Lifestyle associated diseases and risk of pulmonary hypertension in patients with idiopathic pulmonary fibrosis

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KEYWORDS
Idiopathic pulmonary fibrosis; Lifestyle related diseases; Pulmonary hypertension

Abstract  Background: Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease of unknown etiology. It is possible that lifestyle-related diseases may affect either the initiation or progression of IPF. Comprehensive data are lacking from Egypt. The aim of the study was to investigate the following hypothesis that lifestyle-related diseases may increase the risk of development of IPF; and augment the risk of progression and development of pulmonary hypertension (PH) in IPF patients.

Study design: A case approach prospective study.

Methods: A total of 92 patients with IPF were included in the study. Sixty-seven were females and 25 cases were males, their age ranged from 14 to 82 years. Detailed medical history, clinical manifestations, laboratory and radiological findings, cardiac and pulmonary assessments were recorded and compared with the diagnostic criteria for lifestyle-related diseases.

Results: The adjusted OR of GERD was 0.48 (95% confidence interval [CI], 0.13–1.71), the adjusted OR for DM was 0.12 (95% CI, 0.03–0.56) and the adjusted OR for hyperlipidemia was 0.30 (95% CI, 0.07–1.27). There were no differences between the clinical characteristics of patients with IPF and PH and patients with IPF without PH that could be related to lifestyle related diseases.

Conclusion: Lifestyle related diseases may be a risk factor for IPF. IPF patients are more often slightly younger, obese and females. However, there was no prevalence of any of those diseases in IPF patients with PH as PH is considered a prognostic indicator of IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is considered a major subtype of idiopathic interstitial pneumonias according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) International Multidisciplinary Consensus...
Classification of idiopathic interstitial pneumonias [1]. It is defined as “a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and is associated with the histopathological and/or radiological pattern of usual interstitial pneumonia” [1].

IPF has a poor predictable clinical course with an increased mortality rate [2]. Clinical and demographic data on IPF show substantial differences in different world regions [3]. Worldwide, the prevalence estimates for IPF range from 6 to 32 per 100,000 [4]. Comprehensive data are lacking from Egypt and the Middle East. However, a study from Saudi Arabia included 330 patients with intestinal lung diseases (ILD), out of which 23% had IPF [5]. Patients with IPF are usually between 50 and 70 years of age and symptoms typically presenting 2–4 years before the onset of the disease. The most common presenting symptoms of IPF are dry cough and moderate to severe dyspnea on exertion [2,4].

Several epidemiologic studies show the potential risk of cigarette smoking [6,7], associated comorbidities such as gastroesophageal reflux disease (GERD) [8–10] and ischemic heart disease (IHD) [11,12] and occupational dust exposure as a confound factor(s) to the progression of IPF [6,13,14]. Also, lifestyle-related diseases, such as obesity, hypertension, diabetes mellitus (DM), hyperlipidemia, and hyperuricemia are an important contributing factor(s) that may affect the initiation or progression of IPF [15,16].

Pulmonary hypertension (PH) is a common complication of IPF and may be found in patients with preserved lung function. As the symptoms of PH in IPF are nonspecific, the development of PH in a patient with IPF can be easily overlooked. Possible pathogenic mechanisms of PH in IPF include vascular destruction, pulmonary hypoxic vasoconstriction and vascular remodeling due to overexpression of cytokines and growth factors. Several studies show that IPF patients with PH have decreased exercise capacity and a worse prognosis [17,18]. So it is important to investigate for PH in these patients due to its prognostic significance. Doppler echocardiography is a useful noninvasive tool for the detection of PH. However, right heart catheterization remains the gold standard diagnostic test [17].

Patients and methods

Study design

A case approach, prospective study during the period from January 2013 to January 2015 approved by the Human Ethics Committee of Cairo University, included all IPF patients admitted to the chest diseases department, Kasr Al-Aini Hospital, Cairo University and Embaba Chest Hospital. All subjects gave informed consent to the study.

Diagnosis of IPF was made when the patient met the criteria corresponding to the international consensus statement of IPF of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) recommendations [1]. They stated that the major and minor criteria proposed in ATS/ERS (2000) consensus statement [19] have been eliminated and mentioned that the diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease and drug toxicity).
2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.
3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

The aim of the study was to investigate the following hypothesis that age, sex, occupational and environmental exposure to birds, cigarette smoking and/or lifestyle associated diseases, such as obesity, GERD, arterial hypertension, ischemic heart disease (IHD), diabetes mellitus (DM), hyperlipidemia, and hyperuricemia may increase the risk of development of IPF; and augment the risk of progression and development of pulmonary hypertension (PH) in IPF patients.

The following data were collected:

- Clinical data including sex, age, body mass index (BMI), duration of illness, occupational history, history of raising birds, smoking status and the presence of co-morbidities e.g., IHD, DM, GERD, arterial hypertension, hyperlipidemia, hyperuricemia were recruited.
- Measurements of arterial blood pressure.
- Results of Laboratory findings including total leukocyte count (TLC), plasma level of C-reactive protein (CRP), fasting blood sugar (FBS), lactate dehydrogenase (LDH), total cholesterol (T-chol), triglycerides and uric acid (UA) levels.
- Serological blood tests to rule out UIP associated collagen vascular diseases.
- Results of pulmonary function tests including spirometry measurements (forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) ratio, FVC (% predicted value), FEV1 (% predicted value), forced expiratory flow FEF 25–75% (% predicted value) and 6-Minute Walk Test (6-MWT)).
- Results of arterial blood gas measurements.
- High resolution computed tomography of the chest (HRCT) to declare the typical pattern of UIP.
- Findings of electrocardiograms and echocardiograms.
- Results of pathological confirmation of UIP pattern either by video-assisted medical thoracoscopic lung biopsy or open lung biopsy whenever possible.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), median, range, frequencies (number of cases) and/or percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Pearson Chi square ($\chi^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Multivariate logistic regression analysis models were used to test for the preferential effect of the independent variable(s) on the occurrence of pulmonary hypertension. $P$ values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).
Results

Our study included 102 patients, 92 patients were diagnosed with IPF, and 10 patients were excluded due to associated collagen vascular disease diagnosed by positive medical history, clinical examination and positive autoimmune tests. The diagnosis of IPF was based on the absence of an indictable etiology for ILD by clinical history and examination, the presence of the typical radiological pattern of UIP on HRCT scans of the chest and/or the pathological results of either video-assisted medical thoracoscopic lung biopsy or open lung biopsy. There were fifteen cases with positive histopathological confirmation, 9 cases were diagnosed by video-assisted medical thoracoscopic lung biopsy and 6 cases were diagnosed by open lung biopsy. The results of pulmonary function tests were also used to assist the diagnosis.

The patients were predominantly females (67 patients, 72.8%) and all were housewives. There were 25 male patients (27.2%); their occupational histories were 7 workers in wood industry, 5 cases were working in a petrochemical factory, 4 cases were working in agriculture, 4 cases were employees, 2 cases were working in a sugar factory, 2 builders and a single case the patient was a physician.

Most of our patients were overweight with mean BMI 27.98 ± 5.8 kg/m² and 30 patients were diagnosed with obesity. Their age ranged from 14 to 82 years (50.7 ± 13.9 years), the duration of illness ranged from 6 months to 22 years (5.9 ± 4.6 years) and 31 patients (33.7%) were on home oxygen at presentation.

There were 22 (23.9%) female patients raising birds and 17 (18.5%) male patients with positive smoking history. Patients’ co-morbidity, laboratory and radiological findings are shown in Table 1. All patients had progressive dyspnea on exertion and basal fine crackles by auscultation. They had moderate reduction in FVC and FEV₁ and showed restrictive pattern in spirometry. Respiratory and cardiac testing of our patients is shown in Table 2.

There were 52 IPF patients with pulmonary hypertension. They had PH via echocardiography. Comparisons of the clinical characteristics, respiratory and cardiac testing between IPF patients with and without pulmonary hypertension are shown in Tables 3 and 4.

Discussion

In Egypt, little attention has been paid to confirm the role of age, sex, occupational and environmental exposure, cigarette smoking and/or lifestyle associated diseases, such as obesity, arterial hypertension, IHD, DM, GERD, hyperlipidemia, and hyperuricemia in the disease development of IPF; and the effect of these factors in influencing the development and progression of PH in those patients. The identification of risk factors for IPF is critically important as it may inform prevention strategies, early diagnosis, and novel therapies. In our study we tried to investigate those associations and IPF prospectively.

It is clear that the prevalence and incidence of IPF are higher in older age groups, however in our study, the mean age of IPF patients was 50 ± 13 years, their mean BMI was 27 ± 5 kg/m² among them 30 (32.6%) patients were diagnosed

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Co morbidity, laboratory and radiological findings in patients at initial presentation.</th>
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<tbody>
<tr>
<td>Parameter</td>
<td>Number (Percentage)</td>
</tr>
<tr>
<td>Class I obesity</td>
<td>17 (18.5)</td>
</tr>
<tr>
<td>Class II obesity</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Class III obesity</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>31 (33.7)</td>
</tr>
<tr>
<td>Overweight</td>
<td>30 (32.6)</td>
</tr>
<tr>
<td>Underweight</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>GERD</td>
<td>31 (33.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (22.8)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>24 (26.1)</td>
</tr>
<tr>
<td>IHD</td>
<td>8 (8.7)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20 (21.7)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16 (17.4)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>52 (56.5)</td>
</tr>
<tr>
<td>Elevated CRP level</td>
<td>30 (32.6)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>38 (41.3)</td>
</tr>
<tr>
<td>Elevated LDH level</td>
<td>82 (89.1)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Radiological HRCT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral extensive fibrosis with honeycombing (31.5)</td>
</tr>
<tr>
<td>Bilateral reticulonodular infiltration with traction bronchiectasis (68.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Respiratory and cardiac testing at baseline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>No. (%)</td>
</tr>
<tr>
<td>PH</td>
<td>92 (100)</td>
</tr>
<tr>
<td>PaCO₂ mmHg</td>
<td>92 (100)</td>
</tr>
<tr>
<td>PaO₂ mmHg</td>
<td>92 (100)</td>
</tr>
<tr>
<td>SO₂ %</td>
<td>92 (100)</td>
</tr>
<tr>
<td>FiO₂ %</td>
<td>92 (100)</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>92 (100)</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>92 (100)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>92 (100)</td>
</tr>
<tr>
<td>FEF 25–75 (% predicted)</td>
<td>92 (100)</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure via echocardiography (mmHg)</td>
<td>92 (100)</td>
</tr>
<tr>
<td>6 MWD (m)</td>
<td>92 (100)</td>
</tr>
</tbody>
</table>
as overweight and another 30 (32.6%) patients diagnosed with obesity. Our findings were not going hand in hand with a study conducted by Sherbini et al., which included 134 IPF patients from Saudi Arabia, the mean age and BMI of their patients were 64 ± 13 years and 29 ± 8 kg/m² respectively [20]. Also, our results disagreed with those of a Japanese study; conducted by Enomoto et al., where, most of their patients were of advanced age (the mean age of their patients was 65.4 years) and their mean BMI was 22.5 kg/m² (19.2% of them were diagnosed as obese) [16]. The relatively old age of IPF patients was more evident as 36% of IPF patients were smokers compared to 18.5% smoking prevalence among our IPF patients [20]. On the other hand, Enomoto et al., most of their patients were males (female patients were 21.1%), and there was a high prevalence of smoking history among their patients (84.6%) [16]. It seems that smoking among our patients didn’t play as much role as the other previous studies; however, more recent studies showed that there is no significant association between IPF and smoking status [10,23,26]. The female predominance especially in the Middle East region may indicate the possible role of genetic polymorphisms that needs to be examined in further studies.

Also, the occupational history of our patients was similar to a multicenter hospital-based case control study from 2010 to 2011 performed in Egypt where; Awadalla et al., found significant associations for occupations in woodworking and chemical/petrochemical industry for men and raising birds and farming for women and risk for development of IPF [27].

Our patients presented with a wide range of the duration of illness from 6 months to 22 years with a mean of 5.9 ± 4.6 years. Almost more than half of the IPF patients (56.5%) had pulmonary hypertension and 33.7% were on home oxygen at presentation. In Saudi Arabia, Sherbini et al., showed that although 66% of their patients had slowly progressive IPF, only 12% had PH and 53% of them were on home oxygen at presentation [20]. They also stated that there was a similitude between their results and other studies in Saudi Arabia [5,28]. The difference between our results and those of Sherbini et al., probably indicates delayed diagnosis and referral of IPF patients to hospitals for proper management.

GERD was relatively common in our IPF patients (31 cases, 33.7%), a finding supports the hypothesis that GERD and chronic micro-aspirations increase the risk of IPF [29–32]. However, an Egyptian study conducted by Embarak et al., on 20 IPF patients confirmed the presence of abnormal distal acid exposure in 85% of their IPF patients compared to 35% of 20 non-IPF patients. The prevalence of GERD was much higher among their patients. Also, they found a good correlation between the degree of pulmonary fibrosis (HRCT score) and the number of both distal and proximal reflux episodes in IPF patients [33]. Therefore, those results reinforce the potential role of GERD in the development and/or progression of IPF and that GERD should be searched for and properly treated to prevent its possible effect on pulmonary fibrosis in IPF patients.

Twenty-one (22.8%) of the IPF patients had diabetes, 26.1% had arterial hypertension and 8.7% had IHD. Sherbini et al., found that 42% of their IPF patients had diabetes and 39% had ischemic heart disease which were more common in their cohort than in the general population [20]. A finding had been shown in several studies that the prevalence of DM among IPF patients was significantly higher than in the control groups. DM may increase the risk and pathogenesis of IPF via oxidative stress lung damage that might be produced by advanced glycation end products (AGEs) mediated by hyperglycemia [16,23,34,35].

### Table 3 Comparison between the clinical characteristics of IPF patients with and without PH.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IPF patients with PH (n = 52)</th>
<th>IPF patients without PH (n = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/yr</td>
<td>49.85 (15.45)</td>
<td>51.80 (11.71)</td>
<td>0.507</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>36/16</td>
<td>31/9</td>
<td>0.377</td>
</tr>
<tr>
<td>History of raising birds</td>
<td>11</td>
<td>11</td>
<td>0.479</td>
</tr>
<tr>
<td>Smoking history</td>
<td>9</td>
<td>8</td>
<td>0.742</td>
</tr>
<tr>
<td>Duration of illness/yr</td>
<td>5.66 (4.30)</td>
<td>6.16 (4.92)</td>
<td>0.605</td>
</tr>
<tr>
<td>BMI</td>
<td>28.56 (6.10)</td>
<td>27.22 (5.50)</td>
<td>0.605</td>
</tr>
<tr>
<td>Class I obesity</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Class II obesity</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Class III obesity</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>16</td>
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<td></td>
</tr>
<tr>
<td>Over weight</td>
<td>17</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Under weight</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Associated comorbidity

- GERD: 14 vs. 17, P = 0.117
- Diabetes: 9 vs. 12, P = 0.150
- Arterial hypertension: 13 vs. 11, P = 0.787
- IHD: 4 vs. 4, P = 0.697
- Hyperlipidemia: 12 vs. 8, P = 0.723
- Hyperuricemia: 9 vs. 7, P = 0.659
- Elevated CRP level: 17 vs. 13, P = 0.984
- Leukocytosis: 20 vs. 18, P = 0.528
- Elevated LDH level: 45 vs. 37, P = 0.362

### Predominant HRCT Pattern

- Bilateral extensive fibrosis with honeycombing: 20 vs. 9, P = 0.184
- Bilateral reticulonodular infiltration with traction bronchiectasis: 32 vs. 31

Values of age, duration of illness and BMI are expressed as mean (standard deviation).
We found that 21.7% of the IPF patients had hyperlipidemia, a finding similar to that of Enomoto et al., where hyperlipidemia was present in 19.2% of their IPF patients vs 46% of the control group. Also, Sherbini et al., stated that 11% of their IPF patients had dyslipidemia. This finding raises interest about the potential role of hyperlipidemia and elevated levels of fatty acids and their role in increasing oxidative stress via NADPH oxidase activation; that induce pulmonary fibrosis and accelerate its progression due to oxidant/anti-oxidant imbalance.

Hyperuricemia was present in 17.4% of our IPF patients compared to 5.9% among IPF patients in Enomoto et al., study. Uric acid is the final product of purine degradation which is markedly elevated during a wide variety of diseases. CRP is a marker of systemic inflammation and production of inflammatory markers such as CRP and interleukin-6. CRP is an acute phase protein produced primarily from the liver and is stimulated by the release of cytokines, such as interleukin-6. CRP appears to play an important role in neutrophil chemotaxis or modulating vascular permeability in ways that could potentially be protective in the disease process. CRP may play a pathogenic role by inhibiting neutrophil chemotaxis or modulating vascular permeability in ways that could potentially be protective in the disease process. CRP is an acute phase protein produced primarily from the liver and is stimulated by the release of cytokines, such as interleukin-6. CRP is a marker of systemic inflammation that is elevated during a wide variety of diseases. Several in vitro and animal model studies have suggested that CRP may play a pathogenic role by inhibiting neutrophil chemotaxis or modulating vascular permeability in ways that could potentially be protective in the disease process.

In our study, we compared the impact of age, sex, environmental exposure to birds among females, cigarette smoking among males and even the duration of illness between IPF patients who had PH and those without PH. They were all non-significant. To avoid the possibility of confounding of every factor, we examined the adjusted OR for the most common 3 factors by multivariate analysis. We found that PH and hyperlipidemia, hyperuricemia, and CRP in IPF patients compared to the control group. CRP is an acute phase protein produced primarily from the liver and is stimulated by the release of cytokines, such as interleukin-6. CRP is a marker of systemic inflammation that is elevated during a wide variety of diseases. Several in vitro and animal model studies have suggested that CRP may play a pathogenic role by inhibiting neutrophil chemotaxis or modulating vascular permeability in ways that could potentially be protective in the disease process.

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or cell death. Serum LDH is a sensitive marker for cell injury, but is a non-specific test since the concentration is elevated in different circumstances of cell injury caused by ischemia, as by excess heat or cold, starvation, dehydration, injury, exposure to bacterial toxins, after ingestion of certain drugs, and from chemical poisonings [51]. Consequently, we didn’t find a significant difference in the laboratory findings of serum LDH level in IPF patients with PH and those without PH as serum LDH is difficult to be used as a valid biomarker of disease activity in ILD since its concentration is defined by many factors.

Several studies showed that the BMI, FVC%, DLCO%, baseline PaO₂ measured by ABGs 0.92 (95% CI, 0.85–1.01) and the adjusted OR of the 6-min walk 1.00 (95% CI, 0.99–1.01), there was a significant difference between the two groups. The current results suggest the importance of initial evaluation and follow up of PH for IPF patients. However, it also showed that the BMI and FVC% had no significant predictive value among our IPF patients with PH and the only variant that had significance was the 6-min walk test.

Conclusion

IPF patients are more often slightly younger, obese and females. Only 17 patients were smokers, they all were males. Occupational hazards among wood and chemical/petrochemical industries for men and raising birds and farming for women might be risk factors for development of IPF. Lifestyle associated diseases, such as obesity, GERD, arterial hypertension, ischemic heart disease (IHD), diabetes mellitus (DM), hyperlipidemia, and hyperuricemia may influence the risk of development of IPF; a finding like the epidemiological estimates from other studies. However, none of the previous factors have showed any impact on disease progression of IPF, as there was no prevalence of any of those independent factors on IPF patients with PH as PH is considered a prognostic indicator of IPF.

Our results may enhance the understanding of the natural history of IPF, strongly encourages more clinical evaluation for early diagnosis and management of PH in those patients. Research on new approaches to recognize and re-evaluate those patients for proper management is required.

Conflict of interest

No conflict of interest.

References

Pulmonary hypertension in idiopathic pulmonary fibrosis patients


