

Association between idiopathic pulmonary fibrosis and gastroesophageal reflux disease: a meta-analysis

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1. Background

Idiopathic pulmonary fibrosis (IPF) is a chronic and fatal lung disease, presenting with progressive dyspnea and non-productive cough. Its incidence is between 3 and 9 cases per 100 000 people per year in North America and Europe.¹ IPF has a poor prognosis, its median survival from diagnosis ranging from 2 to 3 years. Treatment exists, but show only small benefits.

Relating to pathogenesis, animal models have identified lung inflammation as part of the disease process leading to pulmonary fibrosis.² Among other causative factors related to this pulmonary inflammation, gastroesophageal reflux disease (GERD) is thought to play a pathogenic role because of its presumed association with chronic microaspirations. In humans, May EE and al. suggested few decades ago that GERD might be linked with the disease process of pulmonary fibrosis.² Many studies since demonstrated the increased prevalence of GERD among individuals with IPF.³⁴⁵⁶ More recently however, a systematic review underlining this increased prevalence also noted that the causal relationship between GERD and idiopathic pulmonary fibrosis had not been established and that there was still scant evidence about antireflux therapy in idiopathic pulmonary fibrosis patients.⁷

Since this systematic review, robust studies have been published on the matter, as Savarino and al's work in 2013. This case-control trial analyzed oesophageal motility, acid reflux and markers of gastric aspiration and their correlation with GERD and IPF. Among other findings, they demonstrated that there is good correlation between the degree of pulmonary fibrosis and the

severity of GERD, as well as between the degree of pulmonary fibrosis and the presence/concentration of gastric content in the lung.⁸

Moreover, recent works suggested that treatment of GERD might be beneficial in treating IPF : in a retrospective study, Lee and al. found that reported use of anti-GERD medications was associated with decreased radiographic fibrosis scores on chest computed tomography and was an independent predictor of longer survival time.⁹ In another study, surgical treatment of end stage IPF patients showed that gastric fundoplication allowed stabilisation of the pulmonary disease whereas control patients deteriorated.¹⁰

Current consensus suggest that clinicians should use regular antacid treatment for patients with IPF, but this recommendation is conditional, having a very low confidence in estimates of effect.¹¹

In order to clarify the pathogenesis of IPF and to intervene efficiently in its progression, it appears crucial to redefine the strength of association between IPF and GERD. Thus, a systematic review and meta-analysis of the data published to this date is indicated.

2. Methods

2.1 Criteria for considering studies for this review

2.1.1 Types of studies

All published prospective and retrospective cohort studies and case control trials that present association measure between IPF and GERD will be included.

2.1.2 Types of participants

We will include cohort studies and case control trials in which adult participants have idiopathic pulmonary fibrosis defined as a pulmonary fibrosis without identifiable aetiology. These observational studies will be selected if they reported a measure of association relating GERD to lung fibrosis.

Adult patients will be defined as being over 18 years of age. Studies analyzing multiple lung pathologies will be accepted, however, only data reported for idiopathic pulmonary fibrosis will

be analyzed. Diagnosis of GERD in included patients will have to be made on a clinical basis or with diagnostic methods such as pHmetry or esophagogastroduodenoscopy (OGD).

2.1.3 Other Limitations

There will be no publishing date restrictions. Only studies written in English and French will be included.

2.2 Exclusion criteria

The following will be excluded:

- Experimental animal studies
- Studies without control group and case reports
- Review articles
- Editorial and correspondence articles

2.3 Search methods for identification of studies

2.3.1 Electronic searches

We will search PubMed, Embase, Ovid, Web of Science and Google Scholar databases for original articles published in French and English. The following strategy will be used [IPF – or related terms, MeSH major topic] AND [GER- or related terms, MeSH major topic].

2.3.2 Searching other resources

We will check reference lists of included studies for additional related references.

2.4 Data collection and analysis

2.4.1 Selection of studies

Two reviewers (DBM and EL) will successively apply these searching criteria to the titles and

abstracts of all citations obtained. If the title of an article or its abstract suggests any possibility that it might be relevant, the paper will be retrieved and independently assessed by the same reviewer for a final decision about its inclusion into the review. We will resolve any disagreement by consensus or, if required, we will consult a third person (YL). Agreement between coders will be measured using quadratic weighted Kappa statistics. All the duplicates or multiple reports of the same study will be identified and only the first published paper or the original paper will be analyzed. We will record the selection process and keep a log of reasons for rejection of citations identified from the searches to complete a PRISMA flow diagram.

2.4.2 Information extraction

The two reviewers will look for the following information from all papers selected for inclusion: the study design and the association measure (relative risks [RR] or odds ratios [OR], with their 95% confidence intervals [CI] or variance estimates) between GERD and IPF.

The extracted data will be documented in a data extraction form and will include: demographics of participants, a description of the diagnostic method of GERD (symptoms, pHmetry, OGD) and association measures.

2.4.3 Assessment of risk of bias in included studies

The studies validity will be evaluated by systematically considering two important sources of bias that can be found in observational studies. These questions will be apply for all included study¹²:

- 1) Are exposure and control groups similar to important determinant except the exposure? (Selection bias)
- 2) Are the outcomes measured in the same way in for exposed and non-exposed participants? (Information bias)

2.4.4 Missing data in included studies

Authors of the original investigations will be contacted to obtain information on any missing data or any other missing detail. Studies with attrition of greater than 20% will be considered at high risk of bias. Where it is not possible to obtain the missing data from the authors, studies will be included in the meta-analysis only if available data allows it. Other studies with missing data will be excluded.

2.4.5 Subgroup analyses

A priori subgroup analyses will be conducted to identify sources of heterogeneity and bypass the potential bias induced by suspected confounding factors. Subgroup analysis will be done for : (1) exposure to tobacco (2) Study design (if cohort and case-control studies yield different results), (3) Diagnosis method for GERD (clinical diagnosis, pHmetry, endoscopic) and (4) age-group. In addition, we plan a posteriori analyses to assess the impact of each individual study on heterogeneity.

2.5 Assessment of bias in conducting the systematic review

2.5.1 Assessment of heterogeneity

Heterogeneity in each meta-analysis will be determined using the Chi^2 . Heterogeneity will be interpreted following the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions¹³. A P value less than 0.1 will be interpreted as statistically significant for heterogeneity and further analysis of the I^2 will be interpreted as followed:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of publication bias will be done if 10 or more studies are obtained for the meta-analysis. A funnel plot will be used to evaluate the presence of publication bias.

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