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Review Article

Where We Now Stand: Unraveling the Link between COPD and NAFLD

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Abstract

Chronic obstructive pulmonary disease (COPD) and non-alcoholic fatty liver disease (NAFLD) are both prevalent and significant contributors to global morbidity and mortality. Despite their distinct pathophysiological mechanisms and target organs, emerging evidence suggests an interrelationship between these two conditions. This review aims to explore the current understanding of the potential link between COPD and NAFLD, discussing shared risk factors, underlying mechanisms, and clinical implications. Through an examination of epidemiological studies, biological pathways, and therapeutic approaches, we aim to illuminate the bidirectional relationship between these diseases and emphasize the need for integrated management strategies.

Keywords: *Chronic Obstructive Pulmonary Disease (COPD); Non-Alcoholic Fatty Liver Disease (NAFLD); Global Morbidity and Mortality*

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder characterized by airflow limitation and chronic inflammation, predominantly caused by long-term exposure to noxious particles, such as tobacco smoke [1]. On the other hand, non-alcoholic fatty liver disease (NAFLD) refers to a spectrum of liver conditions ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, in the absence of significant alcohol consumption [2]. NAFLD is commonly associated with metabolic conditions, including obesity, diabetes, and dyslipidemia [3].

While COPD and NAFLD have traditionally been considered separate diseases, growing evidence points to an important overlap in their pathogenesis, risk factors, and cardiovascular outcomes [4]. The coexistence of these two diseases in a significant number of patients has prompted the need for a closer examination of their interrelationship. This review delves into the possible connections between COPD and NAFLD, highlighting shared pathways that may contribute to their co-occurrence, as well as the implications for clinical practice.

Recent epidemiological studies have shed light on the possible association between COPD and NAFLD [4-7]. Both conditions are increasingly prevalent, particularly in individuals with common risk factors such as smoking, obesity, and metabolic syndrome [4,5,8,9]. The exact prevalence of NAFLD in patients with COPD is difficult to determine due to variations in diagnostic methods and study populations, but several studies suggest that NAFLD is more common among COPD patients compared to the general population [9,10].

A study by Wagih., *et al*. (2022) [11] found that up to 50% of patients with COPD had evidence of NAFLD, suggesting a strong association and demonstrated that patients with COPD are more likely to have metabolic disturbances that predispose them to NAFLD, such as insulin resistance and dyslipidemia [11,12]. These findings support the hypothesis that COPD and NAFLD may share a common pathophysiological basis, potentially influenced by systemic inflammation and metabolic dysregulation.

Moreover, the co-occurrence of COPD and NAFLD appears to be associated with worsened clinical outcomes. For instance, patients with both conditions tend to have more severe pulmonary symptoms, decreased quality of life, and higher mortality rates compared to those with COPD alone [12-14]. This suggests that the interplay between these diseases could exacerbate the overall burden of disease, making it crucial to understand the mechanisms linking COPD and NAFLD [4,12].

Several risk factors are common to both COPD and NAFLD, suggesting a potential overlap in their pathophysiology. These risk factors include:

- **Smoking:** Smoking is the most well-established risk factor for COPD, and evidence suggests that it may also contribute to the development and progression of NAFLD [5,9]. Cigarette smoke is known to cause systemic inflammation, oxidative stress, and endothelial dysfunction, which can promote liver steatosis and inflammation. Additionally, smoking has been associated with insulin resistance, a key factor in the development of NAFLD [12].
- **Obesity and metabolic syndrome:** Both COPD and NAFLD are closely linked to obesity and metabolic syndrome, conditions characterized by a cluster of metabolic abnormalities such as hypertension, dyslipidemia, and insulin resistance. Obesity contributes to the development of NAFLD by promoting fat accumulation in the liver, while also exacerbating COPD symptoms due to increased systemic inflammation and oxidative stress. In turn, NAFLD may contribute to obesity-related metabolic disturbances, creating a vicious cycle that worsens both conditions [12,13].
- **Chronic systemic inflammation:** It is a hallmark of both COPD and NAFLD. In COPD, inflammation of the airways and lungs leads to tissue damage, while in NAFLD, inflammation of the liver (non-alcoholic steatohepatitis, or NASH) drives the progression of liver injury [5]. The inflammatory mediators such as cytokines (e.g. TNF-α, IL-6), adipokines, and acute-phase proteins are elevated in both diseases, suggesting a common inflammatory pathway that may link COPD and NAFLD [5].
- **Oxidative stress:** It plays a central role in the pathogenesis of both COPD and NAFLD. In COPD, exposure to environmental pollutants and cigarette smoke results in the generation of reactive oxygen species (ROS), which damage lung tissue and contribute to airway inflammation. Similarly, in NAFLD, oxidative stress leads to liver cell damage and the progression to NASH. The presence of oxidative stress in both conditions may serve as a common link that accelerates the pathophysiology of both diseases.
- **Insulin resistance:** It is a key feature of NAFLD, and emerging evidence suggests that it may also play a role in the development of COPD [5,9]. Insulin resistance leads to dysregulation of lipid metabolism and fat deposition in the liver, which is the hallmark of NAFLD [5,7]. Furthermore, insulin resistance is associated with systemic inflammation and increased oxidative stress, both of which contribute to the pathogenesis of COPD [5,9]. This suggests that insulin resistance may represent a common metabolic dysfunction that contributes to the co-occurrence of COPD and NAFLD [7,8].

Understanding the biological mechanisms underlying the link between COPD and NAFLD is crucial for developing therapeutic strategies. Several potential mechanisms have been proposed. Both COPD and NAFLD are characterized by chronic inflammation, which may lead to shared pathological consequences [4,5,18]. In COPD, chronic airway inflammation results in the release of pro-inflammatory cytokines, which can increase the permeability of blood vessels and lead to systemic inflammation. This inflammation can extend to the liver, promoting the accumulation of fat and the development of NAFLD. Similarly, in NAFLD, hepatic inflammation releases pro-inflammatory cytokines, which may contribute to systemic inflammation and exacerbate pulmonary dysfunction.

Both diseases are associated with oxidative stress, which may act as a central mechanism linking COPD and NAFLD. In COPD, cigarette smoke and other environmental pollutants increase the production of ROS, which can damage lung tissue and promote inflammation. In the liver, ROS generated by hepatic steatosis and NASH can lead to cellular damage, further promoting inflammation and fibrosis [14]. The concurrent presence of oxidative stress in both organs may amplify the progression of both diseases.

Metabolic abnormalities such as insulin resistance, dyslipidemia, and altered adipokine levels are common to both COPD and NAFLD. In COPD, insulin resistance and increased visceral fat accumulation may exacerbate the inflammatory and metabolic processes that drive liver dysfunction [14,15]. Conversely, NAFLD may worsen metabolic dysfunction by increasing insulin resistance, creating a feedback loop that accelerates both pulmonary and hepatic pathology.

Hypoxia, a hallmark of advanced COPD, may also contribute to the development of NAFLD. Chronic low oxygen levels in COPD lead to the activation of hypoxia-inducible factors (HIFs), which regulate cellular responses to oxygen deprivation [6,16]. HIFs are involved in processes such as glucose metabolism, fat storage, and inflammation. These pathways are also implicated in the pathogenesis of NAFLD, suggesting that hypoxia in COPD may predispose individuals to liver steatosis and inflammation [17].

The figure 1 demonstrates the link between COPD and NAFLD, highlighting how pulmonary issues impact metabolic health. COPD is marked by chronic bronchial inflammation due to smoke exposure, leading to airflow limitation and systemic hypoxia. The smoke in the image represents smoking's role in triggering both lung and systemic inflammation [5,14]. Hypoxia from COPD increases oxidative stress and chronic inflammation, driving insulin resistance. This contributes to metabolic syndrome, which includes visceral fat accumulation and sets the stage for NAFLD. Visceral fat build-up, worsened by high-fat diets and insulin resistance, leads to liver fat deposition. Gut microbiota imbalances, linked to COPD and NAFLD, exacerbate systemic inflammation and create a feedback loop affecting both conditions [6]. COPD and NAFLD influence each other: COPD's inflammation can worsen insulin resistance, and NAFLD's metabolic impact can affect lung function. Understanding hypoxia, visceral fat, and gut health is key for comprehensive care.

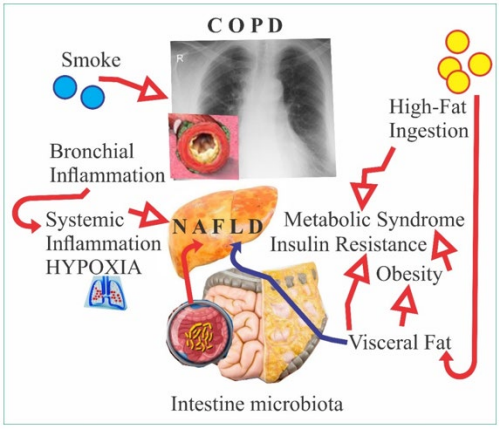

Figure 1: *Interconnected pathophysiological pathways between COPD and NAFLD.*

Ultrasound description of nonalcoholic fatty liver disease (NAFLD)

On the B-mode ultrasound image, the liver demonstrates characteristic findings consistent with NAFLD. The liver parenchyma appears hyperechoic, indicating an increased echogenicity due to adipose tissue accumulation. The anteroposterior diameter of the liver is noted to be enlarged, exceeding 13.5 cm, which suggests hepatomegaly (Figure 2).

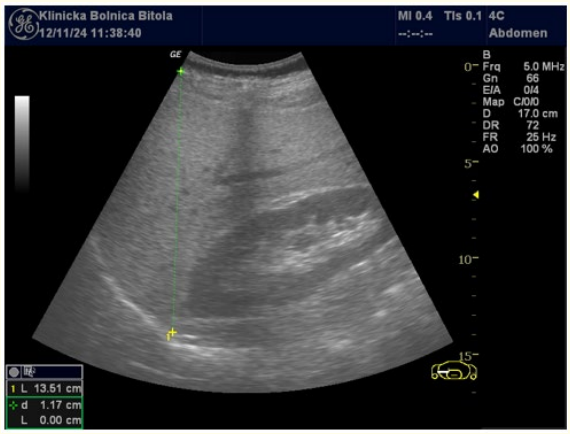

Figure 2: *B-mode Ultrasonography demonstrating non-alcoholic fatty liver disease (NAFLD) in male patients with chronic obstructive pulmonary disease (COPD).*

The echotexture of the liver is described as microgranular, reflecting a coarse texture that disrupts the usual homogeneity of the hepatic tissue. On grayscale imaging, the liver's echogenicity surpasses that of the adjacent kidney parenchyma, confirming the increased fat content within the liver cells.

Despite these significant parenchymal changes, the portal vein remains within normal limits, measuring less than 8 mm, which indicates the absence of portal hypertension. The deeper structures, including the hepatic vasculature and the diaphragm, are less clearly visualized and appear blurred. This is due to increased attenuation of the ultrasound beam, secondary to the elevated density of the liver tissue from fatty infiltration.

Overall, these findings on B-mode ultrasound align with a diagnosis of NAFLD, characterized by diffuse fat accumulation within the liver without the signs of advanced fibrosis or cirrhosis.

Doppler ultrasonography description of the hepatic artery flow

The Doppler ultrasonography of the liver in this 59-year-old male patient with COPD) and NAFLD reveals characteristic flow patterns in the hepatic artery. The examination was conducted with the following technical parameters: peak repetition frequency (PRF) set at 2.6 KHz, a frame rate of 5 Hz, gain at 65 dB, and a depth setting of 17 cm.

Hepatic artery flow findings:

- **Peak systolic velocity (PSV):** The hepatic artery demonstrates a PSV of 25.83 cm/s, indicating moderate systolic flow within normal hemodynamic ranges but potentially affected by liver parenchymal changes associated with NAFLD.
- **End-diastolic velocity (EDV):** The EDV measures 8.50 cm/s, which suggests maintained diastolic perfusion despite the underlying liver condition.

- **Pulsatility index (PI):** The PI is calculated at 1.06, reflecting the variability in flow velocity between systole and diastole. This value is within the expected range but may indicate subtle alterations in arterial compliance or downstream resistance influenced by liver changes due to NAFLD.
- **Resistance index (RI):** The hepatic artery RI is 0.64, a value that is within the normal range. This suggests preserved arterial resistance without significant impedance to flow, despite the presence of fatty liver disease.
- **Mean hepatic artery velocity:** The mean velocity of 20.27 cm/s supports consistent, albeit mildly altered, blood flow characteristics through the hepatic artery.

Technical observations: The Doppler trace demonstrates a well-defined waveform with adequate spectral window visibility. The liver's hyperechoic parenchyma, noted on the corresponding B-mode image, contributes to subtle changes in Doppler waveforms by influencing acoustic properties and attenuation. Despite NAFLD, the Doppler findings indicate that the hepatic artery continues to supply blood effectively, although potential changes in microvascular flow could align with the patient's comorbid conditions, including COPD.

Figure 3 illustrates the doppler waveform, highlighting the PSV of 25.83 cm/s and EDV of 8.50 cm/s, along with a PI of 1.06 and RI of 0.64. The mean hepatic artery velocity is shown to be 20.27 cm/s. This image provides a clear representation of the maintained flow dynamics within the hepatic artery despite the liver's fatty infiltration associated with NAFLD and the patient's comorbid COPD.

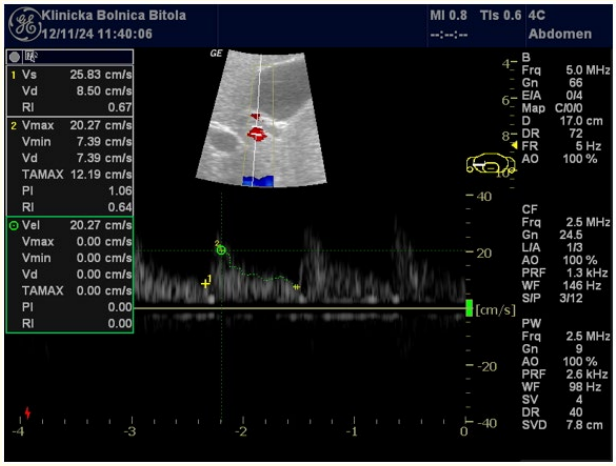

Figure 3: *Doppler ultrasonography of hepatic artery in a 59-year-old male with COPD and NAFLD: Hemodynamic assessment.*

Table 1 provides a detailed summary of key functional respiratory parameters used to assess lung function in individuals with chronic obstructive pulmonary disease (COPD).

Parameters	LLN	Predicted	Best	%Predicted	Z-score
FVC (L)	2.05	2.62	1.99	76	-1.83
FEV1 (L)	1.55	2.03	0.97	48	-3.64
FEV1/FVC (%)	68.5	78.3	48.7	62	-4.97
PEF (L/s)	4.05	5.45	1.23	23	-4.96
ELA (years)		59	91	154	
FEF25-75% (L/s)	1.04	2.06	0.56	27	-2.43

FET (s)		6.00	4.04	67	
FIVC (L)	2.05	2.62	1.1	42	-4.42
FEV1/VC (%)	68.5	78.3			
FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 second; FEV1/FVC: The ratio of FEV1 to FVC; PEF: Peak Expiratory Flow; ELA: Expiratory Lung Age; FEV25-75%: Forced Expiratory Volume between 25% and 75% of FVC; FET: Forced Expiratory Time; FIVC: Forced Inspiratory Vital Capacity; FEV1/VC: The ratio of FEV1 to Vital Capacity					

Table 1: *Overview of functional respiratory parameters in COPD.*

Figure 4 illustrates the graphical interpretation of severe airway obstruction obtained through spirometry analysis using the SPIROBANK II device (Serial Number Y1426). The graph plots volume (in liters) on the x-axis and flow (in liters per second) on the y-axis, visually demonstrating the spirometric findings.

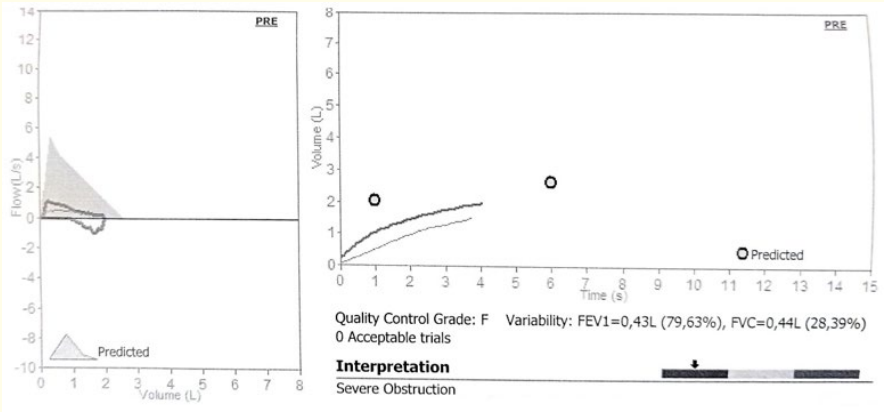

Figure 4: *Graphical representation of severe obstruction based on spirometry analysis using SPIROBANK II.*

The arrow positioned on the horizontal bar graph indicates the severity of the obstruction, providing a clear depiction of the degree of impairment. This visual cue enhances the understanding of how flow-volume loops reflect restrictive and obstructive patterns in respiratory function.

These parameters help in diagnosing and evaluating the severity of airflow obstruction and overall pulmonary function:

- **FVC (Forced vital capacity)**: The total volume of air that can be forcibly exhaled after full inhalation, measured in liters. It indicates the capacity of the lungs and helps in assessing restrictive lung diseases;
- **FEV1 (Forced expiratory volume in 1 second)**: The volume of air expelled in the first second of a forced exhalation. It is a critical parameter for diagnosing the severity of airflow limitation in COPD;
- **FEV1/FVC (%)**: The ratio of FEV1 to FVC, expressed as a percentage. A reduced FEV1/FVC ratio is a hallmark of obstructive lung disease, indicating the degree of airflow limitation;

- **PEF (Peak expiratory flow)**: The maximum speed of exhalation measured in liters per second. It reflects the patient ability to quickly expel air from the lungs;
- **ELA (Estimated lung age)**: An estimation in years of the patient's lung condition compared to a healthy individual, highlighting the impact of COPD on lung function;
- **FEF25-75% (Forced expiratory flow at 25-75%)**: The average flow rate during the middle half of the FVC. It is an indicator of small airway function and can be sensitive to early changes in COPD;
- **FET (Forced expiratory time)**: The duration of the complete forced expiration, measured in seconds. Prolonged FET can indicate obstructed airflow;
- **FIVC (Forced inspiratory vital capacity)**: The maximum volume of air inhaled after a complete exhalation, providing insight into inspiratory capacity and
- **FEV1/VC (%)**: The ratio of FEV1 to vital capacity, which further assists in evaluating the degree of obstruction and respiratory impairment.

If the spirometry test shows a reduced FEV1 and a decreased FEV1/FVC ratio, this suggests moderate to severe airflow obstruction. If the FVC is also below the expected range, it may indicate a restrictive component or a combined obstructive and restrictive pattern. In summary, spirometry results showing a reduced FEV1, FEV1/FVC ratio, and potentially reduced FVC would indicate moderate to severe obstructive lung disease with or without restriction, which is typical in conditions like COPD.

Conclusion

COPD and NAFLD are two prevalent diseases that are increasingly recognized as interrelated. Shared risk factors, including smoking, obesity, and systemic inflammation, contribute to the pathogenesis of both conditions. Emerging evidence suggests that the coexistence of COPD and NAFLD may worsen clinical outcomes and increase the risk of disease progression. Understanding the underlying mechanisms linking these diseases is essential for developing targeted therapeutic strategies. Further research is needed to better define the pathophysiological connections between COPD and NAFLD, and to elucidate the shared inflammatory, metabolic, and oxidative stress pathways that contribute to their coexistence. Such insights could pave the way for innovative, multifaceted treatment approaches that address both conditions simultaneously and improve patient outcomes.

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