Idiopathic Pulmonary Fibrosis and Diabetes Mellitus: A Meta-Analysis and Systematic Review

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Abstract

**Background:** Idiopathic pulmonary fibrosis (IPF) is a chronic diffuse interstitial lung disease, of which the etiology has been poorly understood. Several studies have focused on the relationship between IPF and diabetes mellitus (DM) in the past years but have failed to reach a consensus. This meta-analysis aimed to examine the association between diabetes to IPF.

**Methods:** We accumulated studies investigating the association between DM and IPF from databases including Medline, Cochrane Library, Embase, Web of Science, and China National Knowledge Infrastructure. RevMan 5.3 and the Newcastle-Ottawa Scale (NOS) were utilized to analyze the data and assess the quality of the included studies. The value of odds ratio (OR) with 95% confidence interval (CI) was used as the measure to estimate the risk of DM in IPF. Heterogeneity was assessed by $I^2$ statistics. We also performed subgroup analysis, meta-regression, and Egger's test for bias analysis.

**Results:** Nine case-control studies with 5,096 IPF patients and 19,095 control subjects were included in the present meta-analysis, which indicated that DM could increase the risk of IPF (OR: 1.65, 95% CI: 1.30-2.10; $P < 0.0001$). Meta-regression and subgroup analysis negated the influence of covariates like cigarette smoking, age and gender, but the heterogeneity existed and could not be fully explained.

**Conclusion:** The meta-analysis indicated that DM is highly probably related to IPF. Further rigorously designed studies are required to confirm the present findings and investigate the possible mechanisms behind the effect of DM on IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal pulmonary disease with an annual cumulative prevalence of 18.2 cases per 100,000 persons in America[1] while a median survival of only 3–5 years[2, 3]. IPF is characterized pathologically by proliferation and differentiation of lung fibroblasts. In the past decade, the understanding of IPF pathogenesis has shifted from an inflammatory-driven process[4] to aberrant activation of the alveolar epithelial cells hypothesis[5], which may be connected with cigarette smoking, genetic factors, chronic viral infections, etc, based on collaborative guidelines[6]. Nevertheless, the exact etiology of IPF remains unclear.

In recent years, it has been observed that IPF patients are often additionally diagnosed with diabetes mellitus (DM), resulting in increased research interest in the correlation between these two diseases. Firstly, two earlier case-controls studies[7, 8] were successively conducted in Japan but obtained opposite conclusions. Subsequent clinical observational researches[9, 10] suggested that DM increased the risk of IPF, which inspired experiments related to antidiabetic treatment for IPF. Interestingly, using mice animal models, it was revealed that metformin could reverse established lung fibrosis[11–15], however, a post hoc analysis[16], which investigated the effect of combinations therapy in IPF (pirfenidone/pirfenidone + metformin), concluded that metformin had no effect on clinically relevant outcomes. Furthermore, another pooled analysis demonstrated that metformin might increase the risk of disease progression when in combination with proton pump inhibitors, angiotensin II receptor blockers or thyroid medications[17].

Due to the conflicting results in the existing studies, it remains controversial whether DM is truly correlated with IPF and to date, the evidence for the relevance between DM and IPF has not been systematically evaluated. Hence, in the present study, we conducted a meta-analysis and systematic review, aiming to assess the association between DM and the incidence of IPF.
Materials And Methods

We performed meta-analysis and wrote this report referring to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) proposal[18] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[19].

Literature Search

We searched databases including Medline, Cochrane Library, Embase, Web of Science and China National Knowledge Infrastructure. The following items were searched in databases as keywords or random words: “pulmonary fibrosis”, “diabetes”, “risk factors” and such searches were additionally filtered for articles published in any language leading up to September 30, 2020 (Complete search strategy presented in Appendix 1)

Inclusion criteria and exclusion criteria

Case-control studies or cohort studies were selected. The case groups were all diagnosed with IPF in accordance with clinical history, High-Resolution Computed Tomography (HRCT), and when available, lung biopsy. Also, a calculated measure of association between DM and IPF was required. Studies focusing on progression or prognosis of IPF and studies lacking general information about control groups were excluded.

Data Extraction

Two researchers (L.B. and L.Z.) managed data extraction independently, reviewing the title, abstract, and full text of each article, and discussed or consulted a third researcher (T.P.) when disputations arose. The following are included: (1) basic information of each study including author, publication year, study design, etc; (2) characteristics of case and control groups; (3) diagnostic methods of MD and IPF; (4) the number of diabetics in case and control groups; and (5) potential sources of biases.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used for quality assessment of included studies, covering three domains: selection of groups, comparability of groups and ascertainment of exposure[20]. The NOS score ranges from 0 to 9 stars and studies that receive 5 stars or more are regarded as high quality. We evaluated the diagnostic criteria of IPF and DM in each study for the possibility of selection bias. Cigarette smoking, age, gender, environmental exposure and genetic factors, which may induce IPF and bring about information bias, were deemed as covariates and all taken into consideration when estimating whether control subjects were adequately selected.

Statistical Analysis

In our meta-analysis, odds ratio with 95% confidence interval (95%CI) was used as the effect measure. Heterogeneity was assessed by $I^2$ statistics and random effect model was chosen when heterogeneity was significant ($I^2 > 50$%), otherwise, fixed effect model was selected. Forest plots were used to display the results from individual studies and pooled estimates, and $P<0.05$ were regarded as statistically significant. Trial Sequential Analysis (TSA) was used for estimate of evidence size and reliability of the conclusion[21, 22]. We also performed sensitivity and subgroup analyses to assess resources of heterogeneity. Meta-regression and Egger’s test[23] were utilized for bias analysis. Data analysis was performed using RevMan 5.3, Stata 12, and TSA 0.9 beta.

Results
Study Selection and Characteristics

As is briefly illustrated in Fig. 1, out of the 1528 articles reviewed, 9 studies[7–10, 24–28] from 5 countries finally met our eligibility. All studies were case-control and distinguished as high-quality by NOS assessment. General population was selected as control groups in six studies[7, 8, 10, 25–27], one study included only healthy volunteers[24], and the remaining two[9, 28] included patients with other chronic pulmonary diseases. IPF was diagnosed based on clinical history, HRCT, and lung biopsy while diagnosis of DM could be established with any objective method such as fasting blood glucose or simple by clinical symptoms combined with clinical history. More details are displayed in Table 1.
| Study                  | Country | Design     | NOS | IG  | CG            | Method of IPF Diagnosis                                                                 | Method of DM Diagnosis                          |
|-----------------------|---------|------------|-----|-----|---------------|-----------------------------------------------------------------------------------------|-------------------------------------------------|
| Enomoto et al[7] 2003 | Japan   | Case-      | 8   | 52  | 184 people matched for age and sex with no lung disease by chest radiographs              | ATS/ERS criteria[65]                            | FBG > 6mmol/L and/or HbA1c > 6% in combination with any treatment history |
| Miyake et al[8] 2005  | Japan   | Case-      | 8   | 104 | 56 acute bacterial pneumonia, and 4 common cold, matched by age and sex                  | ATS/ERS criteria[65]                            | Medication or diet treatment history            |
| Gribbin et al[10] 2009| United Kingdom | Case-     | 6   | 920 | 3593 control subjects matched by age, gender and general practice                        | Read Code (diagnostic terms) in THIN database    | Read Code                                       |
| Ma.C et al[9] 2010    | Mexico  | Case-      | 6   | 97  | 560 patients, 461 with other pulmonary diseases and 98 with otorhinolaryngologic problems | ATS/ERS criteria[65]                            | FPG > 6mmol/L. Clinical history and medication therapy were also referred to |
| Garcia-Sancho et al[24] 2011 | Mexico | Case-       | 8   | 100 | 263 healthy control subjects matched for age, sex, and place of residence                | ATS/ERS criteria[65]                            | Clinical symptoms and medication history        |
| Kim et al[25] 2015    | Korea   | Case-      | 7   | 460 | 1925 control subjects matched with age, gender, and smoking habits                      | ATS/ERS/JRS/ALAT criteria[64]                   | FPG > 6mmol/L together with clinical history    |
| Dalleywater et al[27] 2015 | United Kingdom | Case- | 8   | 3211| 12307 control subjects, matched for age, sex, and general practice                      | A new diagnosis prior to previous                | Read Code                                       |

NOS: Newcastle-Ottawa Scale. IPF: Idiopathic Pulmonary Fibrosis. DM: Diabetes Mellitus. IG: IPF Group. CG: Control Group. THIN: The Health Improvement Network. FBG: Fasting Blood Glucose. FPG: Fasting Plasma Glucose. ATS: American Thoracic Society. ERS: European Respiratory Society. JRS: Japanese Respiratory Society. ALAT: Latin American Thoracic Association.
| Study                  | Country | Design     | NOS | IG  | CG     | Method of IPF Diagnosis                                                                 | Method of DM Diagnosis                  |
|-----------------------|---------|------------|-----|-----|--------|----------------------------------------------------------------------------------------|----------------------------------------|
| Zhong et al[28] 2016  | China   | Case-Control | 6   | 108 |        | 115 patients without respiratory failure or other underlying disorders                  | FPG > 6mmol/L and/or 2-hour PG > 11.1mmol/L |
|                       |         |            |     |     |        | Guidance for Diagnostic and Treatment of Pulmonary Fibrosis (Chinese Thoracic Society 2002) |                                        |
| Xu et al[26] 2020     | China   | Case-Control | 7   | 44  |        | 88 patients without evidence of lung disease on computed tomography, matched for age and sex | FPG > 7mmol/L. Clinical history was also used for diagnosis |
|                       |         |            |     |     |        | ATS/ERS criteria[6]                                                                        |                                        |

NOS: Newcastle-Ottawa Scale. IPF: Idiopathic Pulmonary Fibrosis. DM: Diabetes Mellitus. IG: IPF Group. CG: Control Group. THIN: The Health Improvement Network. FBG: Fasting Blood Glucose. FPG: Fasting Plasma Glucose. ATS: American Thoracic Society. ERS: European Respiratory Society. JRS: Japanese Respiratory Society. ALAT: Latin American Thoracic Association.

Meta-Analysis

A total of 5,096 IPF cases and 19,095 control subjects were involved in the analysis (Fig. 2), suggesting that DM and IPF should be related (OR: 1.65, 95% CI: 1.30–2.10; \( P < 0.0001 \)), based on statistical reliability verified by the subsequent trial sequential analysis (Fig. 3). The heterogeneity was significant (\( I^2 = 68\% \)) with no obvious sources of biases found among the sensitivity analyses (Fig. 4). Therefore, we performed subgroup analyses to investigate factors that possibly contribute (Table 2). The result remained consistent in separate analyses regardless of community or hospital controls, and irrespective of diagnostic criteria of IPF/DM or characteristics of control groups (healthy subjects, general population or patients with pulmonary disorders). When smoking status, age, and gender were accounted for in case and control groups, the heterogeneity still existed as before.
### Table 2
Subgroup Analysis

| Study Characteristic                                      | Study | IPF (D/T) | Control Group (D/T) | OR    | 95%CI       | P value | Heterogeneity |
|----------------------------------------------------------|-------|-----------|---------------------|-------|-------------|---------|---------------|
| Groups matched by age and sex[7, 8, 10, 24–27]           | 7     | 698       | 4891                | 2142  | 18420       | 1.43    | 1.16–1.76     | \(P=0.0007\) | \(I^2=55\%\) |
| Smoking status matched in both groups[8–10, 25]           | 4     | 203       | 1581                | 598   | 6138        | 1.52    | 1.05–2.19     | \(P=0.02\)  | \(I^2=65\%\) |
| Control groups made up of general population[7, 10, 25–28]| 6     | 721       | 4795                | 2135  | 18212       | 1.49    | 1.19–1.88     | \(P=0.0007\) | \(I^2=66\%\) |
| Control group with pulmonary diseases[8, 9]               | 2     | 24        | 201                 | 23    | 620         | 2.23    | 0.56–8.88     | \(P=0.25\)  | \(I^2=79\%\) |
| Healthy control group[24]                                | 1     | 30        | 100                 | 50    | 263         | 1.83    | 1.08–3.09     | ...           | ...          |
| Community controls[7, 24]                                | 2     | 47        | 152                 | 71    | 447         | 2.50    | 1.24–5.06     | \(P=0.01\)  | \(I^2=59\%\) |
| Hospital controls[8–10, 25–28]                           | 7     | 728       | 4944                | 2137  | 18648       | 1.47    | 1.17–1.84     | \(P=0.008\) | \(I^2=61\%\) |
| Diagnosis of IPF based on ATS/ERS criteria[7–9, 24–26]   | 6     | 170       | 857                 | 402   | 3080        | 2.09    | 1.34–3.29     | \(P=0.001\) | \(I^2=66\%\) |
| Diagnosis of DM based on FBG[7, 9, 25, 26, 28]           | 5     | 193       | 761                 | 395   | 2872        | 2.38    | 1.43–3.97     | \(P=0.0009\) | \(I^2=72\%\) |
| Diagnosis of DM based on subjective methods[8, 24]        | 2     | 43        | 204                 | 57    | 323         | 1.62    | 1.02–2.58     | \(P=0.04\)  | \(I^2=0\)   |

D: Diabetes. T: Total. IPF: Idiopathic Pulmonary Fibrosis. DM: Diabetes Mellitus. FBG: Fasting Blood Glucose. ATS: American Thoracic Society. ERS: European Respiratory Society.

### Bias Analysis

All elements that could induce IPF were considered as potential sources of biases. Firstly, cigarette smoking is a known risk factor for IPF[29] and in the five included studies[7, 24, 26–28], smokers or ex-smokers were much more in case groups than in controls. In the following subgroup analysis (Table 2), when we selected the other four studies[8–10, 25] in which the smoking habits between case and control groups were similar, the association remained statistically significant (OR: 1.52, 95% CI: 1.05–2.19; \(P=0.02\)), which coincided with the outcome of the meta-regression (Fig. 5, \(P=0.351\)), suggesting that smoking was unlikely to distort the final results. Next, considering that age and gender are related to IPF despite inexplicable reasons[6], seven studies[7, 8, 10, 24–27] in which these two factors were well-balanced were used to inform another analysis, yet again concluding that DM correlated with IPF (OR: 1.43, 95% CI: 1.16–1.76; \(P=0.0007\)). Still, there remained two potential sources of biases that the included literatures did not sufficiently address (Table 3). In light of a multicenter case-control study[30], environmental exposure was likely responsible for the incidence of IPF, which has been gradually acknowledged in recent years. Though three studies[8, 9, 24] took this into consideration, unfortunately, only one study matched case and control groups. However, in that single study[9], DM was proven to be the most dangerous factor for IPF in the logistic regression model (OR: 4.3, 95% CI: 1.9–9.8). Genetic factor, which was considered as one of the covariates according to the guidelines by ATS/ERS[6], was not...
referred to in any study except one[24]. Additionally, case and control groups in this study were regrettably unmatched. Thus, the impact it had on final conclusions was difficult to evaluate. Publication bias existed ($P = 0.016 < 0.05$) judged by the Egger's test (Fig. 6).

### Table 3

| Study                | Environmental Exposure (IG/CG) | Family IPF (IG/CG) |
|----------------------|--------------------------------|-------------------|
| Enomoto et al[7] 2003| Not stated                      | Not stated        |
| Miyake et al[8] 2005 | 31.7%                           | Not stated        |
| Gribbin et al[10] 2009| Not stated                      | Not stated        |
| Ma.C et al[9] 2010   | dust 56.7%                       | Not stated        |
|                      | smoke 66.0%                      | Not stated        |
|                      | chemicals 28.9%                  | Not stated        |
| Garcia-Sancho et al[24] 2011 | Matched by place of residence | 20%               |
|                      | Matched by place of residence   | 8.7%              |
| Kim et al[25] 2015   | Not stated                       | Not stated        |
| Dalleywater et al[27] 2015 | Not stated                  | Not stated        |
| Zhong et al[28] 2016 | Not stated                       | Not stated        |
| Xu et al[26] 2020    | Not stated                       | Not stated        |

IG: IPF Group. CG: Control Group.

### Discussion

**Main Findings and Clinical Inspiration**

In the present meta-analysis, it was revealed that the prevalence of diabetes was increased markedly in IPF cases compared with controls, which suggests that DM is an independent risk factor for IPF. However, the conclusion lacks persuasiveness for that all of the included studies are retrospective case-control studies which are easily affected by recall bias. Additionally, the interpretation of the outcome is in the limitation of the significant heterogeneity, which could not be satisfactorily explained.

Interestingly, a recent review[31] clarified the common features between IPF and pulmonary complications in diabetics. These include clinical characteristics (injury of lung function mainly manifested in decline in FVC, FEV1[32] and $DL_{CO}[33−37]$), HRCT imaging (the frequently presented UIP pattern[38, 39]) and histopathological changes (thickening of the basal lamina of lung capillaries[40, 41], increased amount of collagen in the alveolar walls[42], etc), all of which indicated that IPF and diabetes are closely related. This conclusion validated the findings of our meta-analysis as well.
as equipping them with biological plausibility. However, even if the manifestations are proven to be pulmonary fibrosis, it is still unclear whether a causal relationship exists between DM and IPF.

Therefore, understanding the exact pathological mechanisms is crucial; namely, how persistent hyperglycemia, a known characteristic of diabetes, gradually contributes to the pulmonary lesions. Studies found that a high glucose concentration could result in nonenzymatic glycation with the ultimate formation of advanced glycation end products (AGEs), which may target type IV collagen in the alveolar basement membrane, thicken the basal lamina both in epithelial and capillary of alveoli and eventually lead to a decrease in pulmonary elasticity and compliance[43–45]. This hypothesis has become recognized as an explanation for the pathological abnormalities of interest, including injured pulmonary function in diabetic individuals. Furthermore, some investigators hold the view that oxidative stress (OS), which refers to an imbalance between free radicals and antioxidants in the body, is intimately connected with the onset of IPF. On one hand, OS can directly enhance nonenzymatic glycation[46], but on another, OS participates in the activation of nuclear factor-kappaB (NF-κB)[47], which is presumably the central part in initiating processes of alveolitis. One study[48] shows that inhibiting the activation of the transcription factor NF-κB could reduce lung injury and fibrosis. Hürdag C et al.[49] discovered that OS could decrease superoxide dismutase (SOD), increase nitric oxide synthase (NOS), and contribute to overproduction of nitric oxide (NO) and peroxynitrite (ONOO−), potentially giving rise to damage of lung tissue and ultimately pulmonary fibrosis[50, 51]. In addition, inflammatory cytokines play a crucial role, among which transforming growth factor-beta1 (TGF-β1) attracts the most attention. TGF-β1 was found overexpressed in hyperglycemia, which has been documented to promote proliferation and differentiation of fibroblasts, activation of myofibroblasts and deposition of extracellular matrix (ECM)[52–56], all of which will eventually bring about lung fibrosis.

Although the possible pathophysiologic mechanisms do explain the disease process, we acknowledge that multiple factors may induce pulmonary fibrosis and that it is also indeterminate to what extend IPF is affected by diabetes. Thus, to solidify the association between DM and IPF, the beneficial effect of antidiabetic therapy should be established. Currently, pirfenidone and nintedanib are the only options with a proven impact on pulmonary fibrosis. However, gastrointestinal adverse events are common[57–59] and IPF will progress inevitably in all patients, so more effective measures are still necessitated. The discovery that metformin is effective on reversal of pulmonary fibrosis[11–15, 60] brings a new dawn for IPF. Unfortunately, no clinical placebo-controlled trials have ever been attempted, which are less likely to be realized, in consideration of the application of antifibrotic drugs with definite efficacy (pirfenidone and nintedanib). Consequently, trials that place more importance on combination therapies with metformin and pirfenidone/nintedanib are essential in the future; considerations may include whether the effect of antifibrotic treatment will be improved, adding metformin on the basis of original dose of pirfenidone/nintedanib, or whether the effect will be maintained, combining metformin and low-dose pirfenidone/nintedanib, for the sake of reducing adverse reactions. Besides, since persistent hyperglycemia may promote the occurrence and development of pulmonary fibrosis, further research should investigate the suitable threshold of blood glucose for IPF or ILD patients and whether timely and effective hypoglycemic therapy would prevent the incidence or progression of the disease. We expect such findings could further strengthen the evidence linking IPF with DM.

**Strengths and Limitations**

In our meta-analysis, we screened literatures in strict accordance with inclusion and exclusion criteria, designed the study with high quality, and finally demonstrated that DM and IPF are very likely interrelated. This study provides insight that future studies may employ in developing curative antifibrotic treatments and improving the prognosis of IPF patients. Nevertheless, there remain several limitations in our study. Firstly, the heterogeneity was significant, and a reasonable interpretation is still absent. The wide range of prevalence of DM (from 10–61% in IPF groups and from 3–43% in control groups) in the studies has attracted our attention, which could be responsible for major heterogeneity; we
assumed this to be secondary to multiple factors including diagnostic criteria of diabetes (subjective or objective methods) and IPF (discrepancy among different editions), selection of populations (with or without underlying diseases), and regional differences. However, the internal causal relationship has not been established to date. Secondly, given that the result is based on case-control studies, which are susceptible to confounding factors, the potential sources of biases have always been a focus. Even though influence of smoking, age, and gender was ruled out in our bias analysis, other covariates such as genetic factor might also cloud the association between DM and IPF, especially considering that at least 30% of patients have predisposing genetic factors which could increase the risk of pulmonary fibrosis\(^\text{61–63}\). Besides, two studies\(^\text{10, 27}\) from the UK are based on the THIN database (in Gribbin's research, IPF cases are from the period 1991–2003 while in Dalleywat's, cases are from 2000–2011), which may be one of the contributory reasons of the notable publication bias, and repeated cases might cause type I errors (false positive conclusions).

**Conclusion**

The association between diabetes and IPF was briefly referred to in ATS/ERS clinical practice guideline updated in 2011\(^\text{64}\), but not in the newest edition\(^\text{6}\) perhaps owing to the contradiction of existing evidence. Our study favors the hypothesis that DM and IPF are associated, based on the present meta-analysis and systematic review. However, the curative effect of antidiabetic therapy in IPF remains to be further confirmed and the risk of disease progression that combination therapies might carry is worthy of caution as well.

**Abbreviations**

ATS, American Thoracic Society  
DLCO, diffusion capacity for carbon monoxide of the lung  
DM, diabetes mellitus  
ERS, European Respiratory Society  
FEV1, forced expiratory volume in the first second  
FVC, forced vital capacity  
HRCT, High-Resolution Computed Tomography  
ILD, interstitial lung disease  
IPF, idiopathic pulmonary fibrosis  
NF-Kb, nuclear factor-kappaB  
NOS, Newcastle-Ottawa Scale  
TGF-\(\beta\), transforming growth factor-\(\beta\)  
THIN, The Health Improvement Network  
TSA, trial sequential analysis  
UIP, usual interstitia pneumonia
Declarations

Ethics approval and consent to participate:
Not applicable.

Consent for publication:
Not applicable.

Availability of data and materials:
All data generated or analysed during this study are included in these published article[7-10, 24-28].

Competing interests:
All of the authors have no competing interests.

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Author's contributions:
Xianmei Zhou and Hailang He contributed conception, design, and quality control of the study. Le Bai was in charge of literature search, data extraction, and manuscript writing. Li Zhang and Tingyu Pan helped with data extraction. Wei Wang and Dian Wang managed data analysis. Cassidy Turner edited the language.

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