)	8 (2; 12)	30 (56.6)	4.5 (1; 10)	4.9 (3.7; 6.1)	5.6 (5.1; 6.1)	5.6 (4.2; 7.0)	4.4 (3.7; 5.1)
IPF	17 (64.5)	8 (2; 11)	14 (53.9)	6.5 (1; 10)	4.7 (3.0; 6.4)	5.8 (5.1; 6.4)	6.5 (4.6; 8.5)	4.1 (3.2; 5.2)
NSIP	6 (85.7)	4 (1; 10)	5 (83.3)	4 (1; 10)	3.3 (0.1; 7.0)	5.7 (3.9; 7.5)	4.2 (0.3 ;8.1)	4.2 (2.1; 6.3)
Others	15 (71.4)	9 (2; 17)	11 (52.4)	4 (1; 12)	5.6 (3.6; 7.5)	5.4 (4.5;6.3)	4.8 (2.4; 7.1)	4.7 (3.6; 5.8)

ED=Erectile Dysfunction. IQR=interquartile range. CI=confidence interval. IPF=idiopatic pulmonary fibrosis. NSIP=non-specific interstitial pneumonitis

Table 3. Crude odds ratio (OR) and adjusted OR for moderate-to-severe erectile dysfunction by relative changes in key variables in a multiple logistic regression model. Age was omitted from the model, as age and 6MWT distance were significantly interdependent. BMI: body mass index. DLCO: carbon monoxide lung diffusion (in % of expected value). 6MWT: 6 minute walking test

Variable	OR	adjusted OR
Age, years OR per 5 year increase	**2.63** (1.25; 5.53)	
BMI OR per 5 BMI point increase	1.07 (0.93; 1.23)	1.79 (0.72; 4.47)
DLCO OR per 10%-point increase	0.98 (0.94; 1.02)	0.95 (0.73; 1.23)
6MWT distance OR per 50 meter increase	**0.60** (0.41; 0.89)	**0.58** (0.38; 0.91)

BMI=body mass index. DLCO=carbon monoxide lung diffusion capacity. 6MWT=6 minute walking test. OR=odds ratio
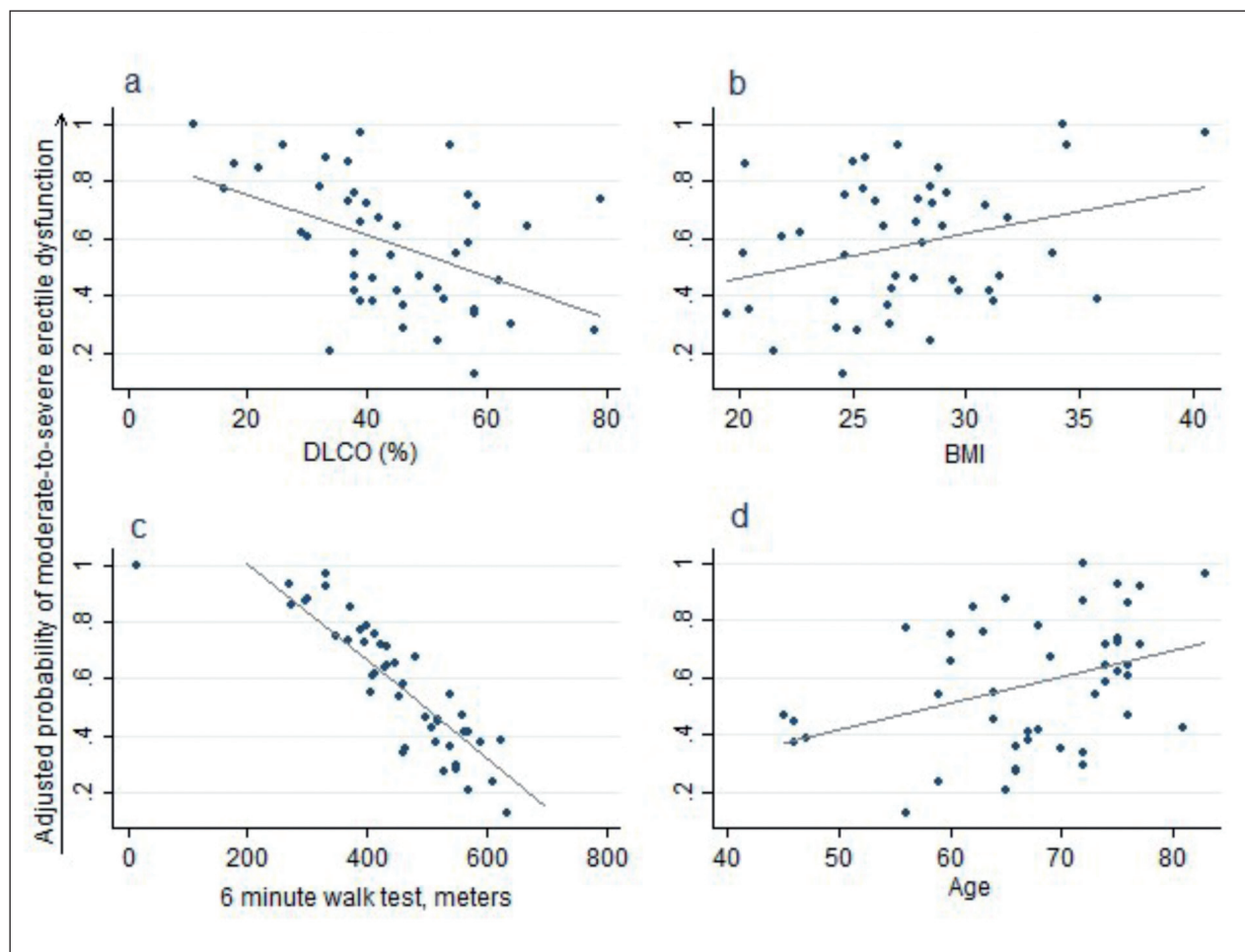
Fig. 1. Probability of moderate to severe erectile dysfunction as a function of carbon monoxide lung diffusion (DLCO) (panel a), body mass index (BMI) (panel b), 6-minute walking distance (6MWTD) (panel c) and age (panel d), in a logistic regression model. Two models were established; one including DLCO, BMI and 6-minute walking distance; the second including DLCO, BMI and age, as 6-minute walking distance and age showed significant collinearity

as well as in a multivariate model (Table 3 and Figure 1).

A trend for higher risk of ED with increasing number of comorbidities was observed; OR for moderate to severe ED per additional comorbidity was 1.21 (0.77; 1.90). Steroid use was not associated with presence of ED (OR=0.47 (0.14; 1.62)). Betablocker treatment was independently associated with higher risk of moderate to severe ED (Table 4), while prescription of one or more of betablockers, antidepressants and thiazide diuretics showed a strong trend of correlating with moderate to severe ED; OR=8 (0.92; 69.45), p=0.059.

Treatment of erectile dysfunction

Based on information from patient records, only two patients received medical treatment for ED (6.7% of patients with moderate or severe ED); both with a phosphodieasterase-5 (PDE5) inhibitor (Sildenafil and Tadalafil). In addition, three patients were treated with a PDE5-inhibitor for other medical conditions (one for pulmonary hypertension, one for Raynaud's phenomenon and one for progressive IPF). All five patients treated with PDE5-inhibitors had an EF score of less than 16, equivalent to moderate or severe ED. Based on patient records, no pa-

Table 4. Prevalence of smoking, comorbidities and certain medicinal prescriptions among patients with mild or no ED, versus moderate to severe ED

	No or mild ED	moderate to severe ED	p-value
Smoking			
Present smokers	4 (17.4%)	2 (6.9%)	0.239
mean pack years	40 (25.3; 55.7)	45 (32.1; 57.9)	
Former smokers	12 (52.2%)	22 (75.9%)	0.075
mean pack years	25.3 (13.2; 34.5)	24.0 (17.7; 30.2)	
Never-smokers	7 (30.4%)	5 (17.2%)	0.262
Medication			
Betablockers	0	6 (20%)	**0.023**
Thiazides	0	1(3.3%)	0.377
Antidepressants	1 (4.35%)	1 (3.33%)	0.848
Steroids	8 (34.8%)	6 (20.0%)	0.226
Number of comorbidities			
0	12 (52.2%)	13 (43.3%)	0.523*
1	4 (17.4%)	6 (20.0%)	
2	4 (17.4%)	6 (20.0%)	
3 or more	3 (13.0%)	5 (16.7%)	

Total n=53 as information in the erectile function domain was missing for one patient. On smoking status, n=52 as smoking information was missing for further one patient. ED= erectile dysfunction
* p-value for the presence of comorbidities vs. no comorbidities.

Discussion

The present study is the first to investigate systematically the prevalence of ED among patients with ILD. We found a high prevalence of ED; 70% of patients reported some degree of ED, and almost half of participants reported severe ED. We found a trend towards higher risk of ED with low DLCO, high BMI and presence of comorbid diseases, while the risk of ED significantly increased with older age and with concurrent use of betablockers. A strong and significant correlation was found between low 6MWT walking distance and the risk of ED.

The prevalence of ED in ILD is considerably larger than in the background population; an Indian study reported a prevalence of 43.5% among males above 60 years(26), and a population-based study in Portuguese men from 18-70 years found the prevalence of sexual problems to range from 2.9% to 23.2% (27). Also high compared to studies in other

tients used intracavernous alprostadil injections, intraurethral alprostadil applications, vacuum devices, or had received a penile prosthesis.

chronic diseases, including diabetes (37% to 75%), stroke (48%) and arterial hypertension (23% to 46%), we found a high prevalence of ED. The prevalence of ED was in keeping with previous reports in systemic sclerosis (81%) (28) and COPD (67 to 76%) (29-31).

Age was identified as an important, non-modifiable risk factor for ED, as also described in previous studies(2,28). Many of our participants had IPF, a disease entity that almost always occurs at a high age. In clinical practice, the effect of age on the presence of ED among ILD patients may therefore play a substantial role. Importantly, we also saw a trend of increasing ED prevalence with decreasing lung diffusion capacity, and a significant correlation with 6-minute walking test distance. These findings underscore that ED is a very real problem in many ILD patients and should be actively considered by health professionals, especially in older patients with poor lung function. The correlation with the 6 minute walking test probably also reflects the multifactorial nature of ED, as this test is a functional measure, incorporating the effect of comorbidities, physical shape and age. A recent study in men with acute myocardial infarction showed a positive effect of home-based training on ED (32). The effect of physical

training on ED in ILD remains to be evaluated but keeping the strong correlation with the walking distance test in mind, one could speculate that physical training may very well also improve ED in ILD.

We also observed an insignificant trend of higher risk of ED with increasing number of comorbidities. The insignificance is likely due to a relatively low number of observations. Comorbidities may contribute to the development of ED not only in the general population but also in patients with ILD, but whether treating co-morbidities leads to improvement in ED has not been established. From a clinical point of view, the exact physiological cause of ED in a certain patient is of less importance; the key message is that ED is common in ILD, and especially in elderly patients, in those with short walking capacity, and probably also in those with comorbid diseases, and should be addressed routinely in the care for ILD patients.

In the background population, pharmacotherapy with phosphodiesterase-5 inhibitors is recommended as first-line treatment. We found a disturbingly low coverage of treatment for ED: Over 90% of patients with moderate or severe ED did not have records of receiving specific treatment for ED. Despite the fact that we obtained treatment information from patient records and not from interview or a standardized questionnaire, the existence of a common electronic medical prescription interface for general practitioners and hospital department ensured a high coverage in medicinal data. As ED is associated with reduced quality of life (31,33), anxiety and depression (34), it is critical for physicians dealing with ILD, as well as with other diseases correlated with ED, to be familiar with guidelines for medical treatment of ED (35). It is worth mentioning that several patients included in this study had subsequently started adequate treatment, though systematic follow-up was beyond the scope of this cross-sectional study.

The mechanism behind development of ED in ILD is not clearly established and may include multiple factors, including comorbid diseases as well as specific disease mechanisms in ILD. A recent study in patients with COPD found significant correlation to chronic hypoxia (31) confirming previous findings from two smaller studies (16, 17). Surprisingly, we did not observe a significant correlation with either resting oxygen saturation or with maximum desaturation in the 6-minute walking test. Further research is needed to elaborate on the pathology of ED in ILD including longitudinal evaluation of the timing of ED onset and trajectory of ED development during ILD progression. Also, the impact of psychological mechanisms needs further attention; for example, patients with ILD may refrain from sexual activity due to fear of severe dyspnea.

The present study has some limitations. Firstly, comparison to a non-ILD, age-matched control group would allow a more thorough evaluation of the impact of ILD on sexual function. Nevertheless, this observational study clearly demonstrates the magnitude of this problem in ILD and underscores the need to increase the awareness and to break down barriers for communication about the problem. . Secondly, the multicenter design and the inclusion of all ILD types may, on the one hand, be more representative of all men affected by these diseases, but on the other hand, may lead to difficulties in standardizing data collection. Although centers were asked to recruit participants consecutively, there is always a risk of recruitment bias. Also, studies including self-completed questionnaires imply a risk of participation bias as indicated by the slight differences observed between participants and non-participants. Moreover, comorbidity status was retrieved by scrutinizing patient files and not with a validated questionnaire.

In conclusion, we found a high burden of ED in ILD patients. The risk of moderate to severe ED was associated with high age and with low 6-minute walking distance. Also, we found an insignificant trend for a higher risk of ED with increasing number of comorbidities. Therefore, health professionals should actively consider ED, especially in patients with poor walking distance, high age and comorbidities. Treatment coverage of ED is currently very low and it is important that physicians caring for patients with ILD are familiar with current guidelines for specific treatment of ED.

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