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Prevalence of Obstructive Sleep Apnoea in Patients with Idiopathic Pulmonary Fibrosis

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Abstract

Background: Over the last years, increasing attention has been focused on the prevalence of obstructive sleep apnea (OSA) in idiopathic pulmonary fibrosis (IPF). Objective: To determine the prevalence of OSA in a group of patients diagnosed with IPF. Materials and Methods: Analytic retrospective study. Data were collected from the medical records of all patients diagnosed with IPF who had polysomnography requested as part of the study protocol in patients with interstitial lung diseases (ILD). Results: 36 patients were studied, 26 of who were male. The mean age was 67.55 ± 6.39 years old. Mean forced vital capacity (FVC) was 2.12 ± 0.76 liters. The mean body mass index (BMI) was 28.78 ± 4.24. The Epworth Sleepiness Scale (ESS) average was 7.55 ± 5.01 and the mean apnea hypopnea index (AHI) was 12.69 ± 19.40. Of all the patients studied, 17 (47.22%) had OSA with an AHI ≥ 5. Of these, 9 (25%) had AHI ≥ 10. In the group of patients with OSA (n = 17), 9 (52.94%) had mild OSA (AHI between 5 and 15) and 8 (47.05%) moderate to severe OSA (AHI ≥ 15). Conclusions: In our series of 36 patients with IPF we found a prevalence of OSA of 47.22%. We found no correlation between ESS and the BMI with the presence of OSA in these patients, suggesting that these assessments may be less than optimal screening tools for OSA in IPF.

Keywords

Idiopathic Pulmonary Fibrosis, Obstructive Sleep Apnea, Polisomnography, Prevalence

Subject Areas: **Respiratory Medicine**

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a lethal form of chronic, progressive fibrosing interstitial lung disease

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(ILD) of unknown etiology with a higher prevalence in men over 60 years of age with history of tobacco smoking [1]. IPF is always associated with histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP), has a poor prognosis and is marked by progressive worsening of dyspnea and lung function [2]. The median survival time from diagnosis is 3.5 years [3].

The current focus of IPF research is on the molecular genetics of pathologic events likely to occur at the epithelial-mesenchymal interface of the alveolus [4]-[9]. *In vitro*, studies using lung fibroblast from IPF patients have contributed to the theory that myofibroblasts have a prolonged survival after being activated by an unknown injury, shortened survival of lung epithelial cells, or both [10]. Even though, risk factors have been identified for this disease (e.g. environmental, exposures, genetic determinants, smoking [11], pollutants, gastro-esophageal reflux [12] [13], occupational exposures, [14], viral infections [15] and old age [16]). IPF's origin and onset are not fully understood. It has been previously suggested that the onset involves alveolar epithelium micro-injuries that lead to dysregulation of cellular homoeostasis in the alveolar epithelial-mesenchymal unit and the reactivation of developmental signaling pathways (e.g. transforming growth factor: TGF-β [17], wingless-type like (Wnt) [18], sonic hedgehog (SHH) [19], and Notch [20]). The resultant cell dysfunction and death result in progressive scar tissue formation, and eventual distortion of pulmonary anatomical structural relationships with disruption of lung homoeostasis [21]. Some authors hypothesize that IPF originates from long term recurring stretch injury to the peripheral and basal lung in individuals with a genetic predisposition. One of the proposed triggers could be ventilatory efforts associated with obstructive sleep apnea (OSA), which may trigger the process of "aberrant healing". The generated disease is present in more peripheral areas of the lung based on well-known heightened mechanical stretch factors in this anatomical compartment; in essence a mechanical rather than inflammatory damage [10].

Over the last years, attention has been focused on the prevalence of sleep disorders, especially OSA, in patients with IPF. In the general population, the prevalence of OSA is between 5% and 10% [22]. Three prospective studies found the prevalence of OSA in patients with IPF to be excessively larger compared with that reported in the general population, even after adjustment for age, with prevalence of between 59% and 90% [23]-[25]. This increased risk of developing OSA is not restricted to IPF, as studies involving different populations of patients with interstitial diseases, especially systemic sclerosis and sarcoidosis, have shown similar findings [26] [27]. To this point, in 2013, we published a prevalence of 48.8% of OSA in patients with ILD, and found that the group of patients with OSA had a higher involvement of nocturnal oximetry measured by CT90 (percentage of total time the layout of the PSG with lower pulse oximetry 90%) [28].

2. Materials and Methods

Data were collected from the medical records of all patients diagnosed with IPF (based on criteria identical to those published in the ERS/ATS 2011 guidelines) who were managed at a specialized hospital respiratory diseases on an outpatient basis during the period from January 1, 2010 to December 15, 2014. All idiopathic pulmonary fibrosis (IPF) patients at our institution are studied routinely with polysomnography (PSG) by protocol.

The following variables were recorded: sex, age, body mass index (BMI), Epworth Sleepiness Scale (ESS), lung function parameters (FVC: Forced Vital Capacity, DLCO: Pulmonary Diffusing Carbon Monoxide), symptoms consistent with gastro-esophageal reflux (GER), apnea-hypopnea index (AHI) and cumulative percentages of time spent at saturations below 90% (CT 90). The presence of symptoms consistent with GER was assessed by focused interview with the patient. Depending on their AHI, patients were classified as normal (AHI < 5), mild OSA (AHI ≥ 5 but <15) and moderate to severe OSA (AHI ≥ 15). According to WHO obesity criteria, patients were classified as normal (BMI value between 18.5 and 24.9 kg/m^2), overweight (BMI between 25 and 29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) [29]. For the Epworth Sleepiness Scale (ESS), the cutoff used to define daytime sleepiness was 10.

In all cases, overnight polysomnography was performed using a 23-channel digital system (ATI®PENTATEK®) and included the following parameters: electroencephalogram, EOG, ECG, nasal thermistor and pressure transducer for measuring airflow, chest and abdominal bands to measure ventilatory effort, continuous oximetry, snoring microphone and monitoring of anterior tibial. Apnea was defined as cessation of airflow (90% compared with baseline) for more than 10 seconds; hypopnea to reduced flow amplitude 50% to 90% associated with oxygen desaturation of at least 3% and/or arousal in the electroencephalogram. OSA is considered an apnea-hypopnea index (AHI) of 5 or more events per hour. CT90 was defined as the percentage of recording time with

oxygen saturation below 90%. Significant desaturation was considered a value greater than 20% (CT90 ≥ 20). All polysomnography studies were performed without supplemental oxygen.

Data from pulmonary function testing were collected in all patients. Spirometry and diffusing capacity of carbon monoxide (DLCO) adjusted to hemoglobin was performed. Pulmonary function test were performed according to ATS/ERS 2005 standards and benchmarks used were NHANES III [30]-[33].

The results were expressed as mean and standard deviation. Given the sample size and non-Gaussian distribution, chi-square test was used to compare percentages; the test for nonparametric Mann-Whitney test to compare numeric variables and Spearman test to analyze the correlation of numerical variables. Was considered statistically significant a p value < 0.05. Data were analyzed using Graph-Prism 4.0 software.

3. Results

In total, 36 patients diagnosed with IPF, 26 men (72.3%) and 10 women (27.7%) were included. The mean age was 67.55 ± 6.39 years old. In 32 (88.9%) the diagnosis of IPF was made by high resolution computed tomography (HRCT) showing a "UIP radiological pattern" and in 11.1% (n = 4) by surgical lung biopsy. Eleven patients (30.5%) had chronic oxygen therapy requirements. The mean forced vital capacity (FVC) in absolute values was 2.12 ± 0.76 liters and in percentage of predictive value 61.97% ± 15.8%. The pulmonary diffusing carbon monoxide (DLCO) average, expressed in absolute values, was 9.80 ± 3.69 and percentage of predicted 46.38% ± 18.19%. The mean BMI was 28.78 ± 4.24. (**Table 1**: Characteristics of patients). The ESS average was 7.55 ± 5.01 and the mean AHI of 12.69 ± 19.40. Of the total, 17 (47.22%) patients had an AHI ≥ 5 and nine of them (25%) had an AHI ≥ 10.

Comparing IPF groups with and without OSA we could not find statistically significant differences, except for mean AHI. (**Table 2**: Comparison of patients with and without OSA).

In the group of patients with OSA (n = 17), 9 (52.94%) had an AHI between 5 and 15 (mild OSA) and 8 (47.05%), an AHI ≥ 15 (OSA moderate to severe) (**Figure 1**). When we analyzed the correlation between BMI and CT90 in all our study population (patients without OSA, with mild OSA and with severe OSA), we founded a Spearman r = 0.39 (p = 0.015) (**Figure 2**). As regards the analysis of correlation between BMI and AHI, a correlation coefficient of Spearman (r) of 0.31 with p = 0.06 (not significant) (**Figure 3**) was found. With regard to the Epworth Sleepiness Scale (ESS), compared with the AHI, a correlation coefficient of Spearman (r) of 0.16 with p = 0.35 (not significant) was found. However, when the correlation between BMI and CT90 only in OSA patients, a Spearman correlation coefficient (r) of 0.01 with a (non-significant) p = 0.39 and high dispersion was observed (**Table 3**: Comparison of the characteristics of the three groups of IPF patients: no OSA, mild OSA and moderate to severe OSA).

Table 1. Characteristics of the study population.

Age	67.55 ± 6.39 years old[#]
BMI (kg/m^2)	28.78 ± 4.24[#]
ESS	7.55 ± 5.01[#]
FVC (liters)	2.12 ± 0.76[#]
FVC (%)	61.97% ± 15.8%[#]
DLCO	9.80 ± 3.69[#]
DLCO%	46.38% ± 18.19%[#]
Requirements LTOT (%)	11 (30.5%)
AHI	12.69 ± 19.40[#]
CT 90	34.26 ± 37.94[#]
CT90 ≥ 20 (%)	18 (50.61%)
AHI ≥ 5 (%)	17 (47.22%)

[#]Mean ± standard deviation.

Table 2. Comparison of the characteristics of the groups of IPF patients with and without OSA.

Variables	AIH < 5 n = 19 (52.77%)	AIH ≥ 5 (OSA) n = 17 (47.22%)	p
Age (years old)	67.68 ± 6.14[#]	67.41 ± 6.85[#]	p = 0.90
Men	14 (73.68%)	12 (70.58%)	p = 0.86
BMI (kg/m^2)	28.18 ± 4.09[#]	29.45 ± 4.43[#]	p = 0.30
ESS	6.89 ± 4.96[#]	8.29 ± 5.10[#]	p = 0.33
FVC (liters)	2.07 ± 0.68[#]	2.16 ± 0.85[#]	p = 0.89
FVC%	61.68 ± 14.64[#]	62.29 ± 17.59[#]	p = 0.91
DLCO	10.23 ± 4.20[#]	9.31 ± 3.07[#]	p = 0.47
DLCO%	47.55 ± 19.24[#]	45.06 ± 17.41[#]	p = 0.69
LTOT requirements	6 (31.57%)	5 (29.41%)	p = 0.82
Gastro-esophageal reflux	5 (26.31%)	6 (32.29%)	p = 0.82
AHI	2.33 ± 1.30[#]	24.27 ± 23.48[#]	p = 0.0003
CT90	31.82 ± 41.14[#]	37 ± 35.05[#]	p = 0.68
CT90 ≥ 20	8 (42.10%)	10 (58.82%)	p = 0.50

[#]Mean ± standard deviation.

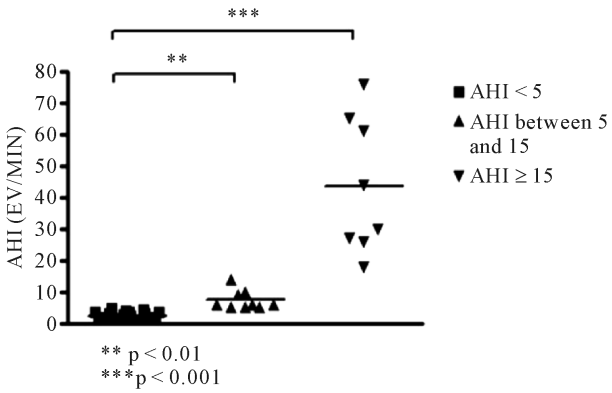

Figure 1. Comparison of AHI between the tree groups of patients.

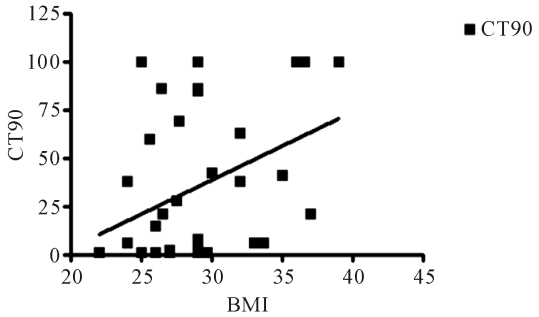

Figure 2. Correlation between BMI and CT90 in studied population. p = 0.015.

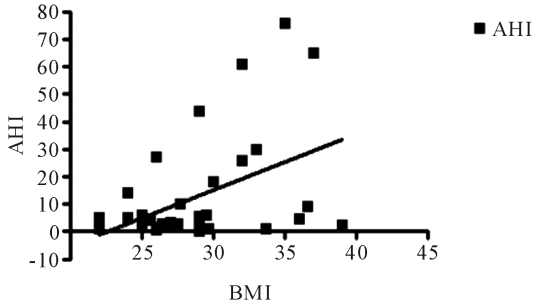

Figure 3. Correlation between BMI and AHI in studied population. p = 0.06.

Table 3. Comparison of the characteristics of the tree groups of IPF patients: no OSA, mild OSA and moderate to severe OSA.

Variables	Patients without OSA AIH < 5 n = 19 (52.77%)	Patients with mild OSA AIH between 5 and 15 n = 9 (25%)	Patients with moderate to severe OSA AHI ≥ 15 n = 8 (22.22%)
BMI (kg/m^2)	28.18 ± 4.09[#]	27.42 ± 4.36[#]	31.75 ± 3.45[#]
Gastro-esophageal reflux	5 (26.31%)	3 (33.33%)	3 (37.5%)
ESS	6.89 ± 4.96[#]	7.11 ± 3.51[#]	9.62 ± 6.45[#]
FVC	2.07 ± 0.68[#]	1.97 ± 0.58[#]	2.38 ± 1.09[#]
FVC%	61.68 ± 14.64[#]	61.11 ± 13.16[#]	63.62 ± 22.49[#]
DLCO	10.23 ± 4.20	8.00 ± 2.39	10.99 ± 3.18
DLCO%	47.55 ± 19.24	40.77 ± 16.44	50.57 ± 18.29
CT90 mean	31.82 ± 41.14	44.5 ± 44.08	28.56 ± 20.8
AHI	2.33 ± 1.30[#]	7.30 ± 3.09[#]	43.37 ± 21.5[#]
LTOT requirements	6 (31.57%)	4 (44.44%)	1 (12.5%)

[#]Mean ± standard deviation.

4. Discussion

The prevalence of OSA in patients with ILD remains a controversial issue, especially regarding mechanism and relevance in these diseases. Recent studies have shown a high prevalence in IPF [24] [34] [35] despite previous studies describing a lower frequency of sleep-disordered breathing in patients with IPF [36] [37].

Using night polysomnography (PSG) a higher prevalence of obstructive respiratory events associated with sleep has been described. According to a paper published by Mermigkisin 2010 [25], the prevalence of OSA with AHI ≥ 5 was 59% in patients with IPF and the respiratory events in REM phase correlated with the TLC whereas DLCO correlated with the average oximetry during sleep. Recently, it have been released a study of 50 patients with ILD, 17 of them with IPF, where the frequency of OSA was 68%. The mean AHI was 11.4 ± 12.5 and OSA was more common in patients with IPF (p = 0.009) [26].

In recent years there have been several studies that assessed the prevalence of OSA in patients with IPF (**Table 4**).

Remains unclear the real question about if OSA is a cause or a consequence of IPF. Different research studies are trying to know the possible mechanicals triggers responsible of the aberrant repair in IPF, one raising hypothesis could be that the Müller's maneuver (the reverse of Valsalva's maneuver) could contribute with the injure of the alveolar epithelial cells. In OSA, this maneuver is a recurrent fact: after a forced expiration, an attempt at inspiration is made with closed mouth and nose, whereby the negative pressure in the chest and lungs is made

Table 4. Publications about prevalence of OSA in IPF.

Author and publication year	Population	Prevalence of OSA	Mean BMI
Mermigkis 2007 [34]	Retrospective study 18 patients with IPF	11 (61%) had OSA	33.2
Lancaster 2009 [24]	Prospective study 50 patients with IPF	44 (88%) had OSA: 20% mild OSA and 68% moderate-severe OSA	32.2
Mermigkis 2010 [25]	Prospective study 34 patients with FPI	20 (59%) had OSA: 44% mild OSA land 15% moderate OSA	27.3
Kolilekas *et al.* 2013 [23]	31 patients with FPI	28 (90%) had OSA: 38% mild OSA and 51.6% moderate-severe OSA	28.7
Pihtili *et al.* 2013 [26]	Prospective. Patients with BMI ≥ 30 were excluded	In patients with IPF n = 14, 82% had OSA	

very subatmospheric. This situation may be related with epithelial cell stretching, endothelial cell stress failure, hypoxia-reoxygenation damage and GER, all factors associated with the mechanisms of the pathophysiology in IPF [10]. In agree with Mermigkis and his coworkers, we think that is crucial to try to identify and treat OSA in patients with IPF [38].

Although some retrospective studies have suggested an association between the degree of lung restriction and risk and severity of sleep-related disorders in patients with IPF, this has not been demonstrated in prospective studies with larger numbers of patients [23] [24] [34]. The only correlation between lung volumes and PSG parameters reported by Mermigkis and coworkers was in total lung capacity (TLC) and index apnea hypopnea REM (AHI) sleep. In our study, we found no statistically significant differences between patients with IPF with and without OSA with regard to lung function parameters.

Excessive daytime sleepiness measured by the Epworth Sleepiness Scale (ESS) has not proven to be a good predictor of OSA in patients with ILD [23] [24] [26]. In our study, comparing the ESS and AHI the Spearman correlation coefficient (r) was 0.16 (with a non-significant p) which would mean that the ESS is not a good predictor of OSA in patients with IPF.

We have published a series of 41 patients with ILD, of which 48.8% had an AHI ≥ 5 and 20% had AHI ≥ 15 [28]. As in this series, ESS did not correlated with the presence of OSA. Although in our group, 11 patients (30.5%) required long term oxygen therapy (LTOT) and 18 (50.61%) presented a CT90 ≥ 20.

As previously published by Kolilekas *et al.* [23], we found no relationship between BMI and PSG parameters (AHI and CT90). In our series, the correlation between BMI and CT90 was 0.39 with r ($p = 0.015$) (**Figure 2**) and the correlation between BMI and AHI was r 0.31 ($p = 0.06$) (**Figure 3**); suggesting the presence of apnea or nocturnal desaturation in this group of patients was related to the presence of obesity.

Recent publications suggest that sleep breathing disorders are common in patients with IPF and other diffuse parenchymal lung diseases and that these may be under diagnosed. In our series of 36 patients with IPF we found a prevalence of OSA of 47.22%. No correlation between ESS and the BMI with the presence of OSA in patients with IPF, making both poor screening tools.

Our study has several limitations such as their retrospective characteristics and the limited number of patients. However it is a study in one center specializing in respiratory diseases where polysomnography is a standard of care in patients with IPF.

There are still many unanswered questions. Does the presence of OSA have real impact on the natural history of patients with IPF? Are there potential benefits of treatment in these individuals using positive pressure ventilation and oxygen therapy? Would therapy have a measurable effect on the underlying disease or on the quality of life? Further studies are needed to clarify these questions and hopefully provide guidance to those involved with the care of patients with IPF.

5. Conclusion

In our series of 36 patients with IPF we found a prevalence of OSA of 47.22%. We found no correlation between ESS and the BMI with the presence of OSA in these patients, suggesting that these assessments may be less than optimal screening tools for OSA in IPF.

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