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Editorial

Impaired Pulmonary Function as a Potential Contributor to Reduced Exercise Capacity Associated with MAFLD

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For over a century, fatty liver has been associated with inadequate physical activity.[1] A sedentary lifestyle has long been considered a major contributor to obesity and fatty liver. People with fatty liver are consequently often deemed to be unwilling or unable to increase their physical activity as a therapeutic lifestyle intervention. Research is ongoing toward identifying obstacles to physical exercise in people with fatty liver, exposing intrinsic and extrinsic factors that may sometimes be bidirectional. Several studies have now reported impaired exercise capacity in individuals with nonalcoholic fatty liver disease (NAFLD) and this has variably been attributed to the severity of nonalcoholic steatohepatitis (NASH), left ventricular diastolic dysfunction, obesity, functional iron deficiency, sarcopenia, and reduced fitness. NAFLD has also been associated with reduced pulmonary function,[2] which together with the above-mentioned conditions, could have implications for the capacity and enjoyment of exercise. In 2015, Peng and colleagues[3] published an analysis of 9,976 patients from the Third National Health and Nutrition Examination Survey (NHANES III) cohort that demonstrated a relationship between hepatic steatosis and impaired pulmonary function, specifically a restrictive pattern of lung disease.

As the metabolic syndrome and metabolic dysfunction gain prominence in defining the contemporary phenotype and risk associations of fatty liver, the term metabolic dysfunction-associated liver disease (MAFLD) is increasingly adopted. As MAFLD represents hepatic steatosis with nonidentical inclusion and exclusion characteristics compared with NAFLD, it is timely to examine differences in pulmonary function between the two definitions, as part of defining the multisystem reach of fatty liver. In this journal, Miao and colleagues[4] recently provided additional insights into the effects of MAFLD on pulmonary function in a large cross-sectional study of adults. In their study, middle-aged Chinese patients with MAFLD and/or NAFLD were found to have significantly lower forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). Adults with MAFLD had more severe impairment of pulmonary function compared with those with NAFLD, particularly when associated with type II diabetes mellitus and/or increased adiposity. Saliently, the severity of pulmonary function impairment correlated with both the degree of obesity and probable liver fibrosis, as assessed using noninvasive FIB-4 scoring. While the exact mechanisms responsible for those changes are yet to be fully elucidated, there are several potential pathways that likely contribute to the impairment in lung function.

Normal lung mechanics are largely determined by pulmonary compliance, which is defined as the change in lung volume per change in the thoracic transmural pressure.[5] Changes in thoracic transmural pressure, in turn, are positively affected by the diaphragm, external intercostal, sternocleidomastoid, and scalene muscles, and negatively influenced by factors that impede rib expansion and diaphragmatic excursion. As MAFLD progresses, the liver parenchyma becomes increasingly steatotic, leading to hepatomegaly with higher intrabdominal volume and displacement of the visceral structures, including the abdominal visceral fat compartment. The increased intraabdominal volume causes an increased resistance against diaphragmatic contractions thereby limiting functional residual capacity (Fig. 1).[6–8] A novel finding by Miao *et al.*[4] is that the severity of liver fibrosis determines the degree of impaired lung function with MAFLD. It is plausible that as liver stiffness increases, the diaphragmatic forces required to displace the liver also increase. When coupled with sarcopenia, which is commonly seen in advanced MAFLD patients,[9] these factors will worsen pulmonary function.

Patients with MAFLD may by susceptible to airway inflammatory changes and hyperresponsiveness. Obesity and metabolic conditions such as MAFLD cause increases in circulating inflammatory cytokines and chemokines that in turn lead to airway inflammatory changes and hyperresponsiveness (Fig. 1).[10] Interestingly, glucagon-like peptide-1 receptors (GLP-1R) agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are commonly used in the treatment of diabetes in patients with MAFLD, have been found to improve lung function. GLP-1R is expressed on lung epithelial cells as well as pulmonary leukocytes. GLP-1R agonists, such as liraglutide, dulaglutide, and exenatide, are capable of increasing FEV1 and FVC in diabetes patients (Fig. 1).[7] In contrast, SGLT2 inhibitors not only improve insulin sensitivity, systemic endothelial function, and reduce systemic inflammation, but also reduce

Abbreviations: FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease.

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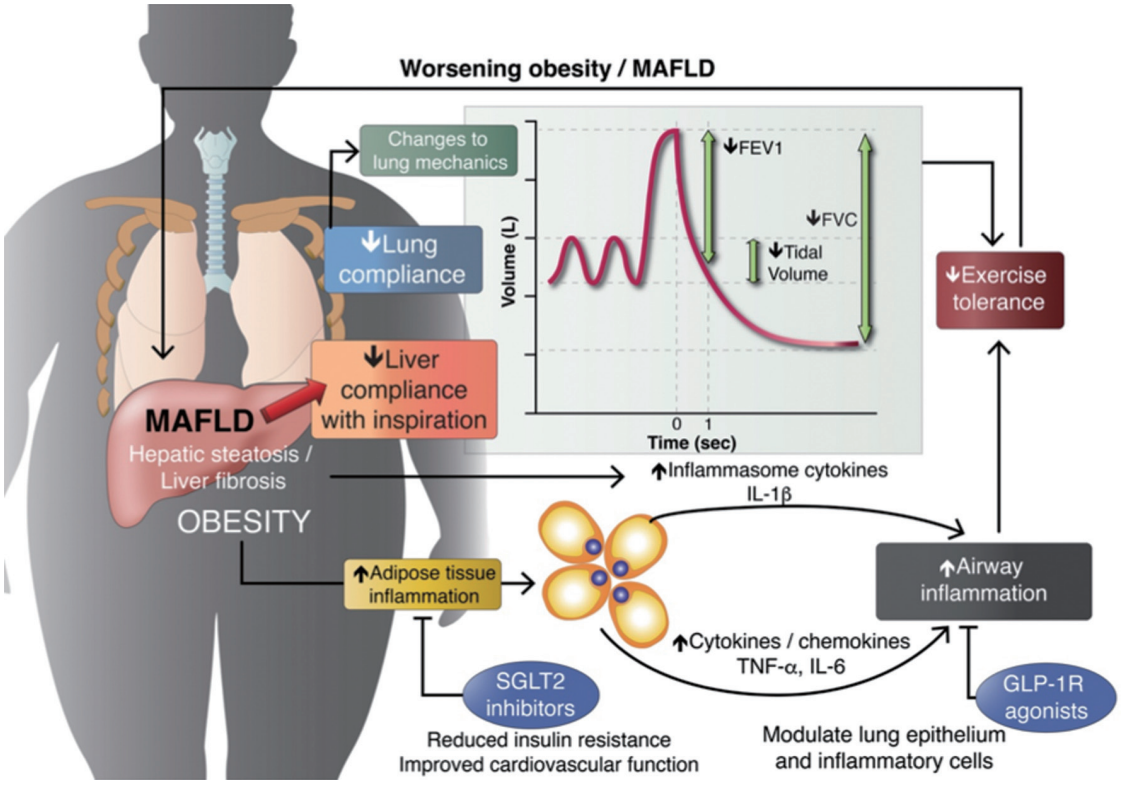

Fig. 1. Effects of metabolic-associated liver disease (MAFLD), obesity, and liver fibrosis on respiratory function and current therapeutic options. MAFLD-associated liver fibrosis reduces lung compliance leading to diminished forced vital capacity (FVC) and forced expiratory volume at 1 s (FEV1). Individuals with obesity have smaller tidal volumes. The increased visceral adiposity seen in obese patients, as well as hepatic inflammatory changes in MAFLD lead to high levels of circulating pro-inflammatory cytokines such as interleukins (IL)-1β, IL6 and tumor necrosis factor alpha (TNF-α). Within the airways, these cytokines contribute to inflammatory changes and increased airway hyper-responsiveness, thereby contributing to respiratory morbidity and impaired exercise tolerance (see reference 8). Separate to their anti-hyperglycemic effects glucagon-like peptide-1 receptor (GLP-1R) agonists are capable of directly modulating airway inflammation by acting on lung epithelium and inflammatory cells, thereby increasing FEV1.[7] Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve insulin sensitivity, reduce systemic adipose inflammation and pulmonary artery pressure,[8] and may improve exercise function.

pulmonary artery pressure and potentially improve exercise function.[8] As knowledge regarding the pathogenesis and systemic metabolic influences associated with MAFLD increase, there will be a need for improved understanding of the therapeutic consequences of various therapies on pulmonary function in patients with MAFLD.

Overall, the results of the study by Miao and colleagues[4] add to increasing observations of impaired pulmonary function associated with fatty liver. Impaired pulmonary function is a plausible additional explanation for reduced exercise capacity in some individuals with MAFLD and reinforces the importance of considering pulmonary impairment as a component of multi-organ impairment with MAFLD, particularly in those with liver fibrosis. This may have implications for understanding obstacles to exercise, as well as for the design of exercise intervention programs for people with MAFLD.

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Conflict of interest

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