The relationship between gastro-oesophageal reflux and pulmonary fibrosis: a never-ending story

Maria Molina-Molina[1,2]

[1]Interstitial Lung Disease (ILD) Unit, Respiratory Department, University Hospital of Bellvitge, IDIBELL, UB, Barcelona, Spain. [2]National Research Network in Respiratory Disease (CIBERES), Spain.

Corresponding author: Maria Molina-Molina (mariamolinamolina@hotmail.com)

Shareable abstract (@ERSpublications)

Higher risk of IPF in the presence of a genetic predisposition to GORD increases the evidence for this causal relationship. Many other factors are involved in this complex story, which will be understood through the integration of different variables. https://bit.ly/3LbiPga
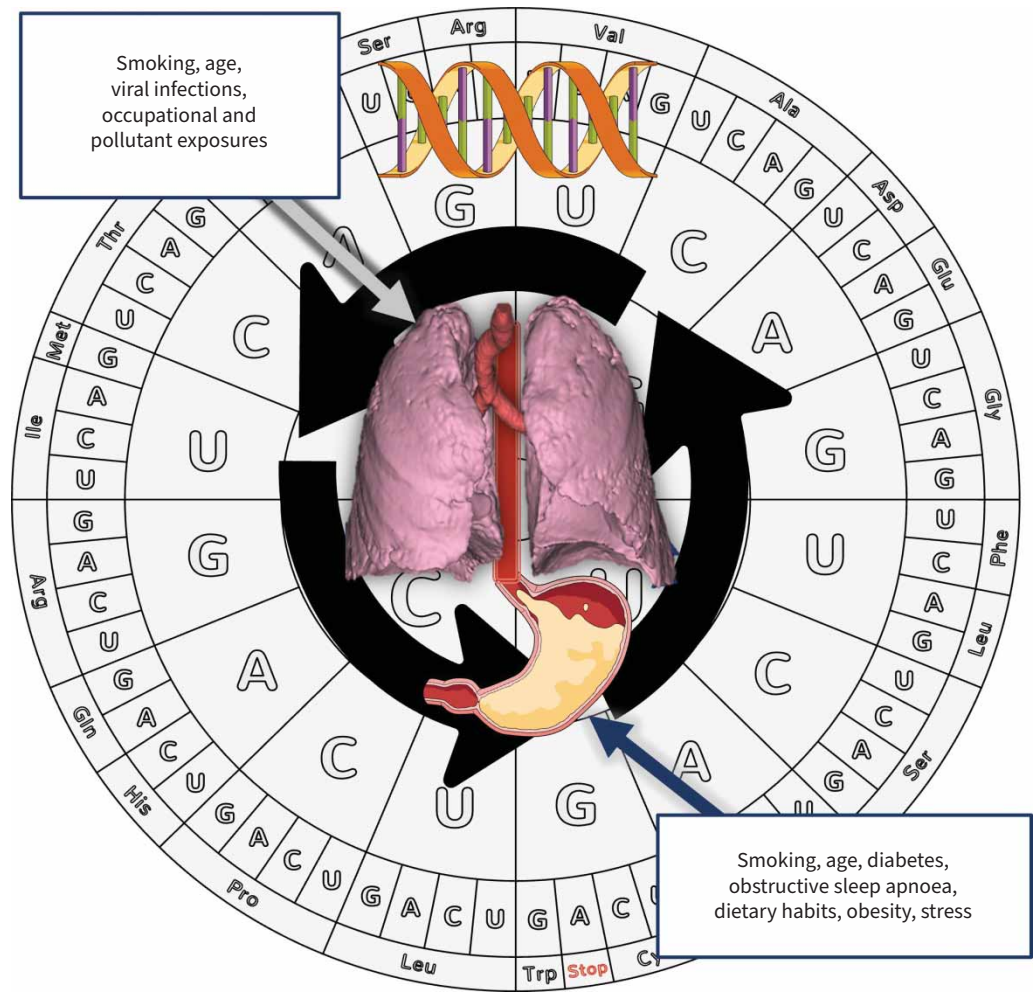
Idiopathic pulmonary fibrosis (IPF) is a lethal interstitial lung disease (ILD), characterised by progressive scarring and distortion of the lung architecture that finally leads to respiratory failure [1, 2]. Although the initial cause of IPF remains unknown, some pathogenic pathways have been identified in the past two decades, which have represented the basis for emerging anti-fibrotic drugs [3]. Furthermore, risk factors for developing the disease and contributing to fibrotic progression have been identified and validated, including genetic mutations, inhaled exposures and gastro-oesophageal reflux disease (GORD) [1–3]. Proper management or reduction of the avoidable risk factors is considered in IPF patient treatment in addition to the approved anti-fibrotic drugs [2]. Although GORD and IPF are two pathological conditions that are frequently associated, no clear relationship of causality has been demonstrated [4]. Some studies hypothesise that microaspiration of gastric material could be involved in lung tissue damage and activation of fibrotic pathways, while others suggest that IPF progression could favour GORD by increasing the negative intrathoracic pressure [4–13].

The present innovative approach to this question taken by REYNOLDS *et al.* [14] investigates the causal relationship between GORD and IPF using a bidirectional two-sample Mendelian randomisation (MR). They found higher risk of IPF (OR 1.61, 95% CI 1.04–2.49; p=0.032) in the presence of genetic predisposition to GORD, but no evidence of causal effect of genetic predisposition to IPF for risk in developing GORD [14]. The main strength of MR analyses is that genetic associations can mitigate confounding of common factors, such as smoking, nutrition or drugs, identified in classical observational associations [14, 15]. Therefore, the study estimates the effect of an individual's lifelong predisposition to GORD on the risk of developing IPF, which would be relevant for preventing or avoiding other strong risk factors for both disorders in these subjects genetically predisposed.

But is genetics enough for the scientific resolution of this causality dilemma? As the authors mentioned in their manuscript, GORD is one of the most prevalent conditions in developed countries [16–19], while IPF is a rare disease. The clinical guidelines for GORD from the American College of Gastroenterology state the different phenotypic presentations and diagnostic considerations for this condition [20]. However, IPF is not included when the guidelines highlight extra-oesophageal consequences, probably because the proportion of patients with GORD that develop IPF represent a minority when compared with the increase of risk of other disorders such as laryngitis, aphonia or even asthma [20]. So, although the genetic predisposition to GORD increases the risk of IPF, epidemiological data shows that only a few patients with GORD will develop IPF. Therefore, other biological and environmental risk factors on top of this genetic signature would be crucial in the development of IPF [3]. Genetic factors contributing to a higher risk for abnormal wound repair, such as MUC5B polymorphism and telomerase-related gene mutations, could also influence the pro-fibrotic pathogenic mechanism induced after the airway acidification due to microaspiration [2, 3]. Genetic variations can have large or small effects on the likelihood of developing

IPF and having changes in several different genes may combine to increase disease risk significantly. However, there is not yet a validated polygenic risk score for IPF development. Furthermore, carrying genetic risk for IPF doesn't always mean developing the disease, as is the case with many other diseases with genetic predisposition. Other genetic factors (modifiers of gene expression, such as some proteins), lifestyle and environmental factors may contribute to the development of both GORD and IPF (figure 1) [1–3]. Thus, IPF is considered polygenic and multifactorial. Furthermore, some relevant studies have analysed the impact of age and age-varying individual exposures on genetic relative risk for some multifactorial diseases [15, 21]. Most genetic risk factors have greatest relative impact on risk of early disease, with a decrease over time [21]. In addition, most genetic variants have age-varying relationships to the exposure for which they are a proposed instrument in MR analyses [15], and this could be the case for GORD and IPF. On the other hand, several previous studies suggested that components of GORD, acid and non-acid, contribute to lung damage and fibrosis [5, 6, 22]. Although an individual's genetic print cannot be altered, lifestyle and environmental modifications (such as healthy weight and nutrition, or smoking cessation) may reduce disease risk. Therefore, the primary current interest in better understanding IPF genetic risk factors is early prevention of additional risks by acting on the treatable factors of the catalysts.

How confident can we be regarding the lack of IPF causality on GORD? The MR analysis by REYNOLDS et al. [14] found no evidence of a causal effect of IPF on the lifetime risk of GORD after adjusting for pleiotropy. However, once IPF has been developed, cough, reduced lung compliance and shortened

FIGURE 1 Factors involved in the relationship between idiopathic pulmonary fibrosis (IPF) and gastro-oesophageal reflux disease (GORD). The genetic background predisposing IPF and GORD, in addition to different environmental risk factors and ageing that impact on the predisposed individual over time, are relevant players in this relationship. Furthermore, once IPF and GORD exist, this interaction may be even stronger.

respiratory movements can enhance transdiaphragmatic pressure gradient, traction on the oesophagus and hiatal hernia [9, 13]. The grade of inspiratory thoracic pressure inversely correlates with the number of proximal refluxes in the oesophagus [13]. Prevalence of GORD and hiatal hernia is higher in IPF than in normal subjects and patients with other respiratory diseases [8, 10, 17–19, 22, 23], ranging from 42% to 87% depending on different factors, including the methodology used for determining these disorders and the stage or severity of IPF [8, 10–12, 17–19]. The diagnosis of GORD is based on a combination of symptom presentation, endoscopic evaluation of the oesophageal mucosa, reflux monitoring and response to therapeutic intervention [20]. But patients with IPF that present GORD may not present typical symptoms [10], so the possibility of GORD in IPF should be considered even in the absence of heartburn [11]. Also, some studies suggest that increased incidence of GORD in IPF may result in part from confounding factors such as smoking and age [7, 24]. Therefore, if the mechanical transdiaphragmatic effect of IPF increases GORD, and both GORD and hiatal hernia may influence IPF progression and exacerbations beyond development, the bilateral relationship between both GORD and IPF could strengthen over time (figure 1).

Finally, would resolving the causality dilemma influence the therapeutic approach to GORD in IPF patients? The impact of treatment of GORD on IPF outcomes is not well established [4], so treating GORD with anti-acid medication or anti-reflux surgery has not been recommended as a treatment for IPF [2]. Since the beginning of this century, different observational studies have shown an increase of prevalence of GORD in IPF, the presence of pepsin in the bronchoalveolar lavage of fibrotic lungs and *in vitro* experimental pro-fibrotic effects, the potential effects of acid and non-acid microaspiration on IPF, and the mortality benefit of anti-acid therapy [11, 22, 23, 25]. Despite the large number of retrospective and prospective studies evaluating the effect of GORD or anti-reflux treatment on IPF, not enough robust evidence exists, neither in favour nor against, the treatment effect of GORD on IPF [4]. Whether this lack of clear benefit means reflux is not a good target, or at least not for all patients, or the evaluated treatments (anti-acid and reducing the hiatal hernia) are not good enough for a disorder that requires an integral therapeutic approach (including dietary habits and position during sleep) remains unclear. However, the last update of the IPF guidelines considers the proper management of a patient's comorbidities as standard of care [2]. Therefore, an IPF patient with GORD will be treated to improve GORD outcomes and symptoms, following pharmacological and non-pharmacological treatment recommendations from experts [2, 20]. Proton pump inhibitors only address one component of GORD; other relevant interventions, such as smoking cessation, avoiding late-night meals or "trigger foods" such as coffee or chocolate, elevating the head of bed during sleep, weight control, and pro-kinetics are also considered [20]. Therefore, the integral treatment of GORD when present in IPF patients is a common practice in the real-life setting, despite presenting a huge variability in GORD diagnosis, management and follow-up.

In conclusion, genetic predisposition is a relevant part of the causality condition of GORD on IPF development but likely not the only one. Integration of the different variables that may be involved in this association is the only way to demonstrate the solution to this dilemma. However, the strong association between both conditions deserves attention for efficient diagnosis and optimal management. The complex story explaining the GORD–IPF relationship has not ended; further studies are needed to validate the causality and understand the underlying mechanisms.

References

1 Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.

2 Raghu G, Remy-Jardin M, Richeldi L, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2022; 205: e18–e47.

3 Pardo A, Selman M. The interplay of the genetic architecture, aging, and environmental factors in the pathogenesis of idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2021; 64: 163–172.

4   Khor YH, Bissell B, Ghazipura M, *et al.* Antacid medication and antireflux surgery in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Ann Am Thorac Soc* 2022; 19: 833–844.

5   Savarino E, Carbone R, Marabotto E, *et al.* Gastro-oesophageal reflux and gastric aspiration in idiopathic pulmonary fibrosis patients. *Eur Respir J* 2013; 42: 1322–1331.

6   Perng DW, Chang KT, Su KC, *et al.* Exposure of airway epithelium to bile acids associated with gastroesophageal reflux symptoms: a relation to transforming growth factor-beta1 production and fibroblast proliferation. *Chest* 2007; 132: 1548–1556.

7   Bédard Méthot D, Leblanc É, Lacasse Y. Meta-analysis of gastroesophageal reflux disease and idiopathic pulmonary fibrosis. *Chest* 2019; 155: 33–43.

8   Baqir M, Vasirreddy A, Vu AN, *et al.* Idiopathic pulmonary fibrosis and gastroesophageal reflux disease: A population-based, case-control study. *Respir Med* 2021; 178: 106309.

9   Johannson KA, Strâmbu I, Ravaglia C, *et al.* Antacid therapy in idiopathic pulmonary fibrosis: more questions than answers? *Lancet Respir Med* 2017; 5: 591–598.

10   Raghu G, Freudenberger TD, Yang S, *et al.* High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J* 2006; 27: 136–142.

11   Ghisa M, Marinelli C, Savarino V, *et al.* Idiopathic pulmonary fibrosis and GERD: links and risks. *Ther Clin Risk Manag* 2019; 15: 1081–1093.

12   Lee JS, Collard HR, Anstrom KJ, *et al.* Antacid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *Lancet Respir Med* 2013; 1: 369–376.

13   Houghton LA, Lee AS, Badri H, *et al.* Respiratory disease and the oesophagus: reflux, reflexes and microaspiration. *Nat Rev Gastroenterol Hepatol* 2016; 13: 445–460.

14   Reynolds CJ, Del Greco M F, Allen RJ, *et al.* The causal relationship between gastro-oesophageal reflux disease and idiopathic pulmonary fibrosis: a bidirectional two-sample Mendelian randomisation study. *Eur Respir J* 2023; 61: 2201585.

15   Labrecque JA, Swanson SA. Interpretation and potential biases of Mendelian randomization estimates with time-varying exposures. *Am J Epidemiol* 2019; 188: 231–238.

16   Ronkainen J, Agréus L. Epidemiology of reflux symptoms and GORD. *Best Pract Res Clin Gastroenterol* 2013; 27: 325–337.

17   Fahim A, Dettmar P, Morice A, *et al.* Gastroesophageal reflux and idiopathic pulmonary fibrosis: a prospective study. *Medicina (Kaunas)* 2011; 47: 28.

18   Gao F, Hobson AR, Shang ZM, *et al.* The prevalence of gastro-esophageal reflux disease and esophageal dysmotility in Chinese patients with idiopathic pulmonary fibrosis. *BMC Gastroenterol* 2015; 15: 26.

19   Sweet MP, Patti MG, Leard LE, *et al.* Gastroesophageal reflux in patients with idiopathic pulmonary fibrosis referred for lung transplantation. *J Thorac Cardiovasc Surg* 2007; 133: 1078–1084.

20   Katz PO, Dunbar KB, Schnoll-Sussman F, *et al.* ACG Clinical Guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2022; 117: 27–56.

21   Jiang X, Holmes C, McVean G, *et al.* The impact of age on genetic risk for common diseases. *PLoS Genet* 2021; 17: e1009723

22   Mackintosh JA, Desai SR, Adamali H, *et al.* In patients with idiopathic pulmonary fibrosis the presence of hiatus hernia is associated with disease progression and mortality. *Eur Respir J* 2019; 53: 1802412.

23   Tossier C, Dupin C, Plantier L, *et al.* Hiatal hernia on thoracic computed tomography in pulmonary fibrosis. *Eur Respir J* 2016; 48: 833–842.

24   Sonnenberg A. Effects of environment and lifestyle on gastroesophageal reflux disease. *Dig Dis* 2011; 29: 229–234.

25   Lee JS, Ryu JH, Elicker BM, *et al.* Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 1390–1394.