



Nonalcoholic fatty liver disease and COPD: is it time to cross the diaphragm?

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Pneumologists should be aware of possible liver comorbidities, including NAFLD, in their COPD patients <http://ow.ly/WudH30btfqE>

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He will manage the cure best who has foreseen what is to happen from the present state of matters.

Hippocrates

In this issue of *European Respiratory Journal*, VIGLINO *et al.* [1] report that nonalcoholic fatty liver disease (NAFLD) is highly prevalent in chronic obstructive pulmonary disease (COPD) and might contribute to cardiometabolic comorbidities.

What is NAFLD?

The term “NAFLD” describes a clinicopathological spectrum of alcohol-like conditions spanning simple steatosis (ectopic, intrahepatocytic accumulation of triglycerides) and nonalcoholic steatohepatitis (NASH) (steatosis plus hepatocyte degeneration and lobular inflammation) with or without fibrosis, cirrhosis and primary liver cancer [2]. The NAFLD spectrum is observed in individuals who have no further reasons to develop chronic liver disease (*i.e.* alcohol, viral hepatitis, *etc.*) other than the full-blown metabolic syndrome (MetS) or its individual traits [3, 4].

The prevalence of NAFLD, paralleling that of obesity and type 2 diabetes, has reached epidemic proportions worldwide and NAFLD is projected to become the leading cause of end-stage liver disease necessitating transplantation by 2020 [5–8]. These impressive data, together with an excess of health-related expenditures [2, 9], easily explain why NAFLD is a major public health issue worldwide.

Genetic modifiers, systemic and hepatic insulin resistance, *de novo* lipogenesis, altered gut microbiota, subclinical inflammation, and oxidative stress are all deemed to play a major role in the physiopathology of NAFLD [2]. Liver histology changes critically dictate the natural history of NAFLD: the fibrosis stage predicts liver-related mortality [10] and, probably, cardiovascular events [11, 12]. Cardiovascular disease is the prime cause of mortality in most studies [13]. This is not surprising given the close and bidirectional relationship of NAFLD with the MetS, of which it may be both a precursor and a consequence [14, 15]. NAFLD patients are also prone to complications of progressive liver disease *per se* as well as to some extrahepatic cancers [2].

Liver biopsy remains the standard procedure for diagnosing NAFLD, especially for detecting NASH and staging fibrosis. However, due to invasiveness and costs, it cannot be proposed to all patients with

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NAFLD, nor is it suitable for epidemiological studies [2–4]. In order to overcome these limitations of liver biopsy, several noninvasive diagnostic tools have been developed. Imaging techniques play a key role in the diagnosis of steatosis and fibrosis, both in clinical practice and in the research arena [2, 16]. A variety of biomarkers and noninvasive indices/scores for predicting steatosis, NASH and fibrosis are also available; most of them, however, require further validation and their diagnostic performance is generally poor [17].

What is the evidence for the association between NAFLD and COPD?

Given its association with a wide range of cardiovascular, renal, endocrine and other manifestations, NAFLD is definitely a systemic disorder [18, 19]. Not unexpectedly, a few studies have reported on the association of NAFLD and pulmonary function, including COPD (table 1) [1, 20–25]. Is this a chance association? The finding that the liver and the lung exhibit a large spectrum of similarities both in health and in disease states (figure 1) strengthens the probability of a nonrandom association between NAFLD and COPD.

In this intriguing context, VIGLINO *et al.* [1] found that NAFLD is highly prevalent in COPD and might contribute to cardiometabolic comorbidities. This prospective cohort study included 111 adult patients with mild-to-severe COPD mainly recruited during out-patient consultations at Grenoble University Hospital (Grenoble, France). After excluding patients with cancer, significant alcohol consumption and secondary causes of liver steatosis, the authors assessed, in their cohort of COPD patients, the prevalence and predictors of liver steatosis, NASH and fibrosis as evaluated through Fibromax, a patented panel of three noninvasive serum biomarkers (SteatoTest for steatosis, NashTest for NASH and FibroTest for fibrosis; BioPredictive SAS, Paris, France).

FibroTest includes measurements of α_2 -macroglobulin, apolipoprotein A1, haptoglobin, γ -glutamyltransferase and total bilirubin, corrected for age and sex. SteatoTest combines FibroTest parameters with body mass index (BMI), alanine aminotransferase (ALT), fasting glucose, triglycerides and total cholesterol. Finally, NashTest is calculated by adding BMI, ALT, aspartate aminotransferase, fasting glucose, triglycerides and total cholesterol to the FibroTest variables. All these tests provide a score ranging from 0.00 to 1.00; the higher the value, the higher the probability of liver lesions.

The data showed that 41.4% of the COPD patients had moderate–severe steatosis (as assessed by SteatoTest ≥ 0.57), 36.9% had borderline–definite NASH (NashTest > 0.25) and 61.3% had fibrosis stage $\geq F0$ –F1 (FibroTest ≥ 0.22), suggesting that progressive forms of NAFLD are frequent in COPD [1].

TABLE 1 Published studies regarding the potential association of chronic obstructive pulmonary disease (COPD) and nonalcoholic fatty liver disease (NAFLD)

First author [ref.]	Series and methods	Findings
RYBAK [20]	373 candidates for liver transplantation; USA	COPD is common and often undiagnosed in candidates for liver transplantation
MINAKATA [21]	410 adults without and 256 with liver diseases, all 666 without known lung diseases; Japan	In these patients, COPD has adverse consequences on functional status Liver disease patients have a significantly high prevalence of COPD, suggesting that the diagnosis of liver disease might help in the early detection of COPD
JUNG [22]	2119 adult males; Korea	NAFLD is strongly associated with reduced pulmonary function and its severity is inversely correlated with pulmonary function
MAPEL [23]	2284 COPD patients and 5959 age- and sex-matched non-COPD controls; USA	COPD patients have a substantially increased prevalence of renal, gallbladder and pancreatic diseases, as well as abnormal creatinine and liver tests, but not diagnosed liver disease
PENG [24]	9976 adults; USA	Individuals with moderate and severe hepatic steatosis are at greater risk for poor pulmonary function, especially in restrictive pattern Impaired pulmonary function is an extrahepatic complication of NAFLD
QIN [25]	1842 adults; China	Impaired lung function is significantly and inversely associated with the prevalence of NAFLD, independent of metabolic confounders
VIGLINO [1]	111 COPD patients; France	NAFLD is highly prevalent in COPD patients Liver steatosis, NASH and fibrosis are primarily linked with obesity, insulin resistance and systemic inflammation NAFLD might contribute to cardiometabolic comorbidities in COPD patients

NASH: nonalcoholic steatohepatitis.

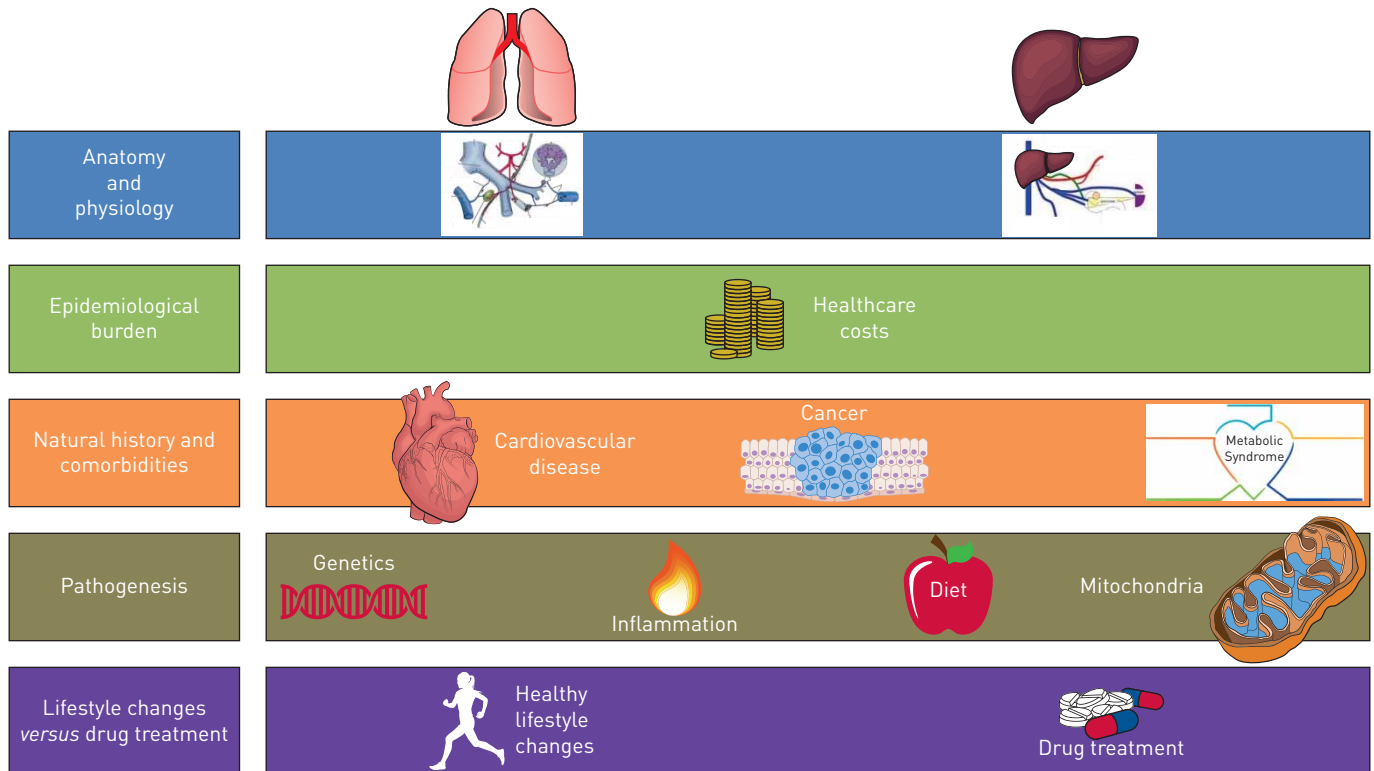


FIGURE 1 The spectrum of analogies linking chronic obstructive pulmonary disease (COPD) and nonalcoholic fatty liver disease (NAFLD). Both the lung and liver are highly vascularised organs with a dual blood supply, are involved in antigen processing and are master regulators of energy homeostasis. Based on their high prevalence and dangerous outcomes, COPD and NAFLD claim a high health and economic toll. Accordingly, more liberal screening policies have been advocated in individuals at high risk of COPD and NAFLD. COPD and NAFLD are increasingly recognised as multisystem diseases with high comorbidity rate, mainly clustered in the metabolic, cardiovascular and neoplastic area. Both COPD and NAFLD are complex noncommunicable diseases determined by environmental factors (unhealthy lifestyle habits) and genetic predisposition. Principles of treatment of COPD and NAFLD include lifestyle changes (smoking cessation, diet and physical activity) as a first step.

Weaker points and strengths of the study

Like most innovative studies, that of VIGLINO *et al.* [1] raises more questions than answers. First, the limitations implicit in the use of Fibromax as a noninvasive tool to detect liver injury need to be highlighted. Fibromax is not particularly popular outside France. It incorporates tests not routinely used in clinical practice, the relative formulas of which are undisclosed and incur a fee for each test applied. NashTest and FibroTest should be used if SteatoTest is positive [26]. Moreover, Fibromax has been validated *versus* liver biopsy, mainly in French cohorts of morbidly obese patients [27]. Data from nonobese individuals, countries other than France or selected cohorts of individuals, such as patients with COPD, are awaited. Second, the study lacks a control group. Third, participation in the study was proposed to consecutive patients but many refused owing to the inconvenience of the study protocol, which raises the risk of selection bias [1].

Despite such limitations, this study is the first to try to estimate the prevalence of NAFLD in COPD patients [1]. Moreover, it provides interesting hints that may pave the way to further translational research, potentially changing our approach to these chronic diseases. Of note, the putative prevalence of moderate–severe steatosis in this cohort of COPD patients was higher than that commonly reported in the general population [5], almost reaching the prevalence of advanced steatosis described in the original cohorts of bariatric morbidly obese patients in which Fibromax was originally validated [27]. Consistently, irrespective of the strategy used to assess liver injury, the prevalence of dysmetabolic traits was high in the cohort of VIGLINO *et al.* [1], suggesting that NAFLD may indeed be a common comorbidity in patients with COPD. The findings that COPD severity was identified as an independent predictor of steatosis, together with other parameters associated with visceral obesity and insulin resistance (*i.e.* BMI and HOMA-IR (homeostatic model assessment–insulin resistance)), and that steatosis was associated with higher levels of inflammatory cytokines [1], are further evidence that reinforces the assumption that NAFLD and COPD share common pathophysiological mechanisms (figure 1).

Conclusion and research agenda

Some authors deem that evidence for the interplay between lung and liver multimorbidities is relatively weak [28]. However, we believe that there are strong epidemiological and clinical grounds supporting the notion that NAFLD and COPD, as highly prevalent, noncommunicable, lifestyle-related systemic disorders with a similar pathogenic background and a high comorbidity rate, mainly clustered in the metabolic and cardiovascular area, are associated not by chance but by pathobiological necessity (table 1 and figure 1). By showing that NAFLD is highly prevalent in COPD and is primarily linked with the metabolic comorbidities of COPD and systemic inflammation, which may also enhance NAFLD progression, VIGLINO *et al.* [1] support this hypothesis, and potentially disclose novel avenues in the translational research and clinical management of patients with COPD and NAFLD.

However, further large, prospective and well-designed confirmatory studies should employ those consolidated diagnostic strategies that are commonly used by hepatologists worldwide to accurately gauge the prevalence and the severity of NAFLD among COPD patients. Specifically, studies should estimate the prevalence of COPD in NAFLD cohorts. Should the association between NAFLD and COPD be confirmed, information from either condition could easily be exploited to promote our understanding of the other disease. For example, network analysis of NAFLD comorbidities should be investigated, such as in COPD [29]. Similarly, a “systems medicine” approach may be suggested for COPD, such as that for NAFLD [19]. Finally, both patients with COPD and those with NAFLD might definitely reap benefits from the same lifestyle changes, including appropriate nutrition and physical activity [2, 30, 31].

In conclusion, pneumologists should be aware of possible liver comorbidities in their COPD patients and hepatologists that the spectrum of extrahepatic disease in NAFLD may be wider than previously appreciated. Thus, for both groups of clinicians, the time has come to cross the diaphragm.

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