

REVIEW

Reflux in idiopathic pulmonary fibrosis

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Key points

- GORD is common in IPF
- It has been implicated in acute exacerbations
- Treatment with anti-reflux medications has been reported to be independently associated with increased survival
- Care needs to be taken in selecting anti-reflux therapy due to risk of cytochrome interactions, which may decrease efficacy of concomitant Pirfenidone treatment.

Gastro-oesophageal reflux disease (GORD) was first implicated in the pathogenesis of pulmonary fibrosis in 1976.¹ Idiopathic Pulmonary Fibrosis presents most commonly in the sixth decade of life and has a dismal median survival of 2–3 years. There have been significant and encouraging increases in knowledge underpinning key mechanisms of pathogenesis in terms of angiogenesis, signaling pathways, pro-fibrotic cell types and early remodelling.^{2–4} Currently, the initiating events remains unknown however many possibilities have been identified. Despite the increased understanding of pathogenesis anti-inflammatory and target specific strategies, with the exception of Pirfenidone and Nintedanib, have been ineffective in terms of survival. An area generating heightened interest is modification of preventative risk factors that may drive more aggressive disease. In recent times micro-aspiration as a result of reflux has been receiving renewed interest. Partially because of its prevalence in idiopathic pulmonary fibrosis (IPF) but also recent data suggest survival benefit in those on anti-secretory medication. We will review the current evidence with regards to association, treatment and impact on the natural history of IPF. We suggest that current evidence leads weight to the concept of GORD as a potential driver of disease progression and responsible for acute exacerbations (AEs) in a subgroup of patients

therefore treatment with anti-reflux medications may form the basis of a lung protective strategy.

Current association

GORD has been implicated in the pathogenesis of pulmonary fibrosis for almost half a century. Early studies in IPF patients awaiting transplantation found the prevalence of reflux to be around 60%.⁵ A retrospective study found that early fundoplication in lung transplant recipients was associated with lower levels of BOS and improved lung function.⁶ These observations led to interest in the role of GORD not only as a possible initiator of injury but also as a driver of more aggressive disease in the form of exacerbations in IPF. Further interest was generated following a case series report of stabilization of disease progression in four patients treated aggressively with anti-reflux strategies.⁷

The association of reflux and IPF has been demonstrated by two robust case control studies. The first demonstrated an association between oesophageal stricture or erosive oesophagitis with a range of pulmonary disorders including pulmonary fibrosis calculating an odds ratio (OR) of 1.36 in American veterans.⁸ The second a case controlled study of 920 IPF patients in the setting of UK general practices found the OR for diagnosis of GORD to be 1.65, a stronger relationship was found for associated medications including antacids 1.71 and ulcer drugs 2.22. These results were largely unchanged when cases and controls that had been prescribed prednisolone were excluded.⁹

Review of the current literature (Table 1) confirms a high prevalence of pathological reflux in IPF patients, depending on criteria used estimated between 60 and 90%.^{10–15} A case control study found that 12% of IPF patients were diagnosed with GORD prior to their IPF diagnosis.⁹ The incidence of GORD in IPF patients is consistently significantly higher in comparison to non-IPF interstitial lung disease (ILD) and obstructive airway disease controls across the studies. Around 50–75% of patients

Table 1. Prevalence of GORD in IPF

Study	Methodology	Prevalence of GORD (%)	Results
Savarino et al. ¹⁰	Prospective	83	IPF patients had significantly higher oesophageal acid exposure, number of acid, weakly-acidic and proximal reflux events compared to DPLD patients and HVs. 48% were symptomatic. No difference in motility between IPF and DPLD
	40 IPF		The total number of reflux events both distal and proximal correlated well to degree of fibrosis
	40 DPLD		Patients with IPF had more bile acids and pepsin in BAL and saliva than DPLD patients and controls
	50 HV		
Allaix et al. ¹¹	Retrospective	61	IPF symptomatic in 60% and only 61% had reflux by pH criteria
	22 IPF + GORD		Oesophageal function largely preserved however UOS hypotensive
	80 GORD		Proximal oesophageal acid exposure was higher and clearance of acid in the supine position was slower
Noth et al. ¹⁷	Retrospective		HH was significantly higher in IPF (39%) than either COPD (13.3) or asthma (16.7%)
	100 IPF		HH correlated with GORD as measured by DeMeester scores
	60 COPD		In IPF, HH did not correlate with lung function, except in those on anti-reflux therapy, who had a better DLCO
	24 asthma		
Hoppo et al. ¹²	Retrospective	82	96% were symptomatic, Oesophageal mucosal injury was found in 71%
	28 IPF		73% HH and 64% had PPI dependence
			Abnormal proximal exposure in 54% but these patients were significantly older
Liang et al. ¹³	Prospective	67	GORD in IPF patients was significantly higher than that in other DPLD patients (26.1%)
	24 IPF		87.5% patients with IPF and GORD had nocturnal acid exposure
	23 DPLD		37.5% of the IPF patients with GORD were symptomatic
			There was no difference in oesophageal motility between groups
Gribbin et al. ⁹	Prospective	12	Odds ratios for diagnosis of GORD 1.65, antacids 1.71, ulcer drugs 2.22
	Case control	Pre- diagnosis	Results were largely unchanged when cases and controls that had been prescribed prednisolone were excluded
	920 IPF		Positive associations for diabetes mellitus 1.31.
	Prospective	36	No significant differences between symptomatic and asymptomatic IPF patients regarding demographics, pulmonary function, presentation or manometric findings.
	28 IPF		
Sweet et al. ¹⁹	Prospective	67	Reflux was prevalent and frequently extended into the proximal oesophagus (50% of those with reflux)
	30 IPF		Reflux was associated with a hypotensive LOS and abnormal oesophageal peristalsis
	Prospective	57	57% of total patients had heartburn and regurgitation
	18 IPF/10 SF		67% of IPF patients had abnormal distal reflux
Raghu et al. ¹⁵	Prospective,	87 IPF	47% of IPF patients had heartburn and regurgitation.
	65 IPF		No significant difference in proximal reflux in IPF and asthma, 63% versus 61%, respectively
	133 asthma		12 from 19 patients receiving PPI during monitoring had abnormal acid exposure by pH probe

DPLD, diffuse pulmonary lung disease; HV, healthy volunteers; LOS, lower oesophageal sphincter; SV, secondary fibrosis; UOS, upper oesophageal sphincter.

are asymptomatic,^{10,13,15,16} suggesting typical symptoms of reflux would be ineffective in screening these patients. A higher incidence of hiatus hernia (HH) on Computed tomography (CT) has been documented in a retrospective analysis of 100 IPF (39%) patients in comparison to COPD (13.3%) and asthma (16.6%) controls. HH are associated with distal oesophageal sphincter dysfunction predisposing to reflux, confirmation was demonstrated by finding a good correlation between HH and DeMeester scores.¹⁷

Recent studies have gone further in assessing risk of micro-aspiration as a consequence of reflux by revealing high prevalence of proximal reflux in IPF patients with GORD at around 50%.^{10,12} In one of these studies patients with proximal acid exposure tended to be more oxygen dependent however this was not statistically significant and there was no difference in lung function. Another found a good correlation between the degree of fibrosis and total number of both distal and proximal reflux

events, which had been previously reported in scleroderma patients with interstitial fibrosis.^{10,18} Previous studies found the severity of reflux did not correlate with severity of IPF.^{15,19} The competing hypotheses are that IPF results in reduced compliance of lung architecture leading to increased negative intra-thoracic pressure, increased respiratory workload and altered oesophageal tone thereby promoting reflux. Or it could be speculated that GORD, a risk factor for micro-aspiration, has a casual relationship to IPF. Unfortunately, there is a lack of data to illuminate the precise relationship in this chicken and egg scenario.

Interestingly, it has been reported that both pepsin and bile salts were found with a significantly increased incidence in both saliva and bronchoalveolar lavage (BAL) fluid retrieved from IPF patients in comparison to non-IPF ILD patients, indicating actual increased aspiration in this patient group. There is also further evidence of weakly acid/non-acid reflux in around 30% of proximal reflux events. Chronic acid injury rat models

have demonstrated the development of obliterative bronchiolitis and parenchymal fibrosis.²⁰ These findings were independent of the pH of the aspirate and have been supported by further cell-based studies which found chenodeoxycholic acid a major component of bile acids significantly induced TGF- β 1 production in primary airway epithelial cells.²¹ In addition exposure of bronchial epithelial cells to gastric juice from patients on anti-secretory therapy is able to induce high IL-8 production indicating significant inflammatory reaction.²² These findings have significant implications for treatment.

There is some evidence that aspiration may lead to AE of IPF, which has been linked to a more rapid step like decline in the natural history of a subgroup of patients.²³ Pepsin in BAL has been demonstrated to be 100% specific and 80% sensitive for aspiration.^{24,25} Investigators have shown that BAL pepsin was elevated in a subgroup of patients with AE of IPF further confirming the major role of micro-aspiration in IPF patients.²⁶ A retrospective case-control study of 32 patients with asymmetrical IPF found that the rate of GORD and AE was significantly higher in the asymmetric group in comparison with the IPF controls. In this group of patients, 62.5% were right lobe predominant and 37.5% were left lobe predominant. They observed that the site of maximal fibrosis corresponded to the preferred left or right posture to fall asleep in 94% of cases.²⁷ Murine models have demonstrated acute lung injury following instillation of gastric juices characterized by increased oxygen requirements, reduced lung compliance and neutrophilic inflammation. Radiological findings are in keeping with diffuse alveolar injury as is seen in AEs of IPF.²⁸

The first study to indicate stabilization of progressive disease in IPF patients was a retrospective case series reported by Raghu in 2006. He described stabilization or improvement (in terms of PFT and exercise test findings) in four patients following employment of aggressive anti-secretory GORD strategies including PPI therapy or fundoplication if needed. No patient manifested an AE of IPF or needed treatment for respiratory problems during a 2- to 6-year follow-up. Interestingly, two patients had deteriorations during the course of follow up, both events correlated with apparent poor compliance and stabilization resulted from adherence to anti-secretory therapy.⁷ Another review of 14 IPF patients awaiting lung transplantation demonstrated stabilization of oxygen requirements in those patients who had undergone fundoplication, but no change in pulmonary function.²⁹ Lee *et al.*³⁰ described 204 patients in which GORD variables; such as history, symptoms and treatment of GORD were significantly associated with longer survival time on an unadjusted analysis. After adjustment, the use of anti-reflux medications was an independent predictor of longer survival time. In addition, the use of anti-reflux medications was associated with a lower radiologic fibrosis score.³⁰ Although an association has been identified there is insufficient evidence to suggest causation. A further report from Lee *et al.*³¹ analysing data of 242 patients from the placebo arms of three trials found patients taking anti-secretory therapy at baseline (51%) had a slower decline in FVC at 30 weeks than those that did not after adjustment for sex and baseline PFT. However, it must be acknowledged that an earlier reports found no difference in rates of death, disease progression or hospitalization in IPF patients on or off anti-secretory therapy.³²

In summary, there is a strong association with GORD ranging from OR 1.36 to 1.65. IPF patients have a high incidence of GORD up to 90%, and are often asymptomatic. Proximal reflux events both acid and non-acid are more common in IPF in comparison

to other diffuse lung diseases. Pepsin in BAL has been demonstrated to be 100% specific and 80% sensitive for aspiration and has been found in one study to be present in BAL in increased prevalence in IPF patients. Pepsin has also been found in BAL in patients with AE indicating a possible role for micro-aspiration as a causative factor in these events. Furthermore, several studies have found good correlation between degree of reflux and the severity of fibrosis on CT. Recently, it has been reported that the use of anti-reflux medications are associated with a smaller decrease in lung function and are an independent predictor of survival. However, it must be noted that currently studies are unable to demonstrate the precise relationship between GORD, micro-aspiration and IPF therefore further investigation is required.

Implications for practice

Current consensus defines the impact of gastro oesophageal reflux disease in IPF as unclear and that the treatment of asymptomatic reflux is weakly recommended in the majority of patients.³³ Review of previously published data provided hints and clues to possible benefits of anti-reflux medications, but more recent data suggest an independent survival benefit. The question is how aggressively we should treat these patients bearing in mind the majority are asymptomatic. Previous studies have documented abnormal acid exposure by pH probe in 12 from 19 patients receiving PPI during monitoring.¹⁵ In addition around 30% of proximal reflux events are non-acid indicating a possible role for motility agents in dealing with non-acid reflux which in its own right has been associated with lung injury. A study investigating the relationship between dinner-to-bed time and GORD found patients with a shorter dinner-to-bed time (<3 h) were significantly associated with an increased OR of GORD 7.45 compared with patients whose dinner-to-bed time was 4 h or more.³⁴ A further study revealed shorter dinner-to-bed time was associated with increased supine reflux.³⁵ This data suggests that full dose anti-secretory medication as well as prokinetics should be considered as part of a lung protective strategy in IPF in addition patients should be advised extend their dinner-to-bed time. It is important to note with the increasing use of Pirenidone that different Proton Pump Inhibitors have differing propensity for cytochrome interactions and therefore unknown potential modulating effects in the efficacy of this drug.

Conclusion

In conclusion it could be suggested that the treatment targets in IPF should be 2-fold. The first would be to employ lung protective strategies to prevent ongoing injury from micro-aspiration, a plausible driver of more aggressive disease in IPF. And secondly to employ targeted anti-fibrotic strategies in patients whom are likely to develop an accelerated course as a result of susceptibility. There is mounting evidence over the last decade associating GORD specifically as the cause of some AEs and it may have a role in pathogenesis. However, it must be noted that much remains unknown regarding the precise relationship namely there is a large discrepancy between the prevalence of GORD in the general population and the prevalence of IPF. Therefore, clarifying this relationship through a randomized clinical trial remains a key question to be addressed.

Conflict of interest: None declared.

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