Respiratory Medicine 129 (2017) 46–52

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Idiopathic pulmonary fibrosis: Clinical behavior and aging associated comorbidities

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ARTICLE INFO

Article history:
Received 13 March 2017
Received in revised form
11 May 2017
Accepted 1 June 2017
Available online 3 June 2017

Keywords:
Comorbidities
IPF
Aging

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible and usually lethal lung disease of unknown etiology. Once considered as a relatively homogeneous, slowly progressive disease, is now recognized that the clinical behavior shows substantial heterogeneity, including an accelerated variant, and the presence of acute exacerbations. In addition, since IPF largely affects individuals over 60 years of age, the patients are at increased risk of several comorbidities that in turn have a remarkable clinical impact on the disease and increases mortality rate. Among others, combined pulmonary fibrosis and emphysema, secondary pulmonary arterial hypertension, lung cancer, and cardiovascular diseases are frequently associated with IPF and impact survival. For these reasons clinical phenotypes and comorbidities should be timely identified and managed. The aim of this review is to describe the common pulmonary and extra-pulmonary comorbidities in IPF, as well as the putative mechanisms involved.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and deadly disease with few and modest therapeutic options and a median survival of 3–5 years following diagnosis [1,2]. The confident diagnosis of IPF is achieved by the presence of a typical pattern of usual interstitial pneumonia (UIP) either by high-resolution computed tomography (HRCT) or histology in an appropriate

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http://dx.doi.org/10.1016/j.rmed.2017.06.001
0954-6111/

clinical setting including the absence of an identifiable etiology (Fig. 1). However, about a third of the IPF patients display atypical HRCT findings and the disease may be confused with another fibrotic lung disorder such as chronic hypersensitivity pneumonitis (cHP) or ILD secondary to autoimmune disease or diagnosed as unclassifiable interstitial lung disease [3, 4]. Moreover, there is substantial overlap in the clinical and functional behavior between IPF and non-IPF disorders and in general, virtually all the ILD patients refer progressive exertional dyspnea and dry cough, and a restrictive functional pattern with decreased forced vital capacity and compliance and hypoxemia at rest worsening with exercise.

Therefore, clinicians face two challenges for the confident diagnosis of IPF; on one hand, a patient with IPF may present atypical tomographic and/or morphologic findings and on the other, a patient with another chronic fibrotic lung disorder, e.g., cHP without identifiable causative antigen, may exhibit chest HRCT or pathological changes mimicking UIP [4]. This diagnostic uncertainty represents an important problem since the prognosis and therapeutic approach is completely different. In this context, it is recommended that patients consulting by a diffuse parenchymal lung disease be evaluated by a multidisciplinary team involving pulmonologists, radiologists, and pathologists experienced in the field of ILD, moreover, the high frequency of connective tissue disease-related ILD requires adding a rheumatologist to the team [5, 6].

Therapy represents a significant challenge in IPF. During a long time, with the notion that the disease represented an inflammatory-driven fibrosis, patients were treated with high dose of corticosteroids and immunosuppressive drugs. However, these drugs not only were unable to modify the progressive and devastating natural course of the disease, but also resulted in higher mortality [7]. From 2014, two putative antifibrotic drugs were approved for the treatment of IPF, nintedanib, an inhibitor of the Src family of tyrosine kinases, and pirfenidone, a small synthetic molecule with unknown mechanisms of action [8,9]. Both drugs reduce the loss of lung function over time and perhaps stabilize a (yet unidentified) subgroup of patients, although survival and quality of life benefits have not convincingly been established with either agent. Moreover, patients that were included in the clinical trials displayed mild or moderate pulmonary function alterations and the drugs were used for relatively short periods of time. It is not yet clear whether these drugs may show similar results in patients with more severe disease, as are usually seen in the real life, and how will be the adverse event profile with long-term (several years) of treatment. However, both drugs opened a new window in the treatment of IPF and some preliminary reports suggest that safety data did not dramatically change over time [10–12].

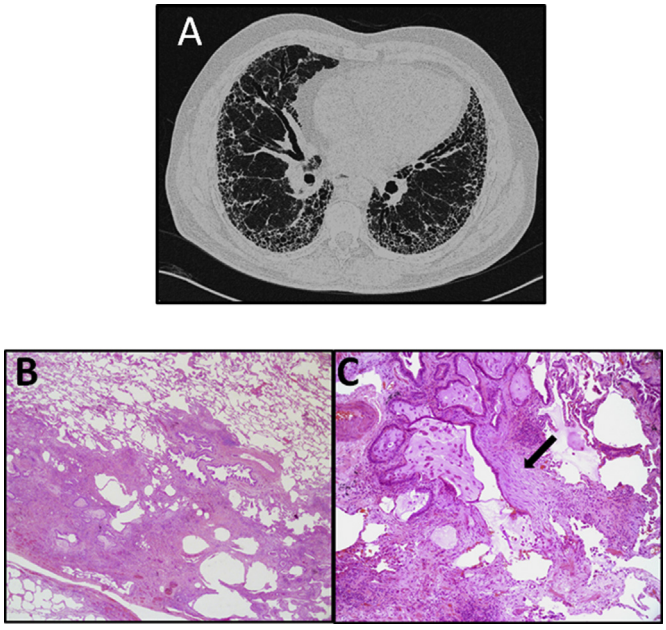

Fig. 1. Hallmarks of usual interstitial pneumonitis A) High-resolution computed tomography showing architectural distortion with subpleural and basal reticulation, traction bronchiectasis, and honeycombing. **B)** and **C)** Pathology of UIP pattern. **B)** Extensive subpleural fibrosis alternating with areas of mild fibrosis and others of uninvolved parenchyma in an appearance named "patchwork pattern". **C)** High magnification of an UIP lung showing architectural distortion by honeycombing and an area of active fibrosing process identified by a large subepithelial fibroblastic focus (arrow).

2. Clinical phenotypes and comorbidities

During a long time the natural history of IPF was considered to be characterized by a slowly progressive course. However, it is now recognized that the clinical behavior shows substantial heterogeneity and different clinical phenotypes have been defined. In addition, since IPF occurs usually in older individuals, they may present some aging-associated comorbidities which affect its clinical course and survival [2, 13]. Thus for example, the incidence and prevalence of some comorbid conditions are remarkably more frequent in patients with IPF compared with age-matched controls. Some of them, for example lung cancer, occur at least in part because they share common risk factors (smoking) and some pathogenic mechanisms (e.g., epithelial genetic instability) while others seem to be a direct consequence of IPF (pulmonary hypertension, ischemic heart disease).

To date however, the clinical course and prognosis of individual patients are difficult to predict because reliable clinical parameters or biomarkers reflecting disease progression are scanty and the studies have been usually retrospective and without verification in independent cohorts.

Most patients progress slowly with or without periods of relative stability while others experience rapid decline and die in a short time after diagnosis [14, 15]. IPF may also be complicated by an acute exacerbation characterized by an acute worsening of dyspnea and lung function that severely worsens survival [16,17].

2.1. Acute exacerbations

A subset of IPF patients, more often those with advanced disease and never smokers, presents episodes of acute clinical deterioration that precede and possibly initiate the terminal phase of the disease [16, 17]. Actually, acute exacerbations result in high in-hospital mortality. The incidence is difficult to estimate but a recent meta-analysis involving six randomized-controlled clinical trials in patients with IPF revealed a weighted average of around 40 acute exacerbations per 1000 patient-years [18].

The acute episode may be "idiopathic" when it is not associated with an identifiable cause, and it is assumed that represent sudden acceleration of the underlying disease process, or secondary when it is trigger by a recognizable cause such as infection, pulmonary embolism, or heart failure among others [17, 19]. Acute exacerbations are characterized by rapid progression of dyspnea within the previous 30 days, with the presence of new bilateral ground-glass opacities or consolidation by radiography/HRCT without pneumothorax or pleural effusion, and a marked decrease in the PaO2 (Fig. 2). When performed, lung biopsy demonstrates diffuse alveolar damage superimposed to a background of UIP with or without concurrent organizing pneumonia [16, 20]. However, differentiate idiopathic from non-idiopathic acute respiratory worsening in the clinical arena is challenging, since for example, exclusion of

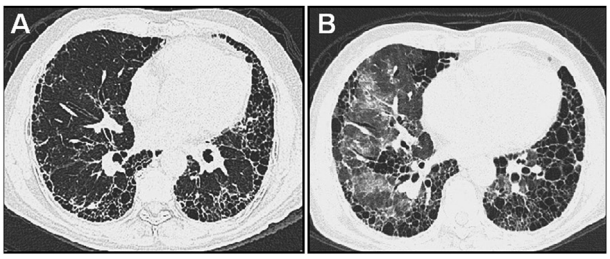

Fig. 2. Acute exacerbation. High-resolution computed tomography showing a pattern of typical usual interstitial pneumonia in panel **A** and the presence new bilateral ground glass attenuation over imposed on the previous UIP lesions in panel **B**.

underlying infection or subtle microaspiration are often not clinically realizable and empiric treatment is often started regardless putative etiology [20]. Moreover, infections and other secondary events that may lead to non-idiopathic acute exacerbation are indistinguishable from idiopathic acute exacerbations of IPF [17].

The pathogenic mechanisms involved in "idiopathic" acute exacerbation are unknown.

A recent retrospective autopsy study involving 12 patients with IPF suggests that acute exacerbation may be a systemic disorder that affects multiple organs [21]. Circulating large cells expressing scavenger receptor A and cells expressing tumor necrosis factor-α were detected before death in most patients and in all cases at autopsy suggesting that may contribute to the extensive capillary endothelial cells injury observed in different tissues. Interestingly, serum and BAL levels of angiopoietin-2 (Ang-2) are increased at the time of acute exacerbation [22]. Ang-2 interferes with Ang-1-induced endothelial Tie2 activation by preventing Ang-1 from binding to the receptor enhancing pulmonary inflammation and permeability.

Transcriptional signature of stable IPF versus AE-IPF suggests that it represents an extension of the molecular process that underlies IPF where the key molecular events are localized to the alveolar epithelium [23]. Among the differentially expressed genes were those related to stress response such as heat shock proteins, α-defensins and mitosis-related genes including histones and CCNA2 a general regulator of the cell cycle. Widespread epithelial proliferation and apoptosis were also detected. Consistent with these findings, increased levels of biomarkers of type 2 alveolar epithelial cell activity has been found in AE-IPF compared to stable IPF [24]. Also, it has been shown a noteworthy increase of fibrocytes during episodes of acute exacerbation, which fell back to pre-exacerbation levels in the few patients who recovered [25]. Fibrocytes express a variety of mediators including several matrix metalloproteinases that may play a role in the process of migration throughout the basement membranes and the interstitial collagen matrix [26].

Likewise, leptin concentration was found higher in subjects with AE-IPF than those with stable IPF and higher in subjects who died than in those who survived to vital status ascertainment [27]. Leptin is a multifunctional cytokine known to increase TGF-β1 signaling in lung fibroblasts.

2.2. The accelerated variant

An accelerated variant of IPF was first described a decade ago according to the duration of symptoms before diagnosis [14]. In this study, it was shown that a subgroup of IPF patients, primarily smoker males, consulting within 6 months after the beginning of symptoms deteriorates faster and their survival was appreciably worst compared to those patients with a slowly progressive course. Global gene expression demonstrated the upregulation of several functional pathways in the rapid progressive patients, mostly operating in alveolar epithelial and mesenchymal cells including genes involved in development, cell migration, myofibroblast differentiation, oxidative stress, and coagulation [14]. These findings allowed the identification of a distinct clinical phenotype of IPF differing in clinical course and transcriptional profile, despite presenting similar alterations in lung function, HRCT scans and histopathology of those with slowly progressive disease. Subsequently, Boon et al. [15] examined the lung gene expression profiles from IPF patients with relatively stable (or slowly progressive) clinical course and those with rapidly progressive IPF. In this study, accelerated progression was identified by changes in pulmonary function tests [a decline of forced vital capacity (FVC) and lung diffusing capacity (DLCO) of $\geq$10% and $\geq$15% respectively], over 12 months. A molecular signature of 134 genes was over represented in the rapid progressive IPF group that included several cell functions like proliferation, migration, invasion and cell death. Interestingly, 90 of the differentially expressed genes (67%) coincided with the genes identified in the previous study [14, 15].

2.3. Combined pulmonary fibrosis and emphysema (CPFE)

Emphysematous lesions are observed in a number of patients with different idiopathic interstitial pneumonias, mainly IPF, and in fibrotic lung disorders of known etiology such as those associated to connective tissue diseases [28, 29]. This syndrome is called "combined pulmonary fibrosis and emphysema (CPFE), and is observed in a subset of IPF patients, usually ever smoker males. Diagnosis of CPFE is based on chest computed tomography showing any grade of emphysema (defined as well-demarcated areas of decreased attenuation with very thin or no wall and/or multiple bullae) usually located in the upper lobes and UIP-like changes located in the lower lobes (Fig. 3) [30].

The exact prevalence of CPFE in IPF patients is still uncertain, but seems to be high (>30%). Patients with both pulmonary fibrosis and emphysema have different pulmonary function tests than patients with pure emphysema or pure fibrosis, and usually exhibit a worst impairment of gas exchange with a disproportionate decrease of DLCO, a misleading almost normal forced vital capacity, and a higher prevalence of pulmonary hypertension than patients with IPF without emphysema [30].

Studies regarding the impact of emphysema on mortality have given contradictory results, in part because the cohorts have included different idiopathic interstitial pneumonias (IIP) that basically have different prognosis. In this context, a recent cluster analysis was used to identify the CPFE phenotypes of IIP patients and to evaluate outcome [31]. Three clusters were revealed and it was demonstrated that presence of emphysema in patients with IPF

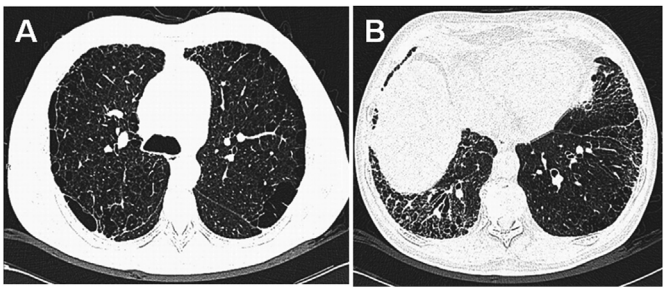

Fig. 3. Combined pulmonary fibrosis and emphysema (CPFE). Panel A: High-resolution computed tomography showing emphysematous areas in upper lobes. **Panel B:** Extensive subpleural fibrosis and bronchiectasis in the lower lobes of the same patient.

results in a marked worse survival rate compared with patients with other IIP and emphysema.

The pathogenic mechanisms leading to CPFE, and whether pulmonary fibrosis and emphysema are two different diseases simply associated with cigarette smoking or if they represent a distinctive pathological condition of a subgroup of patients are still uncertain. Most evidence suggests that they are two diseases running in parallel in smokers. In a review through Medline from 607 patients with CPFE for whom smoking status was recorded 592 (98%) were either current or former smokers [32]. Actually, pathologically significant but clinically unrecognized interstitial fibrosis occurs commonly in cigarette smokers together with emphysematous lesions [33]. In this study, over half of lungs resected for tumors from cigarette smokers, showed fibroblasts foci and some of them extensive thickening of alveolar septa by dense collagen with no or only minimal associated inflammation. Likewise, airspace enlargement with fibrosis was reported in a large cohort of cases as a frequent finding of smoking-related pathological changes encountered in the lung that shows a positive correlation with centrilobular emphysema and UIP like lesions [34]. However, since IPF combined with emphysema is remarkably higher in males, and in both diseases abnormal shortening of telomeres and other conditions associated to accelerated aging have been observed, we cannot rule out that some gender and aging-related mechanisms may play a role [35]. Regarding therapy, it is currently uncertain whether nintedanib and pirfenidone have a similar effect than on IPF alone. It can be recommended under close surveillance together with smoking cessation and supplemental oxygen. Bronchodilator therapy and pulmonary rehabilitation may be empirically prescribed.

2.4. Lung cancer

There is strong evidence indicating that the risk of lung cancer is markedly increased in patients with IPF, and that this association is at least partially independent of smoking habit (Fig. 4) [36]. Actually, around 10% of patients with IPF develop lung cancer, which has a strong deleterious influence on survival [37, 38]. Some of them are diagnosed as having primary lung cancer at the same time of IPF diagnosis, but mostly develop the neoplasia during the follow-up. Squamous cell carcinoma is the most common followed by adenocarcinomas.

The pathogenic mechanisms by which IPF increases the risk of lung cancer are unclear, and may be associated with genetic, epigenetic and architectural conditions. Thus, IPF and lung cancer share a number of genetic alterations that affect critical epithelial cell functions including micro-satellite instability, loss of gene heterozygosity and p53 point mutations [39, 40]. In a recent study, genetic alterations at the microsatellite level, located within or near tumor suppressor genes implicated in lung cancer were detected in the exhaled breath condensate of 11 patients with IPF [41]. Nine patients exhibited loss of gene heterozygosity and five showed micro-satellite instability in at least one microsatellite marker. No healthy subjects exhibited these alterations.

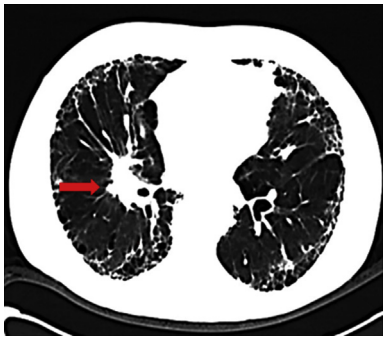

Fig. 4. Lung Cancer in a patient with IPF. High resolution computed tomography shows a large spiculated mass in right hip (arrow).

Global methylation patterns of IPF using human CpG island microarrays has revealed an altered DNA methylation pattern which exhibits great similarity to the methylation pattern of lung cancer [42]. Actually, 65% of the CpG islands having an altered methylation pattern in IPF lungs were also modified in lung adenocarcinoma samples. Also, both diseases share some environmental factors, primarily smoking.

Lung cancer occurring in IPF patients represents a therapeutic challenge. Surgical treatment of lung cancer in these patients is problematic because is often complicated by respiratory function-related morbidity and a high rate of postoperative mortality. However, patients at early stages with mild to moderate level of functional impairment may have better survival [43].

2.5. Pulmonary hypertension

Pulmonary hypertension (PH) is a severe complication of IPF and contributes significantly to morbidity and mortality. The prevalence is difficult to estimate because most studies measure systolic pulmonary artery pressure with transthoracic echocardiogram whose diagnostic accuracy is questionable usually leading to considerable overdiagnosis [44]. In addition, symptoms of PH overlap with IPF making it difficult to diagnose. A combination of disproportionate decrease of DLCO according lung volumes, poor 6-min walk performance, and need for supplemental oxygen is very specific but not sensitive in predicting PH [45].

Prevalence of PH at diagnosis depends of the severity of IPF, and likely of the presence of other comorbidities such as sleep apnea, thromboembolic disease, or heart failure. At baseline, around 10% of patients with mild to moderate disease have PH defined as a mean pulmonary artery pressure >25 mm Hg and a pulmonary capillary wedge pressure $\leq$15 mm Hg, documented by right heart catheterization [46]. By contrast, around 30% of the IPF patients diagnosed with advanced disease have PH also evaluated by right heart catheterization [45, 47]. Hypoxic pulmonary vasoconstriction and the destruction of the pulmonary capillary bed play a major role in the active regulation of pulmonary vascular resistance [47]. Hypoxia has direct effects on pulmonary vascular smooth muscle cells. In addition, impaired release of endothelium-derived vasodilators such as nitric oxide and prostaglandin, and increased expression of the vasoconstrictive peptides like endothelin also contribute to the development of PH [47].

Global gene expression analysis performed in laser capture microdissected pulmonary arteries demonstrated that the pulmonary vascular gene expression signature is similar in patients with coexistent IPF and PH and those with IPF alone and is characterized by uncontrolled vascular cell proliferation and deregulated apoptosis [48]. Interestingly, some of the upregulated genes suggested a role for Wnt signaling in promoting the development of pulmonary hypertension.

To date, no specific anti-hypertensive treatment for pulmonary hypertension secondary to IPF is available. A first approach with sildenafil in patients with advanced disease, although did not reach the primary end point, showed encouraging results improving dyspnea, quality of life, DL_{CO} and oxygen saturation [49]. In a subsequent study, it was found that sildenafil preserves exercise capacity only in IPF patients that have right-sided ventricular dysfunction [50]. In sharp contrast, selective and nonselective endothelin receptor antagonists, e.g., bosentan and ambrisentan,

have not been effective in treating IPF and even may be associated with an increased risk for disease progression and respiratory hospitalizations [51]. In the absence of effective therapy, supplemental oxygen according to the verified hypoxemia and perhaps sildenafil under close follow-up are currently the most prudent therapy.

2.6. Cardiovascular diseases

Several studies have demonstrated that patients with IPF have a higher prevalence of cardiovascular disorders such as ischemic heart disease and atrial fibrillation compared with the general population and even with similarly matched COPD group [52, 53]. It is unclear whether the increased cardiovascular risk of these patients is associated to the increased prevalence of general cardiovascular risk factors, such as obesity, diabetes mellitus, hyperlipidemia, and arterial hypertension [54–56] or whether it is directly related to IPF.

To approach this question, Dalleywater el al, used The Health Improvement Network (THIN), a UK longitudinal database of electronic primary care records and evaluated 3211 incident cases of IPF and 12,307 randomly selected, matched, general-population control subjects. It was found that IPF patients were 31% more likely to have a record of hypertension, and 20% more likely to have a record of diabetes mellitus prior to receiving a diagnosis of IPF compared with controls [57]. Also, IPF patients were more than twice as likely to be former smokers before the diagnosis. However, IPF patients had twice the rate of first-time ischemic heart disease events after their diagnosis compared with the general population, after adjusting for cardiovascular risk factors and prescription of cardiovascular-related drugs. These findings suggest that IPF is an independent risk factor for this disorder. In this context, it is important to emphasize that in the INPULSIS studies 10 patients treated with nintedanib presented myocardial infarction compared with 2 patients in the placebo arm [9].

In general, it is recommended cardiology evaluation and if necessary, appropriate medical treatment for ischemic coronary disease or other cardiovascular disorder.

2.7. Gastro-esophageal reflux disease (GERD)

Different studies indicate that the prevalence of GERD is higher in patients with IPF compared with matched control individuals or patients with other chronic respiratory diseases [58, 59]. Moreover pepsin, a marker of gastric aspiration, has been revealed in the bronchoalveolar lavage (BAL) of most patients with stable IPF, suggesting that occult microaspiration is frequent in this disease which theoretically may lead to repeated subclinical lung injury [60]. Therefore, a vicious circle may exist in these patients where on one hand, decreased lung compliance of the fibrotic lung provokes increased swings in intrathoracic pressure resulting in dysfunctional lower esophageal sphincter, gastro-esophageal reflux, and microaspiration while on the other hand, microaspirations may contribute to the epithelial cell damage [61].

However, it is uncertain whether there is a causal relationship between chronic microaspirations of gastric contents and the development or progression of IPF. A strong pathogenic role is doubtful since gastroesophageal reflux is a highly prevalent disorder (that share several risk factors with IPF including aging and ever tobacco smoking) while IPF is a relatively uncommon disease.

Also, it is still unclear whether the presence of gastro-esophageal reflux (which is often silent) has a prognostic impact of the disease. In one study dealing with 4 patients it was found that empirical treatment with proton pump inhibitors was associated with stabilized or improved lung function, and less hospitalizations due to respiratory problems, including acute exacerbations [62]. In another work, it was found that patients receiving anti-reflux medications (n = 19) showed a modest but significantly better diffusing lung capacity and lower composite physiologic index of severity that those without treatment (n = 14) [63].

Surprisingly however, several recent studies including larger cohorts have shown that IPF patients with GERD display a better survival than those without GERD [64, 65]. Furthermore, most recent evidence including a post-hoc analysis from 624 patients randomly assigned to placebo in 3 clinical trials does not support a beneficial effect of antacid therapy on disease progression [64, 66]. Even more, in the latter study antiacid therapy was associated with a significantly higher incidence of pulmonary and non-pulmonary infections primarily in IPF patients with advanced disease [66]. However, evidence obtained so far has not been derived from prospective studies specifically designed to answer these questions including a randomized controlled trial with anti-reflux therapy.

On the other hand, gastro-esophageal reflux has been proposed as one likely cause of acute exacerbation. Thus for example, elevated BAL pepsin has been associated with acute deterioration in some IPF patients providing some evidence that microaspirations may play a role in triggering these events [60]. Certainly as mentioned, it cannot be ruled-out that by contrary, acute respiratory decompensation leads to increased aspiration through increased intrathoracic pressure swings.

2.8. Obstructive sleep apnea (OSA)

Obstructive sleep apnea seems to be prevalent, and likely underdiagnosed in patients with IPF. For example, two studies found that OSA, defined as an apnea-hypopnea index of >5 events per hour was present in 59% and 88% of the IPF cases respectively, although the studies included small cohorts of patients [67, 68]. Disrupted sleep architecture and intermittent sleep oxygen nocturnal desaturation appears to be associated with worst survival [69]. A recent study showed that the use of continuous positive airway pressure (when appropriate compliance) results in a significant improvement in daily living activities, quality of sleep and life and survival [70].

2.9. Osteoporosis and fragility fracture

Studies regarding IPF and bone status are scanty. Decreased bone mineral density has been reported in thoracic vertebral in patients that were not receiving corticosteroids [71].

In a recent population-based study designed to evaluate the prevalence of osteoporosis and vertebral fractures in IPF patients, it was shown that about third of them have osteoporosis and at least one vertebral fracture [72]. Reduced bone mineral density was associated with significant decreases in FVC and DLCO. Interestingly, although osteoporosis prevailed in females, vertebral fractures were more frequent in males.

2.10. Diabetes mellitus

Several studies performed in populations of different genetic background have found an increased prevalence of diabetes mellitus in patients with IPF [73–75]. In one of these studies, the strongest association was observed with use of insulin, and the result was sustained even when patients with prescriptions for corticosteroids were excluded [75]. The pathogenic mechanisms involved in this association are unclear. High levels of glucose may activate several pathways related to the production of reactive oxidative species and profibrotic cytokines. Interestingly, abnormal

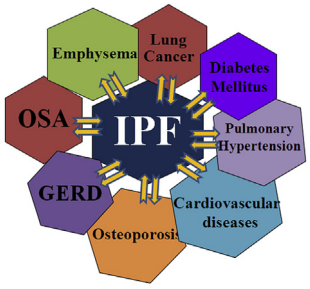

Fig. 5. Several major comorbidities have substantial clinical impact on idiopathic pulmonary fibrosis. In general, there are bidirectional negative effects where IPF increases the risk for the comorbidity, e.g., gastroesophageal reflux, lung cancer, while the comorbidities affect the quality of life and increase the risk for mortality.

telomere shortening has been found associated with type 2 diabetes mellitus and its related conditions, like insulin resistance and impaired glucose tolerance [76]. Telomere attrition and dysfunction is often observed in familial (e.g., telomerase mutations) and sporadic IPF [77].

In conclusion, IPF although usually progressive, displays a marked clinical heterogeneity and is affected by several aging-associated comorbidities resulting in different survival rates (Fig. 5). However, no gene or molecular signature has been consistently identified with predictive or prognostic value for the early distinction of the diverse clinical phenotypes and to help optimize future targeted therapy.

Conflict of interest

The authors do not have conflict of interests with this manuscript.

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