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# Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study

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**Summary**
The etiology of idiopathic pulmonary fibrosis (IPF) remains poorly understood, but some studies have suggested that cigarette smoking or other occupational or environmental exposures, diabetes mellitus, or gastroesophageal reflux may play a role. In this study we evaluated the clinical records of a group of 97 consecutive patients with IPF, and 560 patients suffering 5 different respiratory disorders that were examined as controls: asthma ($n = 111$), chronic obstructive pulmonary disease ($n = 132$), squamous cell lung carcinoma ($n = 118$), lung adenocarcinoma ($n = 101$) and patients with otorhinolaryngology problems but without lung disease ($n = 98$). In bivariate analyses male sex, diabetes mellitus and being former cigarette smoker were associated with IPF. After adjusting by these variables, multivariate analysis revealed that type 2 diabetes mellitus [11.3% in IPF patients vs 2.9% in controls, OR = 4.3 (95% CI: 1.9–9.8), $p < 0.0001$] was an independent risk factor associated to IPF. Our results provide additional evidence of a putative relationship between DM2 and idiopathic pulmonary fibrosis. Experimental research is necessary for thorough assessment of the pathogenic mechanisms involved in this association.


## Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive scarring lung disease that leads to respiratory failure and death.[1] Although the etiology of IPF is still unknown, it is considered a complex disorder with a strong interaction between a genetic background and environmental factors. However, up to now putative genes and environmental factors that consistently increase the risk of IPF have not been identified. Smoking presents the most

*Abbreviations:* COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; DM2, type 2 diabetes mellitus; ORL, patients with otorhinolaryngologic problems; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ATS, American Thoracic Society.

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striking association with both the sporadic and the familial forms of IPF.[2,3] Likewise, some occupational and environmental exposures, primarily to wood and metal dusts, have shown to be associated to increased risk of IPF.[2] Chronic viral infection (Epstein-Barr virus) and gastroesophageal reflux have been also considered as possible risk factors for this disease.[4,5] The incidence of IPF increases with age, and aging contributes to some lifestyle-related diseases. Therefore, it is possible that lifestyle-related disorders such as type 2 diabetes mellitus (DM2) may affect either the initiation or progression of IPF. Actually, in two studies performed in different ethnic populations DM2 was found to be associated with IPF.[6,7]

In this context, the aim of the present study was to identify possible risk factors associated to IPF in a Mexican population. Our results indicated that DM2 is a major predictor of the disease.

## Patients and methods

This was a retrospective case-control, hospital-based study performed at the National Institute of Respiratory Diseases (INER), México. Clinical records of consecutive IPF patients seen at this institute from 2000 through 2005 were reviewed. Diagnosis of IPF was made according to established criteria, and confirmed by lung biopsy in 35% of subjects.[8]

The control group was integrated by patients who were seen as outpatients or were hospitalized at the INER due to selected pulmonary diseases [asthma ($n = 111$), chronic obstructive pulmonary disease (COPD, $n = 132$), squamous cell lung carcinoma ($n = 118$), or lung adenocarcinoma ($n = 100$)] and by patients with otorhinolaryngologic (ORL, $n = 98$) problems but without lung disease. Diagnosis of asthma or COPD were done according to the Global Initiative for Asthma [GINA[9]] and the Global Initiative for Chronic Obstructive Lung Disease [GOLD[10]], respectively. Both types of lung cancer were confirmed by histopathology. Regarding ORL patients, individuals included in the analysis were randomly selected from patients assisting to the ORL department during the study period. Cases and controls were evaluated simultaneously. To confirm specific diagnoses of cases and controls, the clinical records were examined twice through standardized methods. Diagnosis of DM2 was done if the patient had a fasting glucose level higher than 126 mg/dl (7 mmol/l) in the absence of corticosteroids treatment, or the accomplishment of one of the following criteria: a) the patient knew that he or she had DM2 diagnosed by a clinician; b) diagnosis of DM2 was done at INER during the first consult; c) the patient was taking oral drugs for DM2; d) the patient had used insulin. The protocol was accepted by the Bioethics and Science Committee of INER.

### Environmental exposures

Information concerning environmental exposures was obtained from a standardized questionnaire dealing with risk factors for respiratory diseases. This questionnaire was systematically applied by the Social Work Department to any patient admitted to the INER from 1999 onward. The questionnaire was created and validated by one of the authors (RPP) and assesses the following risk factors: age, gender, DM2, smoking habit (current, former, ever); alcoholism (current, former, ever); occupational exposure to dusts, smoke or chemicals; location and characteristics of the home (rural or urban area, construction materials, number of windows and number of hours they remain open, number of individuals living with the patient, presence of children <5 years old, home nearness to a gas station, high-traffic roads, landfills, dairy or poultry farms, and manufacturing plants); home exposure to wood smoke, coal, side-stream tobacco smoke, birds, carpets, dampness and insecticides.

### Statistical analysis

Categorical variables were analyzed through the chi-square test. Interval variables were expressed as mean and standard deviation and were compared by the Student's *t*-test. Odds ratios (OR) were calculated through unconditional

**Table 1** Sociodemographic characteristics of cases and controls ($n = 657$).

| | IPF cases ($n = 97$) | Controls ($n = 560$) | OR (95%CI) |
|---|---|---|---|
| Age (*years*) | $62.6 \pm 11.0$ | $62.3 \pm 12.2$ | 1.002 (0.9—1.02) |
| Male sex | 71/97 (73.2) | 347/560 (62.0) | 1.7 (1.03—2.7) |
| Type 2 diabetes | 11/97 (11.3) | 16/560 (2.9) | 4.3 (1.95—9.7) |
| Past or current occupational exposure to dust | 55/97 (56.7) | 292/560 (52.1) | 1.2 (0.8—1.9) |
| Past or current occupational exposure to smoke | 64/97 (66.0) | 388/560 (69.3) | 0.9 (0.5—1.4) |
| Past or current occupational exposure to chemicals | 28/97 (28.9) | 120/560 (21.4) | 1.5 (0.9—2.4) |
| Tobacco smoke exposure | | | |
| Non-smoker | 53/97 (54.6) | 320/560 (57.1) | 0.9 (0.6—1.4) |
| Ever smoker | 44/97 (45.4) | 240/560 (42.9) | 1.1 (0.7—1.7) |
| Former smoker | 39/97 (40.2) | 168/560 (30.0) | 1.6 (1.006—2.5) |
| Current smoker | 5/97 (5.2) | 82/560 (14.6) | 0.3 (0.1—0.8) |
| Past passive smoker | 36/95 (37.9) | 213/544 (39.2) | 0.9 (0.6—1.5) |
| Current passive smoker | 9/96 (9.4) | 129/542 (23.8) | 0.3 (0.2—0.7) |
| Past or current alcohol use | 39/97 (40.2) | 221/560 (39.3) | 1.03 (0.7—1.6) |

Data correspond to mean $\pm$ SD or to frequencies (%).

logistic regression. Variables introduced into regression models were selected according to a $p < 0.20$ or its biological relevance.

## Results

Ninety seven patients with IPF and 560 controls with different lung or ORL diseases were included in the study. Demographic characteristics are shown in Table 1. As can be seen in this table, both groups did not differ regarding age, occupational exposure to dusts, smoke or chemicals, or alcohol intake. Male gender was slightly more frequent among IPF patients. The most striking difference was related to DM2 and exposure to tobacco smoke. Thus, a higher proportion of subjects with DM2 was found among cases (11.3%) as compared with controls (2.9%, $p < 0.0001$), yielding over a four-fold risk of IPF among DM2 subjects. The increased frequency of DM was even higher in the subgroup of IPF patients who had undergone surgical lung biopsy to confirm diagnosis biopsied: OR 6.8 (2.0—22.6); non-biopsied: OR 3.6 (1.2—9.6). A more in-deep analysis showed that IPF patients had such increased risk compared with almost all of the five subgroups of control patients. Thus, odds ratios (95% confidence intervals) were 4.6 (1.2—26.3) for asthma, 2.7 (0.9—9.2) for COPD, 3.7 (1.03—16.3) for squamous cell cancer, 6.3 (1.3—59.3) for lung adenocarcinoma, and 6.2 (1.3—58.7) for ORL control subgroups. Likewise, IPF patients showed a higher frequency of former smokers (40.2 vs 30.0%, $p = 0.04$), and less current active or passive smokers (5.2 vs 14.6%, $p = 0.01$, and 9.4 vs 23.8%, $p = 0.002$, respectively). The increased percentage of current active and passive smokers in the control group was mainly due to a higher proportion of smokers among COPD and squamous cell cancer patients (data not shown).

Odds ratios and 95% confidence intervals for household characteristics are shown in Fig. 1. All variables lacked statistically significant differences between both groups.

After adjusting by sex, former smoker, current active and passive smoker, multivariate analysis shown that DM2 was the most important independent predictor associated to IPF risk [OR = 4.3 (1.9—9.8) $p < 0.0001$, Table 2].

## Discussion

IPF is the most common idiopathic interstitial pneumonia and the one with the worst prognosis. Thus, despite intensive research an effective therapy for this disease remains elusive. Etiology of IPF is unknown but several epidemiological observations associate the risk of developing this disease to an environmental injury to the lungs. Recognition of these and other risk factors may be crucial to prevent the development of the disease.

In this study, we approached the question about risk factors through a case-control study using a questionnaire administered by social workers to collect information regarding household characteristics, environmental exposures and other pertinent data.

Our results showed that DM2 was significantly associated to a higher risk for IPF. Thus, after adjusting for confounding factors, there was a more than 4-fold increase in odds for developing IPF among diabetics. Similar results

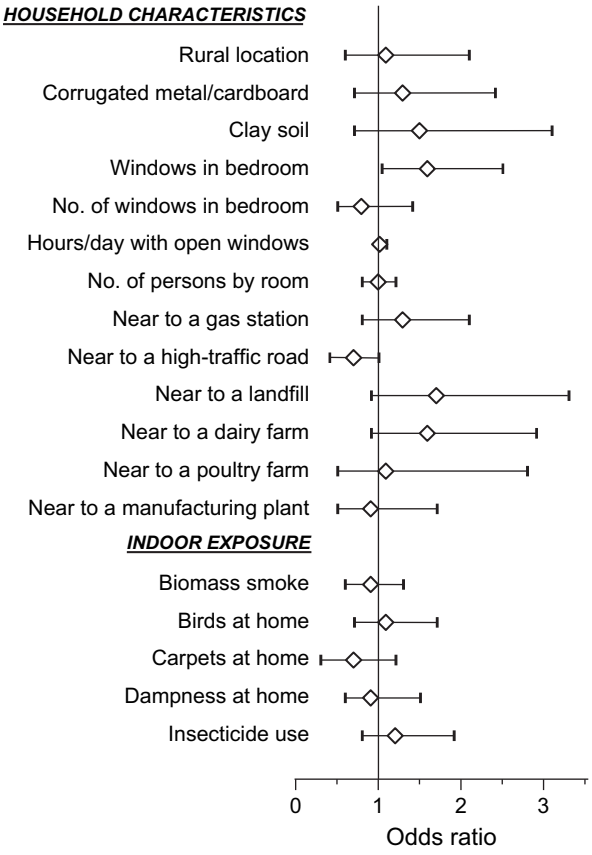


**Figure 1** Odds ratios for developing IPF according to selected variables, as compared with controls.

have been reported in two previous studies involving different ethnic populations.[6,7] In one of them, a case-control study performed in the setting of a longitudinal primary-care database in the United Kingdom showed that IPF was significantly associated to diabetes-related conditions, being insulin use the factor with the strongest association.[7] Interestingly, in this study no association with the smoking status was found. Similar results were reported in a Japanese population, where 64 IPF patients were compared with 184 control subjects without evidence of lung disease in their chest radiographs.[6] In this case-control study, the prevalence of DM2 was 3-fold higher in the IPF group. On the contrary, in a more recent study also performed in Japanese population, IPF patients were

**Table 2** Adjusted odds ratios obtained trough conditional logistic regression[a] for characteristics associated to IPF ($n = 657$).

| | Standardized β-coefficient | Adjusted OR (95% CI) for IPF |
|---|---|---|
| Male sex | 0.55 | 1.7 (1.04—2.9) |
| Type 2 diabetes | 1.46 | 4.3 (1.9—9.8) |
| Former smoker | 1.15 | 3.2 (1.2—8.5) |

[a] Additional independent variables evaluated in (and excluded from) the logistic regression model were ever smoker and current passive smoker.

compared with unmatched controls (inpatients with acute bacterial pneumonia and outpatients with common cold), concluding that diabetes was no associated to IPF.[11]

Studies regarding fibrosis in organs other than the lungs have also found some association with DM2. For example, history of diabetes was an independent clinical parameter associated with advanced fibrosis in patients with chronic hepatitis C.[12] Likewise, the incidence of chronic nonalcoholic liver disease is significantly higher among patients with diabetes.[13] Furthermore, fibrosis is a frequent pathological reaction in tissues affected by diabetic complications.[14] The pathogenic mechanisms implicated in the association of diabetes and IPF are presently unknown. High extracellular and intracellular glucose environment may activate several pathways related to the production of cytokines, growth factors, and reactive oxidative species, which can mediate tissue damage and fibrosis in diabetes. For example, it has been recently shown that connective tissue growth factor (CTGF) mediates high glucose and palmitate induced cardiac myocyte hypertrophy and dysfunction as well as cardiac fibrosis.[15] Interestingly, CTGF has been recently implicated in the epithelial to mesenchymal transition (EMT) of renal tubular epithelial cells which contributes to the renal fibrosis associated with diabetic nephropathy.[16] EMT is also involved in the expansion of the population of fibroblasts/myofibroblasts in IPF lungs, although a putative relationship with diabetes has not been evaluated.[17,18] Many other factors play roles in the pathogenesis of diabetic nephropathy and fibrosis; for instance, both TGF-$\beta$1 and angiotensin II are important factors to promote the development of renal fibrosis.[19] These mediators are also implicated in the pathogenesis of IPF.[20] Furthermore, elevated circulating levels of TGF-$\beta$1 may be part of the molecular link between diabetes, and diseases resulting in organ fibrosis.[21]

A high prevalence of current or former smokers has been reported in several series of IPF patients. In a recent meta-analysis of observational studies examining environmental and occupational risk factors for IPF, a significant increased risk for IPF was associated with cigarette smoking.[2] In a large study including 248 cases and 491 control subjects identified through random-digit dialing, matched by gender, age and geographic region, a history of ever or former smoking was associated with increased risk for the development of IPF.[22] Also, evidence suggestive of an interaction between smoking and agricultural work has been found.[23] However, some contradictory results have also been reported, which may be partially related to the utilization of different control groups (i.e., community or hospitalized controls), small size samples, and uncertainty of IPF diagnosis since several studies were performed before the 2000 year when a consensus diagnosis was published.[2,8,22–24]

In our study, we found by bivariate and multivariate analyses a higher proportion of former smokers in the IPF group. Interestingly however, an increased proportion of current smokers was found among control patients that is explained by the high proportion of them in the COPD and squamous lung cancer subgroups, two diseases strongly associated to cigarette smoking.

Exposure to biomass smoke was explored because in developing countries many households in rural areas or in the periphery of urban areas depend on biomass for cooking and heating, and this exposure has been associated to pulmonary fibrosis in one study and some case reports.[24,25] However, no association was found, probably because the high prevalence of exposure in all subgroups of patients with chronic respiratory disorders. Likewise, none of the other studied factors showed statistical significance.

This study has several potential weaknesses that restrict the power of the results. Among them, the retrospective collection of data and the relatively small sample size limit the statistical power to detect other putative associations between exposures and the disease. This is primarily due to the low prevalence of IPF that makes the number of patients available for conducting etiologic studies usually small. The main strength of our study is the validity of the diagnosis of IPF (ATS consensus) and of the other diseases that constituted the control group.

In summary, our findings indicate that DM2 might constitute a risk factor for developing IPF in Mexican population. The pathogenic mechanisms implicated in this association remain to be elucidated. Further studies are needed to confirm the putative relationship of IPF with smoking.

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## Conflict of interest

Authors have no conflicts of interest to declare.

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