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Sleep disordered breathing in Patients with Interstitial Lung Disease: A systematic review

Abdullah Rashed Alharbi✉

Abdullah Alharbi King Saud University, Kingdom of Saudi Arabia

Corresponding Author:
Abdullah Rashed Alharbi
Abdullah Alharbi King Saud University, Kingdom of Saudi Arabia
E-mail:dr_alharbi99@hotmail.com

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A B S T R A C T

Background: Interstitial lung disease is a severe condition that can reduce patients' quality of life and decrease their productivity. This, in turn, can adversely affect the economy of the patients. Breathing disorder is common among patients with interstitial lung disease. It occurs mostly during sleep and is the major contributing factor to poor sleeps quality. The aim of this work is to examine sleep-disordered respiration in people with interstitial lung disease (ILD) in the medical literature.

Objective: This review article focuses on the influence of nocturnal hypoxemia on pulmonary hypertension and probable causes of the high incidence of obstructive sleep apnoea in ILD patients.

Methodology: The literature was reviewed through searching articles published in Medline, PubMed, Embase, and Ovid databases between 2009 and 2019. The keywords used for the search were a combination of ''Sleep disorders'' AND ''breathing'' AND ''Interstitial lung disease''. The findings obtained were refined and only original articles that investigated breathing problems accompanying sleep in ILD patients were included. The selected articles indicated the target population and types of complications.

Result: The overall trials obtained were 1804. 56 trials were obtained after excluding those on animals and including only those on humans. Ten trials were considered appropriate, which dealt with 2154 patients with interstitial lung diseases. All the studies were prospective with a cross-sectional design, except one, which was a retrospective study.

Conclusion: Patients with idiopathic respiratory fibrosis frequently have obstructive sleep apnea (OSA) . However, early diagnosis of the disease can improve patients' outcomes. Some treatment strategies, like CPAP, can improve patients' quality of sleep and also reduce their mortality.

Keywords: Sleep Disorders; Breathing; Interstitial Lung Disease.

Introduction

lds are a group of disorders, identified through a wide range of fibrotic and inflamed pulmonary parenchyma.[1] Patients with exercise intolerance or lung restriction are at higher risk of having worsened hypoxia. They suffer from denaturation while sleeping, regardless of their wakening hypoxia. They may also suffer from apnea.[2] Sleep-disordered breathing and nocturnal hypoxia can progress to further complications They can reduce the.[3] sleep quality of patients and also increase fatigue in them while they are awakened. If these are accompanied by the activation of the sympathetic nervous system, they can lead to pulmonary hypertension and higher mortality.[4]

Methodology

The literature was systematically reviewed in compliance with the PRISMA checklist recommendations for meta-analysis and systematic review.[5] It was done by examining four electronic databases (Medline, Pubmed, Ovid, and Embase) for eligible trials published between 2009 and October 2019.

Search Strategy

The keywords used for the search included '' Sleep disorders" AND "breathing" AND "Interstitial lung disease".The topics and synopses obtained from the investigation were examined carefully in order not to omit or miss any appropriate research works. The findings were filtered that only original works that investigated sleep- disordered breathing and obstructive sleep apnoea in ILD patients. Moreover, the selected articles highlighted the oxygenation and breathing variables of the examined subjects. Also, all experimental designs from various nations were added. Only the articles published in English language were categorized as related ones that can be examined in the second stage.

Eligibility Criteria

The criteria of inclusion used in selecting the studies

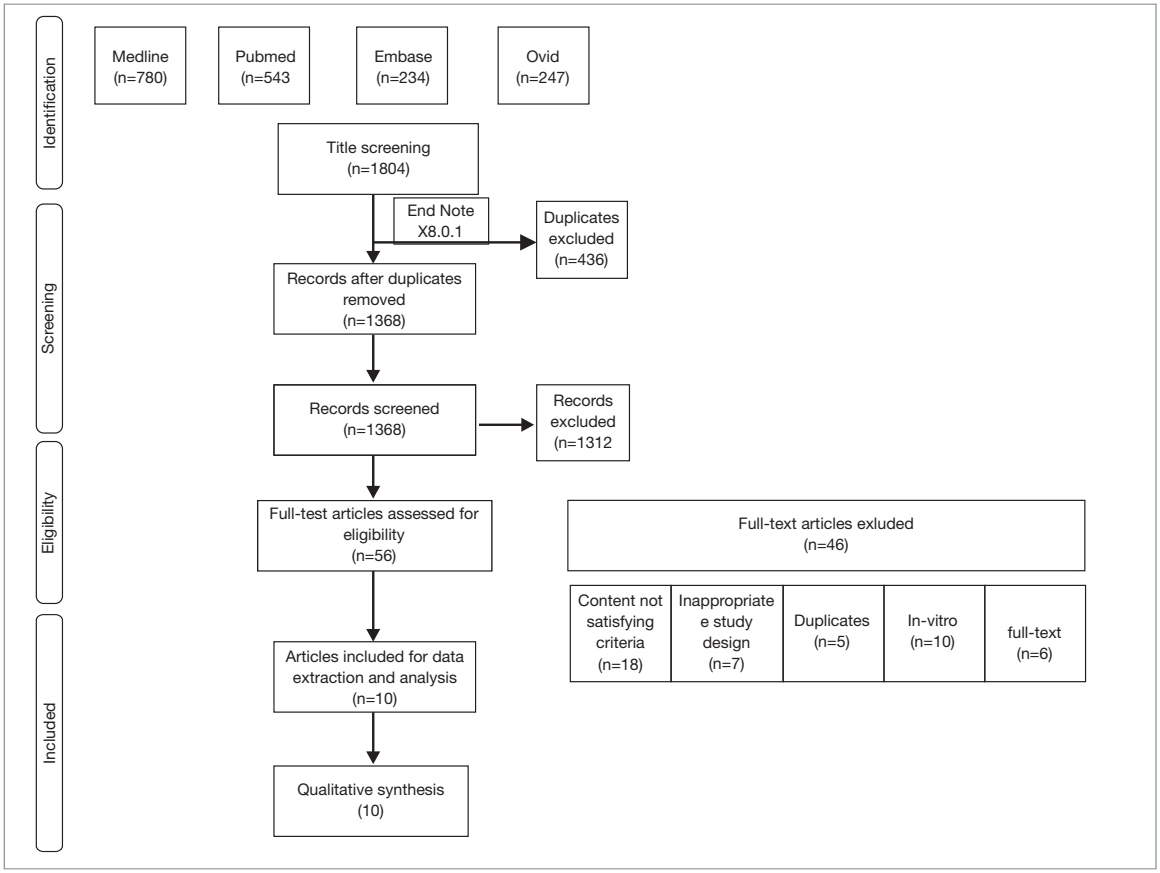

Figure 1. Detailed search strategy

considered in this work were ascertained. Abstracts were studied by manual methods to select the suitable ones. Presenting adequate data on oxygenation parameters as well as vital signs in terms of heart rate and respiratory rate were the inclusion criteria. Only trials that recruited grown-up respondents were selected. Also, references of the articles considered were examined in order to find any works that correlate. Lastly, the sets of data needed were obtained from the last document of suitable trials and summarized. Trials having in vitro or involving animals, data that overlap, not complete, and lacking full-text or unsuitable study design were excluded. Figure 1 shows the complete information of the search method.

Data Review and Analysis

A preliminary review was done in the first step. Data were extracted using a specific excel sheet . The excel sheet was used to revise the data selected from appropriate studies. Any articles published by one study team that investigated similar parameters were revised for double publication. The selected medical articles were evaluated with a tool used for assessing quality, Cochrane.[6]

Data were statistically analysed using correct percentages and frequencies (number of cases) for categorical parameters. Median, interquartile ratios, mean, and standard deviation were used to describe the numerical variables. All statistical calculations were done by IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 21 for Microsoft Windows.

Approval from institutions was obtained before any study was done. Consent form was not obtained since the work does not involve treating patients.

Results

Ten trials published between 2009 and 2019 were considered eligible for the current systematic review after examining the abstracts and the eligibility of the potential abstracts. There were 2154 responses with sleep disordered breathing and interstitial lung disease. Out of the ten studies, 9[7-14,16] had a prospective design, while only one study[15] had a retrospective design. Additionally, six studies[8,9,11,14-16] examined obstructive sleep apnea as sleep-disordered breathing accompanying interstitial lung disease, while one study[7] evaluated the breathing risk factors that may precipitate disordered sleep in ILD patients.

Only Schertel et al.[9] evaluated the difference between day and night respirations in patients with interstitial lung disease. Similarly, Lee et al.[12] examined the difference

Table 1. The articles selected

Author	Year of study	Study design	Sample Size	Objective	Outcome
Cho et al.[7]	2019	Cross sectional	101	To examine the frequency of disord-ered sleep in ILD. To find the precipitating factors to identify possible intervention targets. To detect the varied symptomatology between sleepers with good and poor quality sleep.	The median of the compelled expiratory volume in 1 second was 64% forecast, and vital capacity was 62% predicted. 66% of patients reported poor sleep quality. No great variations in the physiological or physical variables, distribution of gender, body mass index, or spirometry values between patients having good quality of sleep and those without. Poor quality of sleep was linked alone to Epworth Sleepiness Scale (p=0.03) and despair (p=0.003). ILD patients often have poor quality of sleep and are linked to increased signs of lack of sleep and despair. Quality of sleep needs to be assessed routinely, and patients with symptoms may need to be treated for despair combined with sleep disorders to know if there is improvement in their quality of sleep and life health wise.

Gille et al.[8]	2017	Prospe-ctive	45	To ascertain the incid-ence andfactors determ-ining OSA in patients that just have IPF;To examine if obstructive sleep apnea was linked to heart condi-tion, high levels of IPF indicators in the blood and oxidative tension.	The prevalence of moderate-to-acute obstructive sleep apnea and strong obstructive sleep apnea was respectively 62% and 40%. Cardiovascular disease was common among the patients with acute obstructive sleep apnea compared to 41.2% and 40% of the patients having no or slight and moderate obstructive sleep apnea ($p<0.0001$). Moderate-to-acute calcific-ations of coronary artery and ischaemic cardiovascular condition signi-ficantly correlated with acute obstructive sleep apnea. Moderate-to-severe obstructive sleep apnea is highly dominant in IPF events and severe obstructive sleep apnea is highly related CVD, specifically ischaemic heart disease.
Kim et al.[9]	2017	Cross sectional	1690	To determine whether obstructive sleep apnea is associated with the indicators of alveolar epithelial damage and remodeling and sub-medical ILD	The prediction of the mean forced important capability was 97%. The median oAHI was 8.4 events per hour, and 32% had an (apnea-hypopnea index) oAHI of more than 15. After the profiles, centre and smoking were adjusted, an oAHI above 15 was connected to a 4.0% HAA increase and 35% increased odds of ILA. However, these connections differed based on body mass index (BMI). The patients having a BMI below 25 kg/m^2, an oAHI above 15 was linked to a 6.1% HAA increase and 2.3-fold high chances of ILA. The patients having a BMI above 30 kg/m^2 , an oAHI above 15 was connected to 1.8-fold high chances of ILA but was not linked to HAA. Patients having a BMI of 25–30 kg/m^2 had no connections. Higher oAHI correl-ated with increased levels of serum SP-A and MMP-7, mostly in patients having a BMI below 25 kg/m^2. Moderate to acute obstructive sleep apnea correlated with alveolar epithelial damage and extrace-llular matrix remodeling in grown- ups living in communities and subclinical ILD, a relationship which is very strong among people with normal weights. These results agree with the hypothesis that obstructive sleep apnea can lead to quick ILD.

Schertel et al.[10]	2017	Prospective	9	To assess the day and night time breathing course, cough and oxygenation, for over eight months and also distinguish between wakefulness and sleep in patients with IPF.	Nine IPF patients participated. Eight of them (88.9%) were treated with anti-fibrotic medication. Cough prevailed more during wakefulness: the median cough-index was 14.8 per hour and 1.6 per hour during sleep (p=0.0039). There was no difference in oxygenation variables, whereas the rates of breathing and heart were very high during wakefulness. Though the respiratory function tests were stable above eight months, there was an additional increase in the original high breathing rate during wakefulness at follow-up. There was stability in the other breathing variables over time. During wakefulness, the patients with IPF had more cough than during sleep.
Mermigkis et al.[11]	2017	Prospective	92	To examine the influence of CPAP on the IPF and OSA patients' quality of sleep, total life, as well as diseases, and death parameters.	There was great improvement in the quality of sleep and life of 37 patients consisting of the group that complied with CPAP well after one year of CPAP management.18 patients consisting of the poor CPAP compliance group significantly had smaller strength only in a marginal portion of the instruments utilized. While three patients that complied poorly with CPAP died during the 24-month follow-up.But, all the patients that complied well with CPAP did not die.It is very important to identify and treat OSA timely in fatal diseases like IPF. Efficient CPAP management in IPF patients having obstructive sleep apnea made them to improve greatly in their day to day activities including their sleep quality.Adhering well to CPAP seems to reduce death
Lee et al.[12]	2015	Prospective	20	To compare exchange of air and gas during sleep and exercise in a group of patients with IPF, and to evaluate its links to biological indicators selected.	Nine patients presented SDB with apnea-hypopnea incidence (AHI) 5 per hour; only two presented Epworth sleepiness score =10, meaning they have a syndrome of OSA . They had poor quality of sleep. Transcutaneous carbon dioxide stress ($PtcCO_2$) increased overnight by 2.56±1.59 kPa (P = 0.001), implying hypoventilation. During sleep, there was lower saturated oxygen (SaO_2) than during exercise (P<0.01); exercise parameters were connected to relaxing respiratory function. Levels of CRP and CCL-18 increased and were connected to increased $PtcCO_2$

					during sleep (P<0.05). There was negative correlation between CCL-18 and the ability of carbon monoxide (DLCO) to diffuse, mean arterial carbon dioxide ($PaCO_2$) (P<0.05) and arterial oxygen (PaO_2). There was negative correlation between CRP and oxygen uptake (VO_2), DLCO, sleep SaO_2andPaO_2 during exercise(P<0.05). During sleep patients with IPF were more desaturated than during exercise; therefore, nocturnal pulse oxymetry can be added to medical examination. Levels of CRP and CCL-18 correlated with physiological fibrosis indicators.
Kolilekas et al.[13]	2013	cohort	31	To explore the correlation between numerous SBD variables and medical and respiratory function parameters including right ventricular systolic pressure (RVSP).	There was significant increase in desaturated sleep oxygen compared to maximal exercise (p < 0.001). After 6MWT, Maxdiff SpO_2 was directly connected to mortality, SpO_2 and DLCO%, , as well as RVSP, dyspnea, and AHI. The lowest SpO_2 correlated directly with survival and functionality (DLCO%, TLC% in addition to maximal and submaximal exercise parameters (6MWT distance, SpO_2 after 6MWT, maximal consumed oxygen /kg, SpO_2 at maximal exercise); there was an opposite correlation between dyspnea score, AHI, and RVSP. The study results show that irregular desaturated sleep oxygen was more than that of peak exercise and makes patients with IPF to survive. Also, they show there is correlation between lung injury and apnea incidents which induce acute irregular desaturated sleep oxygen that aggravates respiratory arterial hyper- tension and causes patients to survive IPF.
Pihtili et al.[14]	2013	Prospe ctive	62	To examine the incidence of OSA in ILD and to examine the correlation between polysom-nography (PSG) results and disease severity, respiratory function, scores of Epworth Sleepiness Scale (ESS) and parenchymal involvement.	50 patients comprised the study group diagnosed with scleroderma (n=18) or stage II-III sarcoidosis and IPF. The incidence of OSA was 68%. The mean apnea-hypopnea index (AHI) was 11.4±12.5. Patients with IPF commonly had OSA (p=0.009). The incidence of fast eye movement-connected sleep apnea was 52.9 %. Patients having a disease severity index ≥3 (p=0.04) had higher incidence of OSA. Patients having diffuse radiological involvement (p=0.007 and p=0.043, respectively) had higher AHI and oxygen desaturation index OSA is

					common in ILD. PSG or smallest nocturnal oximetry need to be done, mostly in patients having radiologically and functionally acute condition.
Pillai et al.[15]	2012	Retrospective	54	To evaluate in case of ILD if OSA will worsen diaphragm/LES dysfunction and elevate the tendency for gastro-esophageal reflux as well as its severity.	OSA and apnea-hypopnea index did not predict the existence of gastro- esophageal reflux in 54 patients,. Irrespective of the location of the body (upright, recumbent), Gastro-esophageal reflux did not occur more frequently or was strong among OSA patients versus the patients not having OSA. IPF patients had chances of having gastro-esophageal reflux nearly seven-times greater than those having other types of ILD. There was no link between respiratory physiology and GER for the whole IPF group and subgroup. OSA seems not to stimulate gastro-esophageal reflux in ILD. Further study needs to be done to know if compensatory mechanisms stemming from the diaphragm hinder gastro- esophageal reflux in ILD patients having OSA and to find out if gastro-esophageal reflux is involved in the development of some types of ILD.
Lancaster et al.[16]	2009	Prospective	50	To evaluate OSA in stable outpatients having IPF.	Fifty subjects were enrolled, with mean age of 64.9 years, and mean BMI of 32.3. 88% of them had OSA. 10 (20%) of them presented slight OSA (AHI, 5 to 15 incidents/h), and 34 (68%) of them presented moderate-to-acute OSA (AHI, > 15 incidents/h). Only six (12%) presented a normal AHI. One subject had no symptom according to ESS and SA- SDQ, but with 24 AHI incidents/h. The ESS sensitivity was 75%, and its specificity was 15%; while the sensitivity of SA-SDQ was 88% and its specificity was 50%. BMI had no strong correlation with AHI ($r = 0.30$; $p = 0.05$). IPF subjects commonly had OSA, and may be under-recognized by experts and primary care givers. ESS and SA-SDQ separately or when combined were not powerful screening tools. Due to the high frequency seen in the sample of this study, it is proper to evaluate sleep and polysomnography formally in IPF patients.

between gas exchange and ventilation during sleep versus exercise in patients with interstitial lung disease.
Other studies have evaluated some interventions done during sleep in ILD patients. Mermigkis et al.[11] evaluated the influence of CPAP in improving the sleep quality of patients with OSA and ILD. Pihtili et al.[14] investigated the correlation between polysomnographic readings and the severity of ILD.
From the study findings, all the articles evaluated the oxygenation and respiratory parameters of sleep-disordered breathing in patients suffering from interstitial lung diseases. Table 1 shows the articles considered in this work.

Discussion

Interstitial lung disease is frequently accompanied by disturbed sleep. Additionally, polysomnography in the study patients shows an elevated sleep fragmentation.[14] Fatigue is also a common problem in these patients, caused primarily by poor quality of sleep.[7]
Some trials in the medical literature showed that sleep-disordered breathing is very frequent in the patient population, with idiopathic pulmonary fibrosis. This review sheds light on an updated overview within the past decade of a sleep-disordered breathing condition in ILD patients.[7-16]
Most recently, Cho et al.[2019], in a cross-sectional study, evaluated the incidence of poor quality of sleep among 101 patients with interstitial lung using the Sleep Quality Index of Pittsburgh. They revealed that patients with interstitial lung disease commonly suffered from poor quality of sleep, which can be positively correlated with depression and anxiety. Furthermore, they recommended a regular evaluation of the sleep quality of these patients.
Another study concerned with sleep breathing problems and their influence on sleep quality is that of Pihtili et al.[14] It examined the frequency of obstructive sleep apnea in patients with ILD and also investigated the correlation between polysomnograph changes and pulmonary function as well as the disease severity and Epworth Sleepiness Scale (ESS).
Through sixty-two patients with either idiopathic lung fibrosis, Pihtili et al.[14] showed that the average apnea-hypopnea index (AHI) was (11.4±12.5). They also revealed that patients with ILD mostly have obstructive sleep apnea, and its incidence increases with the increased severity of the disease. These findings are in line with the outcomes of Lancaster et al.[16]
Also, Mermigkis et al.[11] studied the sleep and life quality of patients with idiopathic pulmonary fibrosis. They evaluated how to use CPAP in treating obstructive sleep apnea in this patient population and improve both their sleep and life quality.
92 idiopathic pulmonary fibrosis patients not previously treated with CPAP were included in the study. The authors initiated CPAP in patients with AHI ≥15 and divided the patients into either good or poor compliant patients with CPAP. The results showed that early treatment of obstructive sleep apnea in patients with idiopathic pulmonary fibrosis could drastically improve the patients' outcomes. Also, it is proved that patients' compliance with CPAP could have a positive impact on mortalityreduction through long term follow up data.
Lee et al.[12] also evaluated gas exchange and ventilation to find the factors disturbing sleep in idiopathic pulmonary fibrosis. In the study, 20 patients were examined using polysomnography, followed by the testing of cardiopulmonary activity the next day. The results showed that patients with idiopathic pulmonary fibrosis are more vulnerable to decreased oxygen saturation levels while sleeping compared to when they are exercising. Kolilekas et al.[13] recruited 31 patients who were newly diagnosed with idiopathic pulmonary fibrosis to examine sleep-disordered breathing and its influence on the survival of this patient population. Similar to Lee et al.[12], Kolilekas et al.[13] revealed that oxygen saturation reduced significantly during sleep in this patient population. It was linked to worsened pulmonary artery hypertension, hence, reduced survival.
Gille et al.[8] recruited forty-five patients who were newly diagnosed with idiopathic pulmonary fibrosis to find if obstructive sleep apnea can be linked to the severity of the disease and if it can be a risk factor for other diseases, such as cardiovascular diseases. There was a significantly positive correlation between obstructive sleep apnea and cardiovascular diseases, especially ischemic heart disease. Also, Gille et al.[8] revealed an increase in inflammatory biomarkers in patients with obstructive sleep apnea.
Similarly, Kim et al.[9] investigated the correlation between obstructive sleep apnea, interstitial lung disease, and inflammatory and injury biomarkers. Kim et al.[9] 's study was the largest of all. By recruiting 1690 patients, the authors showed a positive correlation between moderate to severe obstructive sleep apnea and interstitial pulmonary disease, especially in normal weighed patients.
In a small study carried out by Schertel et al.[10], the research team evaluated cough, oxygenation, and respiration over eight months during wakefulness compared to sleep in patients with idiopathic pulmonary fibrosis. The result showed that cough was more common during the daytime, while other respiratory parameters did not differ significantly in the two states. However, the small sample size of this study makes its findings questionable.
Another interesting study was that of Pillai et al.[15] It showed how the presence of obstructive sleep apnea

with interstitial lung fibrosis can affect the diaphragm morphology, which in turn can change the intrathoracic pressure, thus leading to gastroesophageal reflux (GERD). Through 54 subjects, the study shows that obstructive sleep apnea in ILD does not promote the occurrence of GERD.

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