Predictors of erectile dysfunction among male patients with idiopathic interstitial pneumonias

Doaa M. Magdy[a], Ahmed M. Azouz[a], Randa A. El Zohne[b]

Background Sexual dysfunction is a neglected area among patients with idiopathic interstitial pneumonias (IIPs). Hence, the aim of this study is to identify the prevalence of erectile dysfunction (ED) and its predictors in male patients with IIPs.

Patients and methods A total 65 male patients (45 IIPs and 20 controls) were assessed; clinical data, testosterone levels, pulmonary function tests, arterial blood gases, and self-reported questionnaires on erectile function.

Results The prevalence of ED was 66.7 and 11.1% of them presented with severe ED. The mean age of the patients was 33.4±5.9 years. Of the patients, 60% were smokers and 17.8% were nonsmokers. Regarding comorbid manifestations, 26.7% was hypertensive, 51.1% had diabetes mellitus, 42.2% with dyslipidemia, and 17.8% had ischemic heart disease. The mean duration since the diagnosis of IIPs was 7.46±2.77 years, whereas the mean time since evolution of ED was 2.17±1.3 years. A significant decrease in mean arterial oxygen tension (PaO_2) and oxygen saturation (SaO_2) were observed in the IIPs group. Also, the mean diffusion lung capacity for carbon monoxide (DLCO%) and testosterone level were decreased. A significant decrease in testosterone level among patients with severe diffusion defect was observed ($P=0.000$). The most predictors for ED were PaO_2 (≤60 mmHg), SaO_2 ($\leq88\%$), and DLCO$\leq60\%$.

Conclusion ED is a common problem in patients with IIPs. Thus, physicians should keep in mind that IIPs patients need a comprehensive sexual evaluation. This is the first study to report that low PaO_2, SaO_2, and DLCO$\leq60\%$ were the predictor risk factors.

Departments of, [a]Chest Diseases, [b]Clinical Pathology, Faculty of Medicine, Assuit University, Assuit, Egypt

Correspondence to Dr. Doaa Mohamed Magdy, MD in chest diseases and tuberculosis, Chest, Faculty of Medicine, Assiut University Hospital, Assiut University, Assuit, 71515, Egypt. Tel: +201006261010; fax: 0882413708; e-mail: doaamagdy_2020@aun.edu.eg

Introduction

Idiopathic interstitial pneumonias (IIPs) are heterogeneous diffuse parenchymal lung disorders of unknown etiology characterized by inflammation and/or fibrosis of pulmonary parenchyma. Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of IIP accounting for up to 65%. Other less common entities include nonspecific interstitial pneumonia (IP), desquamative IP, and cryptogenic organizing pneumonia [1].

According to the WHO, sexual health is a state of physical, emotional, mental, and social well-being in relation to sexuality. This means that sexual health has to be seen from a holistic perspective, including physical, psychological, and social aspects of well-being. Sexuality is an important aspect of quality of life that is usually neglected in research studies. In clinical practice, the physicians almost focus on fertility, pregnancy, or contraception, whereas sexual function is not addressed [2].

By definition, erectile dysfunction (ED) is a permanent insufficiency in achieving an adequate erection to have a satisfactory sexual life [3]. Decreased testosterone levels are responsible for loss of sexual desire and function, in addition to the aging process that have led to a decrease in *libido* and erectile function in men

[4,5]. Low testosterone level and ED have been reported among men with chronic pulmonary diseases. The presence of clinical manifestations such as dyspnea, chronic cough, muscle weakness, and diminished physical activity are all major factors for decreased sexual activity [6,7]. In fact, physicians generally ignore sexual dysfunction during their evaluation which is considered a significant comorbidity. Thus, still this topic is a neglected area of research and discussion. The aim of this study is to highlight and draw attention to this important issue.

The purpose of this study was to address the predictors and frequency of ED in patients with IIPs.

Patients and methods

In this observational cohort study, 65 male participants were enrolled in the Chest Department and Clinical Pathology Departments, in a tertiary hospital during the period from May 2017 to December 2017. IP was confirmed in 45 patients based on a review of the clinical history, pulmonary function test results, and

thin-section high-resolution computed tomography images of the lungs.

The study population comprised 15 patients with IPF, 30 with other IIPs and 20 healthy control participants. IIPs were diagnosed and classified according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association diagnostic criteria for IPF and the American Thoracic Society/European Respiratory Society consensus statement on IIPs [1,8].

An informed consent was obtained from the patients. The study was approved by the Faculty of Medicine Ethics Committee.

Inclusion criteria
The selection criteria include all patients who were recruited to the Chest Department and diagnosed as IIPs were selected for the analysis. Baseline high-resolution computed tomography scans were evaluated in all patients according to guidelines [1,8].

Exclusion criteria

(1) Patients with occupational form of interstitial lung disease (ILD), sarcoidosis, and collagen vascular disease associated ILD.
(2) Patients who use medication that may interfere with serum testosterone hormone levels (such as sildenafil and other oral agents for ED).
(3) Patients with malignancy, significant renal, hepatic, metabolic, or endocrine disturbances or neurological diseases were excluded.

All patients were subjected to the following:

(1) Full medical history [age, sex, smoking habit, height, weight, and BMI was calculated as body weight (kg)/height^2 (m^2)].
(2) Pulmonary function tests:
   Resting pulmonary function tests were performed for all patients. Forced expiratory volume in 1 s and forced vital capacity were measured using Zan 300 (Sensor Medics MGA USB, Oberthulba, Germany) [9]. Diffusing capacity for carbon monoxide (DLCO) single-breath method was measured and categorized according to severity (Zan 300; Sensor Medics MGA USB) as recommended in the international guidelines [10].
(3) Arterial blood gas analysis was done. Arterial oxygen tension (PaO$_2$), carbon dioxide tension, and pH were measured using a blood gas analyzer

(ABL-330; Radiometer Medical ApS, Copenhagen, Denmark).
(4) Five-item version of the International Index of Erectile Function (IIEF-5): Self-reported five-question was used to evaluate erectile function. The maximum score is 25 points, and classification is as follows: 1–7, severe ED; 8–11, moderate ED, 12–16: mild–moderate ED; 17–21: mild ED; 22–25, no ED [11].
(5) Serum total testosterone.
A measure of 2 ml venous blood samples was obtained from all patients to measure total testosterone levels. The serum levels of testosterone was measured by chemiluminescent enzyme-labeled immunoassay using Immulite 1000. Total testosterone kit from Siemens 06603687, cat LKTW1 was used [12].

Statistical analysis
The statistical package for the social sciences (SPSS, version 16; SPSS Inc., Chicago, Illinois, USA) software was used to evaluate the data. The results were presented as mean±SD and frequency tables. For comparisons between the two groups, the significance test for the difference between two means (Student's t-test), and for the categorical comparisons, the χ^2-tests were used. A P value of less than 0.05 was considered of statistical significance.

Results
Of the 65 male participants enrolled, 45 male patients with IIPs and 20 were volunteers. Sociodemographic characteristics of all patients are presented in Table 1.

The mean age and BMI were 33.4±5.9 years and 24.4 ±3.34 kg/m^2. No significant differences were observed regarding age and BMI when compared with the control group; 75.6% of patients with IIPs had children, whereas 24.4% of them were having no children. The IIPs group consisted of patients with a history of smoking; 60% were current smokers, 22.2% were former smokers, and 17.8% were nonsmokers. The mean duration since diagnosis of IIPs was 7.46 ±2.77 years; in contrast, the mean time since evolution of ED was 2.17±1.3 years. Regarding the presence of comorbid manifestation, this study demonstrated that 26.7% were hypertensive, 51.1% had diabetes mellitus, 42.2% with dyslipidemia, and finally 17.8% of patients presented with ischemic heart disease. In the IIPs group, total testosterone level was significantly decreased (5.53 ± 1.47 vs. 7.31 ± 1.35 ng/dl) (Table 1).

Arterial blood gases showed that mean PaO$_2$ and mean oxygen saturation (SaO$_2$) decreased in the IIPs group.

Table 1 Sociodemographic characteristics of the studied patients with idiopathic interstitial pneumonias (n=45)

	Patients (n=45)	Control group (n=20)
Prevalence of ED		
Yes	30 (66.7)*	4 (20)
No	15 (33.3)	16 (80)
Age (years)	44.4±9.9	40.3±5.3
Having children		
Yes	34 (75.6)	16 (80)
No	11 (24.4)	4 (20)
Smoking status		
Nonsmoker	8 (17.8)	10 (50)
Current smoker	27 (60)	5 (25)
Former smoker	10 (22.2)	5 (25)
Hypertension		
Yes	12 (26.7)	7 (35)
No	33 (73.3)	13 (65)
Diabetes mellitus		
Yes	23 (51.1)	6 (30)
No	22 (48.9)	14 (70)
Dyslipidemia		
Yes	19 (42.2)	5 (25)
No	26 (57.8)	15 (75)
Ischemic heart disease		
Yes	8 (17.8)	3 (15)
No	37 (82.2)	17 (85)
BMI (kg/m^2)	24.4±3.34	23.8±3.76
Time of ED evolution (years)	2.17±1.3	–
Time since diagnosis of IP (years)	7.46±2.77	–
Hormonal assay		
Serum testosterone (ng/dl)	5.53±1.47*	7.31±1.35

Data are expressed as mean±SD or n (%). ED, erectile dysfunction; IP, interstitial pneumonia. *Significant difference.

Table 2 Pulmonary function tests, arterial blood gas analysis

	IIPs group (n=45)
Arterial blood gases	
pH	7.41±0.02
PaCo$_2$ (mmHg)	38.3±4.5
PaO$_2$ (mmHg)	56.8±10.4
SaO$_2$ (%)	88.53±4.44
Pulmonary function	
FVC actual	2.43±0.84
FVC% predicted	65.6±16.3
FEV$_1$ actual	2.02±0.78
FEV$_1$% predicted	58.8±17.4
FEV$_1$/FVC	79.6±4.2
DLCO actual	4.02±1.7
DLCO%	51.9±17.06

Data are expressed as mean±SD. DLCO, diffusion lung capacity for carbon monoxide; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; PaCO$_2$, arterial carbon dioxide tension; PaO$_2$, arterial oxygen tension; SaO$_2$, oxygen saturation.

Table 3 Prevalence of erectile dysfunction among male patients with idiopathic interstitial pneumonias regarding International Index of Erectile Function (n=45)

IIEF-5 score	Normal	Mild	Mild–moderate	Moderate	Severe
n (%)	15 (33.3)	12 (26.7)	7 (15.6)	6 (13.3)	5 (11.1)

IIEF-5, five-item version of the International Index of Erectile Function.

Moreover, we demonstrated that pulmonary function along with mean DLCO% values in the IIPs group were lower 51.9±17.06% (Table 2).

Using the IIEF-5, this study demonstrated that the prevalence of ED in male patients with IIPs was 66.7%, defined as a score of less than 22. Patients with IIPs had various degrees of ED, 26.7% of them had mild ED; in contrast, 11.1% had severe ED (Table 3).

On comparing total testosterone level with severity of diffusion, a statistically significant decrease in total testosterone level among patients with severe diffusion defect was observed (P=0.000) (Table 4).

This study reported a significant positive correlation between total testosterone level and PaO$_2$ and SaO$_2$ (r=0.830, P=0.000; r=0.835, P=0.000, respectively) (Figs 1 and 2). Also, a positive correlation was found between hormone level and DLCO% (r=0.828, P=0.000) (Fig. 3).

Table 4 Prevalence of erectile dysfunction and serum testosterone levels regarding disease severity (*n*=45)

| Patients (*n*=45)	Mild diffusion (80–60%) (*n*=17)	Moderate diffusion (60–40%) (*n*=17)	Severe diffusion (≤40%) (*n*=11)	*P* value
DLCO% (mean±SD)	68.4±4.67	52.11±3.9	26.18±5.3	0.000*
Testosterone (mean±SD) (ng/dl)	6.92±7.71	5.20±1.01	3.88±2.09	0.000*

DLCO, diffusion lung capacity for carbon monoxide. *Significant difference.
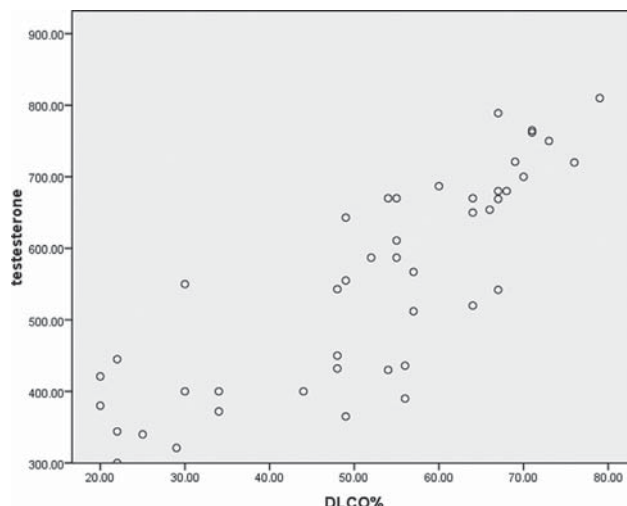
Figure 1
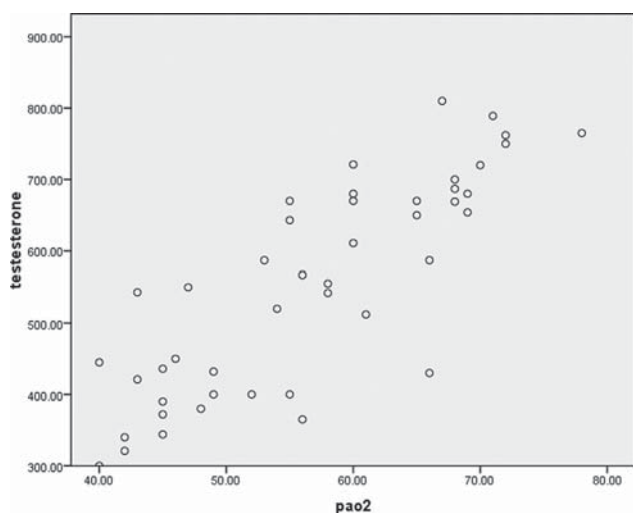
Positive correlation between total testosterone level and arterial oxygen tension (PaO$_2$) (*r*=0.830; *P*=0.000).

Figure 2
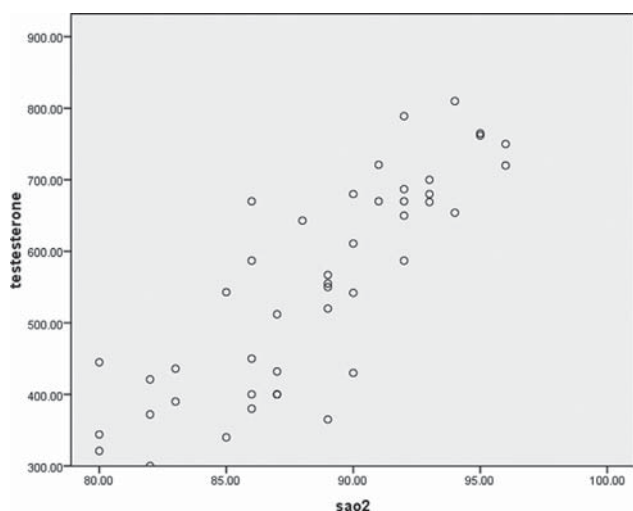
Positive correlation between total testosterone level and arterial oxygen saturation (SaO$_2$) (*r*=0.835; *P*=0.000).

Figure 3

Positive correlation between total testosterone level and diffusion lung capacity for carbon monoxide (DLCO%) (*r*=0.828, *P*=0.000).

Table 5 Logistic regression analysis showing the predictors of erectile dysfunction among male patients with idiopathic interstitial pneumonia

	OR	*P* value	95% CI Lower	95% CI Upper
Smoking	1.050	0.542	−2.167	3.543
Hypertension	1.544	0.451	0.567	3.432
Diabetes mellitus	−0.020	0.811	−3.765	2.653
Dyslipidemia	1.096	0.261	−2.134	7.765
Ischemic heart disease	2.321	0.742	1.786	3.567
PaCO$_2$ (mmHg)	0.203	0.070	−0.567	2.345
PaO$_2$≤60 mmHg	3.132	0.001*	1.167	4.539
SaO$_2$≤88%	2.923	0.000*	0.671	3.559
FEV$_1$	0.008	0.936	−1.578	1.709
DLCO≤60%	2.970	0.001*	0.873	3.078

CI, confidence interval; DLCO, diffusion lung capacity for carbon monoxide; FEV$_1$, forced expiratory volume in 1 s; OR, odds ratio; PaCO$_2$, arterial carbon dioxide tension; PaO$_2$, arterial oxygen tension; SaO$_2$, oxygen saturation. *Significant difference.

Table 6 Correlation coefficient between each of serum testosterone levels and forced expiratory volume in 1 s predicted, diffusion lung capacity for carbon monoxide (%), arterial oxygen tension, and arterial carbon dioxide tension

	r	*P* value
PaCO$_2$ (mmHg)	0.688	0.000*
PaO$_2$ (mmHg)	0.830	0.000*
SaO$_2$ (%)	0.835	0.000*
FEV$_1$% predicted	0.421	0.004*
DLCO%	0.828	0.000*

DLCO, diffusion lung capacity for carbon monoxide; FEV$_1$, forced expiratory volume in 1 s; PaCO$_2$, arterial carbon dioxide tension; PaO$_2$, arterial oxygen tension; *r*, Pearson's correlation; SaO$_2$, oxygen saturation. *Significant difference.

A shown in Tables 5 and 6, logistic regression analysis was done to found the predictors of ED among male patients with IIPs. The most predictor factors for ED were PaO$_2$ (≤60 mmHg), SaO$_2$ (≤88%), and DLCO≤60%. In addition, risk of comorbidities such as smoking, hypertension, diabetes mellitus,

dyslipidemia, and ischemic heart disease were not considered as predictors of ED.

Discussion

IP is not only a pulmonary limited disease but also a chronic illness, which presents with diverse behavior and comorbidities. The presence of comorbidities such as infection, gastroesophageal reflux, pulmonary hypertension, lung cancer, cardiovascular diseases, and obstructive sleep apnea can develop at any time during the course of the disease and, if unidentified and untreated may impair the quality of life, and ultimately impact on disease progression [13]. Obvious sexual dysfunctions such as ED are not included as one of comorbidities among male patients with IIPs that may cause disruption in their natural daily life [14]. Hence, the purpose of this study was to spotlight on this issue as a possible comorbidity among a large proportion of male patients with IIPs and potential risk factors.

Several factors may be anticipated that it will affect sexual activity and ED including the aging process and generally poor health. Also, physical and psychological problems and prescribed medications can decrease sexual activity [15]. Dunn *et al.* [16] reported that 34% of the general population had sexual problems and ED was the most common sexual disorder. Another study showed that the prevalence of ED increases with age [17].

In our study, we demonstrated that the overall prevalence of ED among male patients with IPs was 66.7%. We evaluated the severity of ED and found that 26.7 had mild and 11.1% had severe ED. Similarly, a recent study by Floe *et al.* [18] studied the prevalence of ED among 89 patients with IPF and reported that 70% of patients had ED and 44% of them had severe ED. Furthermore, Kahraman *et al.* [19] investigated the incidence of ED and the factors affecting its frequency in chronic obstructive pulmonary disease patients and reported that 55 (78.6%) of the chronic obstructive pulmonary disease patients had various degrees of ED.

The endocrine function plays a significant role in the regulation of erectile function. Several studies demonstrated that a proper endocrine milieu is necessary: Any alteration of one or more sex hormones can cause ED. Therefore, testosterone is considered as a key factor in sexual function [20]. This study reported a significant decrease in testosterone level among the IIPs group when compared with the control group. Also, a significant decline in hormone level with increase in severity of diffusion defect was observed.

The high prevalence of ED could be explained by the fact that sexual activity causes an increase in cardiopulmonary load. Thus, energy spent during orgasm is equal to the energy required for walking. Therefore, both decreased exercise tolerance and fear of dyspnea may limit sexual activity [7]. In addition, misperceptions, ignorance, and poor physical or psychological status as common factors may contribute to sexual dysfunction [21]. Previous studies have reported that more severe disease has a higher prevalence of ED [5,22].

A significantly lower mean PaO_2 and SaO_2 was observed among male patients with IIPs. Low level of SaO_2 is considered as another contributing factor for ED among those patients. A study conducted by Semple *et al.* [3] demonstrated that seven out of 10 hypoxemic patients with chronic pulmonary disease had no morning erection. Moreover, oxygen therapy had a role in improving sexual dysfunction. Hence, our findings support the fact that as hypoxia increases, the incidence of ED rises.

Furthermore, our results showed a positive correlation between testosterone levels and PaO_2 and SaO_2. Likewise, a positive correlation was found between testosterone level and DLCO%. These findings were consistent with Karadag *et al.* [23]. We demonstrated that most predictors for ED among male patients with IIPs were PaO_2 (≤ 60 mmHg), SaO_2 ($\leq 88\%$), and DLCO$\leq 60\%$.

The major strengths of our study were the analysis of multiple clinical characteristics and comorbidities and the use of an international and valid questionnaire to determine the prevalence and severity of ED (IIEF-5). Second, we measured the sexual hormone level.

Conclusion

Sexuality and sexual dysfunction in patients with IIPs are often overlooked by the medical personnel. Of the patients studied, 66.7% of patients had ED. The most predictors for ED among male patients with IIPs were PaO_2 (≤ 60 mmHg), SaO_2 ($\leq 88\%$), and DLCO$\leq 60\%$. Thus, the physicians should keep in mind that patients with chronic fibrosing pneumonia need a comprehensive evaluation, including their sexual life.

All authors participated in the conception and design of the study. Also, they participated in data collection and statistical analysis and interpretation of data and have drafted the submitted article and revised it critically for important intellectual content. They participated in the final approval of the version to be submitted.

References

1 Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, *et al.* An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; **188**:733–748.

2 Organization WH. *Defining sexual health. Report of a technical consultation on sexual health, 28–31 January 2002. Sexual health document series*. Geneva, Switzerland: World Health Organisation; 2006. p. 35.

3 Semple PD, Beastall GH, Hume R. Male sexual dysfunction, low serum testosterone and respiratory hypoxia. *Br J Sex Med* 1980; **7**:48–53.

4 Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. *Psychosom Med* 1998; **60**:458–465.

5 Karadag F, Ozcan H, Karul AB, Ceylan E, Cildag O. Correlates of erectile dysfunction in moderate-to-severe chronic obstructive pulmonary disease patients. *Respirology* 2007; **12**:248–253.

6 Collins EG, Halabi S, Langston M, Schnell T, Tobin MJ, Laghi F. Sexual dysfunction in men with COPD: impact on quality of life and survival. *Lung* 2012; **190**:545–556.

7 Schönhofer B. Sexuality in patients with restricted breathing. *Med Klin* 2002; **97**:344–349.

8 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al.* ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2018; **198**:44–68.

9 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al.* ATS/ERS Task Force General considerations for lung function testing. *Eur Respir J* 2005; **26**:153–161.

10 Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; **26**:720–735.

11 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**:822–830.

12 Wheeler MJ. The determination of bio-available testosterone. *Ann Clin Biochem* 1995; **32**:345–357.

13 Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis? *Respir Med* 2014; **108**:647–653.

14 Kreuter M, Ehlers-Tenenbaum S, Palmowski K, Bruhwyler J, Oltmanns U, Muley T, *et al.* Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. *PLoS ONE* 2016; **11**:e0151425.

15 Kligman EW. Office evaluation of sexual function and complaints. *Clin Geriatr Med* 1991; **7**:15–39.

16 Dunn KM, Croft PR, Hackett GT. Sexual problems: a study of the prevalence and need for health care in the general population. *Fam Pract* 1998; **15**:519–524.

17 Akkus E, Kadıoglu A, Esen A, Doran S, Ergen A, Anafarta K, *et al.* Turkish Erectile Dysfunction Prevalence Study Group. Prevalence and correlates of erectile dysfunction in Turkey: a population based study. *Eur Urol* 2002; **41**:298–304.

18 Floe A, Hilberg O, Wijsenbeek S, Bendstrup E. Erectile dysfunction is a common problem in interstitial lung disease. *Am J Respir Crit Care Med* 2015; **191**:A1575.

19 Kahraman H, Sen B, Koksal N, Kilinç M, Resim S. Erectile dysfunction and sex hormone changes in chronic obstructive pulmonary disease patients. *Multidiscip Respir Med* 2013; **8**:66.

20 Corona G, Mannucci E, Fisher AD, Lotti F, Petrone L, Balercia G, *et al.* Low levels of androgens in men with erectile dysfunction and obesity. *J Sex Med* 2008; **5**:2454–2463.

21 Thorson AI. Sexual activity and the cardiac patient. *Am J Geriatr Cardiol* 2003; **12**:38–40.

22 Köseoğlu N, Köseoğlu H, Ceylan E, Cimrin HA, Ozalevli S, Esen A. Erectile dysfunction prevalence and sexual function status in patient with chronic obstructive pulmonary disease. *J Urol* 2005; **174**:249–252.

23 Karadag F, Ozcan H, Karul AB, Yilmaz M, Cildag O. Sex hormone alterations and systemic inflammation in chronic obstructive pulmonary disease. *Int J Clin Pract* 2009; **63**:275–281.