Characteristics of gastro-esophageal reflux in patients with idiopathic pulmonary fibrosis

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KEYWORDS
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Abstract  Background:  Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease with a median survival rate ranging from 2 to 3 years from diagnosis. Recent data have illustrated the role of gastro-esophageal reflux (GER) in the pathogenesis and potential management of IPF patients. Although it is recognized that GER is increased among IPF patients, its prevalence and characteristics had been poorly defined.

Patients and methods:  Forty patients were recruited; 20 with a diagnosis of IPF and the other, 20 with interstitial lung disease other than IPF (non IPF patients). All patients underwent pulmonary high-resolution computed tomography (HRCT) scan and impedance-pH monitoring while off anti-secretory therapy. The presence of pulmonary fibrosis was assessed using validated HRCT scores. Reflux features included distal esophageal acid exposure, number of acid/weakly acidic reflux episodes and their proximal migration.

Results:  Seventeen (85%) patients out of 20 with IPF had an abnormal distal acid exposure, compared with 7 (35%) out of 20 non IPF patients (p = 0.003). Percentage total acid exposure time (AET) with pH < 4 was significantly higher in IPF compared with non IPF patients (median (range) 10.1 (5.1–16.3) versus 3 (1.2–8.3), respectively; p < 0.0001). In IPF patients the total (both acid and weakly acidic) numbers of reflux episodes [80 (45–99)], acid reflux [46 (25–57)] and weakly acidic reflux [35 (20–45)] were significantly higher than those of non IPF patients [45 (29–70), 28 (18–40) and 19 (10–30), respectively; p < 0.0001]. Also, more reflux episodes reached the proximal esophagus [54 (28–69)] in IPF patients than non-IPF patients [18 (8–32); p < 0.0001]. In IPF patients there was a significant positive correlation between degree of pulmonary fibrosis (HRCT score) and total number of reflux episodes in both the distal (r² = 0.57, p = 0.008) and proximal (r² = 0.61, p = 0.004) esophagus. In contrast, in non IPF patients a non significant correlation was found between degree of pulmonary fibrosis and total number of reflux episodes in both the distal (r² = 0.17, p = 0.48) and proximal (r² = 0.23, p = 0.34) esophagus.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy [1]. No therapy has been clearly shown to prolong survival [2]. Gastro-esophageal reflux (GER) disease has been previously associated with a number of interstitial lung diseases (ILDs) [3–7].

Recent investigations have demonstrated stabilization or delay of pulmonary fibrosis progression after medical or surgical treatment of GER [8–10]. In particular, Lee et al. [10] showed that the use of GER medications is associated with decreased radiologic fibrosis and is an independent predictor of longer survival time in patients with IPF. However, other studies highlighted that lung injury is independent of acidity and factors other than acid (i.e. foods, pepsin and bile acids) may be involved in its pathogenesis [11,12]. In particular, Mertens et al. [12] showed that exposure of bronchial epithelial cells to gastric juice from patients on anti-secretory therapy is able to induce high interleukin-8 production, the most relevant cytokine for the acute-phase response of inflammation.

In IPF patients, GER has previously been assessed by means of 24-h pHmetry that permits detection of acid reflux only. The recent use of impedance–pH monitoring allows us to detect both acid and weakly acidic reflux and to assess the extent of reflux into the proximal esophagus [13,14]. So, the aim of this study was to further explore the association of GER and pulmonary fibrosis by assessing the prevalence of all kinds of reflux in patients with IPF versus patients with ILD other than IPF.

Patients and methods

Patients

This study was carried out at Chest, Internal Medicine, Tropical Medicine and Radiology Departments and Outpatient Clinics, Zagazig University Hospitals during the period from January 2012 through January 2014. It included 20 patients with a definite diagnosis of IPF. The diagnosis of IPF was based on the absence of an identifiable etiology for ILD and a histopathological/radiological pattern of usual interstitial pneumonia on surgical lung biopsy and high-resolution computed tomography (HRCT) scans [1]. Another 20 consecutive patients with ILD other than IPF, referred for outpatient clinic follow up, were also enrolled for comparison. They were 4 patients with sarcoidosis, 8 patients with systemic lupus erythematosus, 5 patients with mixed connective tissue disease and 3 patients with bronchiolitis obliterans organizing pneumonia, who were diagnosed according to the characteristic histopathological findings on surgical lung biopsy or appropriate autoimmune markers and clinical presentations [15–18].

Methods

All patients were asked to discontinue any medication that would influence esophageal motility (i.e. nitrates, calcium antagonists, domperidone, benzodiazepines and metoclopramide) and acid suppressive therapy ≥ 30 days before the start of the study.

All studied patients were subjected to the following:

1. Thorough medical history.
2. Full clinical examination (general and local examination).
3. Pulmonary investigations

Pulmonary involvement was systematically investigated during the initial evaluation of IPF in all patients, by chest radiography, HRCT scan of the lungs and pulmonary function tests.

a. Pulmonary function tests:

Forced vital capacity (FVC) and forced expiratory volume (FEV1) curves were measured using a computerized pulmonary function device (Sensor Medics 2450, CA, USA). Pulmonary function was considered abnormal if volumes were < 80% predicted values [19].

b. Pulmonary HRCT:

High resolution scanning of the lungs was performed using standardized protocols to identify radiographic abnormalities related to IPF [1]. HRCT scans were evaluated by two experienced radiologists, independently and in a random order without the knowledge of the patients’ status. Any discrepancy in the assessment was discussed further and a consensus was reached. A semiquantitative analysis of the severity of fibrosis on HRCT was calculated by estimating the percentage of the lung affected by fibrosis (i.e. reticular abnormality and/or honeycombing) to the nearest 5% in three zones for each lung according to Best et al. [20]. These numbers were averaged to obtain a net radiologic fibrosis score using a 4-point scale (0 = no involvement, 1 = 1–25% involvement, 2 = 26–50% involvement, 3 = 51–75% involvement, and 4 = 76–100% involvement) [21].

4. Esophageal investigations

a. Manometry testing:

Esophageal manometry was performed by means of multichannel intraluminal impedance-esophageal manometry according to Savarino and Tutuiian [22]. Lower esophageal sphincter (LOS) pressure, upper esophageal sphincter (UES) pressure, peak contraction

Conclusion: IPF patients have greater GER rate compared to non IPF ones. Not only acid reflux, but also weakly acidic reflux is significantly increased among IPF patients.

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amplitude and duration of contraction were all measured. Manometric patterns were reported according to international criteria [23].

b. Impedance–pH monitoring:
Studies were performed off proton pump inhibitor treatment and according to Savarino et al. [24]. GER episodes were classified as acid (pH < 4), weakly acidic (pH 4–7) and weakly alkaline (pH > 7) following established criteria [25].

Number and type of reflux episodes, acid exposure (reflux time (min) and reflux percentage time) and proximal extent (reflux reaching 15 cm above the LOS) were calculated [26]. Total distal esophageal acid exposure <4.2% over 24 h was considered normal [27,28]. Number of reflux episodes <54 was considered normal [29].

Statistical analysis
Statistical analysis was performed with Epi Info™ version 7 and the SPSS version 19 statistical software package (SPSS Inc., Chicago, IL, USA). Differences in proportions were compared using the Chi-squared or Fisher’s exact test. As reflux parameters were not normally distributed, results are reported as median and range. Differences between groups were assessed using Kruskal–Wallis and/or Mann–Whitney tests. The correlation between the severity of pulmonary fibrosis and reflux parameters was calculated using Spearman correlation. \( p \)-value < 0.05 was considered significant.

Results
This study included 20 patients with a definite diagnosis of IPF and 20 with pulmonary fibrosis other than IPF (non-IPF). Table 1 shows no statistically significant differences between studied groups as regards detailed demographic and clinical characteristics.

Table 2 shows similar esophageal manometric parameters between patients with IPF and non IPF patients without statistically significant differences.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IPF (n = 20)</th>
<th>Non IPF ILD (n = 20)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean basal LES pressure, mmHg</td>
<td>14.5 (4.5–33)</td>
<td>16.2 (4–36)</td>
<td>0.70</td>
</tr>
<tr>
<td>Mean proximal contraction amplitude, mmHg</td>
<td>93.5 (45–185)</td>
<td>82 (40–175)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean distal contraction amplitude, mmHg</td>
<td>89.5 (15–200)</td>
<td>79.5 (15–200)</td>
<td>0.36</td>
</tr>
<tr>
<td>Manometric hiatal hernia, no (%)</td>
<td>10 (50%)</td>
<td>7 (35%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mean basal UES pressure, mmHg</td>
<td>57 ± 20</td>
<td>64 ± 18</td>
<td>0.25</td>
</tr>
<tr>
<td>Data are shown in median (range), unless otherwise specified. LES: lower esophageal sphincter; UES: upper esophageal sphincter.</td>
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</table>

Table 3 Esophageal 24-h impedance-pH data in all studied patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IPF (n = 20)</th>
<th>Non IPF ILD (n = 20)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal acid exposure, no (%)</td>
<td>17 (85%)</td>
<td>7 (35%)</td>
<td>0.003</td>
</tr>
<tr>
<td>% total AET (with pH &lt; 4)</td>
<td>10.1 (5.1–16.3)</td>
<td>3 (1.2–8.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total reflux episodes</td>
<td>80 (45–99)</td>
<td>45 (29–70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acid reflux episodes (pH &lt; 4)</td>
<td>46 (25–57)</td>
<td>28 (18–40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weakly acidic reflux episodes (pH 4–7)</td>
<td>35 (20–45)</td>
<td>19 (10–30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proximal reflux episodes</td>
<td>54 (28–69)</td>
<td>18 (8–32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AET: acid exposure time.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 3 shows that 17 (85%) patients out of 20 with IPF had an abnormal distal acid exposure, compared with 7 (35%) out of 20 non-IPF patients \( (p = 0.003) \). Percentage total acid exposure time (AET) with pH < 4 was significantly higher in IPF compared with non-IPF patients (percentage total AET 10.1 (5.1–16.3) versus 3 (1.2–8.3), for IPF versus non-IPF patients, respectively; \( p < 0.0001 \) (Fig. 1). In IPF patients the total (both acid and weakly acidic) numbers of reflux episodes [80 (45–99)], acid reflux [46 (25–57)] and weakly acidic reflux [35 (20–45)] were significantly higher than those of non IPF patients [45 (29–70), 28 (18–40) and 19 (10–30), respectively; \( p < 0.0001 \) (Fig. 2). Also, more reflux episodes reached the proximal esophagus [54 (28–69)] in IPF patients than non-IPF patients [18 (8–32); \( p < 0.0001 \) (Fig. 3).

Figs. 4 and 5 show that in IPF patients there was a good correlation between degree of pulmonary fibrosis (HRCT score) and total number of reflux episodes in both the distal \( (r^2 = 0.57, p = 0.008) \) and proximal \( (r^2 = 0.61, p = 0.004) \) esophagus. In contrast, as shown in Figs. 6 and 7 in non-IPF patients a non significant correlation was found between

**Figure 1** Median values of esophageal total acid exposure time (AET) in patients with idiopathic pulmonary fibrosis (IPF) \( (n = 20) \) and non IPF patients \( (n = 20) \).

**Figure 2** Number and type of gastro-esophageal reflux in patients with IPF \( (n = 20) \) and non IPF patients \( (n = 20) \). Data are presented as median values and range.

**Figure 3** Number of reflux episodes reaching the proximal esophagus in patients with idiopathic pulmonary fibrosis (IPF) \( (n = 20) \) and non IPF patients. Data are presented as median values and range.

**Figure 4** Correlation between degree of pulmonary fibrosis (HRCT score) and total number of reflux episodes in the distal esophagus in patients with idiopathic pulmonary fibrosis (IPF).

**Figure 5** Correlation between degree of pulmonary fibrosis (HRCT score) and total number of reflux episodes in the proximal esophagus in patients with idiopathic pulmonary fibrosis (IPF).
Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease with a median survival ranging from 2 to 3 years from diagnosis [1]. Pulmonary fibrosis can occur after repeated tracheobronchial aspiration of small amounts of gastric contents over long periods of time (i.e. chronic microaspiration) [30,31]. Moreover, recent investigations have demonstrated disease stabilization or delay of disease progression after medical or surgical treatment of GER [8–10]. Until recently, diagnosis and therapy of GER have focused on gastric acid as the main monitoring parameter and treatment target [26]. However, recent studies highlighted that lung injury is independent of acidity and factors other than acid (i.e. foods, pepsin and bile acids) may be involved in its pathogenesis [12,13]. Although it is recognized that GER is increased in IPF patients, its prevalence and characteristics have been poorly defined. The recent use of impedance-pH monitoring allows us to detect both acid and weakly acidic GER and to assess the extent of reflux into the proximal esophagus [13,14]. So, in the current work, we investigated esophageal motility, acid and weakly acidic reflux and proximal migration of refluxate, as well as the correlation between GER and lung fibrosis in patients with IPF. We compared the results with those obtained from patients with ILD other than IPF.

Table 1 shows that IPF patients had a mean age of 66.1 ± 14.8 years. This is in accordance with data from many other studies which illustrated that patients with IPF are often middle aged, usually between 40 and 70 years of age. Approximately two-thirds of patients with IPF are over the age of 60 years at the time of presentation, with a mean age at diagnosis of 66 years [32–37]. Moreover, the incidence of the disease increases with older age [38,39].

In case-control studies, cigarette smoking has been identified as a potential risk factor with the odds ratio (OR) from various regions of the world ranging from 1.6 to 2.9 for the development of IPF in ever-smokers [40–42]. Our study showed that IPF patients tended to have a higher smoking history compared with non-IPF patients, but without statistical significance.

Results of this study showed a higher frequency of GER episodes (both acid and weakly acidic) and reflux episodes reaching the proximal esophagus in patients with IPF when compared with non IPF patients (Table 3 and Figs. 2 and 3), despite similar esophageal manometric parameters (Table 2).

Discussion

Figure 6 Correlation between degree of pulmonary fibrosis (HRCT score) and total number of reflux episodes in the distal esophagus in non IPF patients.

Figure 7 Correlation between degree of pulmonary fibrosis (HRCT score) and total number of reflux episodes in the proximal esophagus in non IPF patients.

Figure 8 HRCT showing reticular pattern, fine fibrotic strands, traction bronchiectasis, and minimal ground glass attenuation.
Also, a good correlation between the degree of pulmonary fibrosis and the severity of GER was found in patients with IPF. These findings, with the non significant correlation between the degree of pulmonary fibrosis and the severity of GER in non IPF patients, suggest that patients with IPF have more severe GER, potentially leading to more extensive lung damage and fibrosis progression. The aforementioned data are consistent with the results obtained by Savarino et al. [26].

The mechanisms determining IPF are not clear. Current concepts implicate epithelial–fibroblast interactions as a result of repeated insults to the lung parenchyma by an unknown noxious stimulus. This prolonged stimulus would determine the development of pulmonary fibrosis over a long period of time [1]. Recent studies have suggested chronic microaspiration of gastric contents into the lungs as the trigger mechanism able to induce pulmonary parenchymal lesions, thus leading to the hypothesis that GER therapy could in part improve symptoms and pulmonary function test parameters [4–10]. This possibility has been recently confirmed, by Lee et al. [10], who observed that the use of GER medication was associated with lower HRCT fibrosis scores and was an independent predictor of longer survival time in 96 out of 204 IPF patients. However, all the above mentioned studies have been performed by means of traditional pH-metry, which limited these investigations to measuring only acid reflux without any information about other chemical types (i.e. weakly acidic reflux), number of reflux episodes, or the risk of proximal esophageal migration of the refluxate. Using combined impedance–pH monitoring, IPF patients were observed to have a very severe degree of overall reflux disease, compared to non IPF patients [26]. Moreover, the present study showed that IPF patients had higher acid and weakly acidic reflux episodes in both the distal and proximal esophagus, thus favoring the risk of microaspiration into the lungs compared to non-IPF patients. Finding an increased number of weakly acidic reflux episodes is of a great importance, since this represents a possible explanation of why medical acid suppression alone might fail in preventing reflux and reflux-associated progression of ILD. Moreover, this finding supports the data from the study of Lee et al. [10], who reported that IPF patients who underwent Nissen fundoplication in order to reduce both acid and weakly acidic GER had an additional survival benefit.

The good correlation we found between the degree of pulmonary fibrosis (HRCT score) and the number of both distal and proximal reflux episodes in IPF patients (Figs. 4 and 5) reinforces the potential role of GER in the development and/or progression of pulmonary fibrosis. But, the non significant correlation which was observed between the degree of pulmonary fibrosis and the number of both distal and proximal reflux episodes in non IPF patients (Figs. 6 and 7) argues against the hypothesis that abnormal GER in IPF subjects is the result of the underlying fibrosis of the lungs but has the potential to represent a factor unrelated to pulmonary stiffness [26].

Despite most (85%) of IPF patients in the present study had abnormal GER (Table 3), only 50% (10 out of 20) complained of GER symptoms (Table 1), this finding is in accordance with previous studies [6,26,43]. Therefore, abnormal acid or weakly acidic GER had been often clinically silent. These results support the idea that all IPF patients with or without apparent reflux symptoms should be carefully evaluated and, eventually, should undergo esophageal impedance–pH to detect asymptomatic GER [26].

In conclusion, IPF patients have greater GER compared to non IPF ones. Acid reflux is predominant, but also weakly acidic reflux is increased among IPF patients. Abnormal GER should be searched for and properly treated to prevent microaspiration of gastric contents and its probable effects on the natural history of lung fibrosis in patients with IPF.

Conflict of interest

We have no conflict of interest to declare.

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