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

Derrick Michael Van Rooyen1 and Oyekoya Taiwo Ayonrinde1,2,3*

1Department of Gastroenterology and Hepatology, Fiona Stanley Hospital, Murdoch, WA, Australia; 2Medical School, The University of Western Australia, Nedlands, Australia; 3Faculty of Health Sciences, Curtin University, Bentley, Australia

Received: 28 February 2022 | Revised: 1 April 2022 | Accepted: 2 April 2022 | Published: 19 April 2022

Citation of this article: Van Rooyen DM, Ayonrinde OT. Impaired Pulmonary Function as a Potential Contributor to Reduced Exercise Capacity Associated with MAFLD. J Clin Transl Hepatol 2022;10(2):181–183. doi: 10.14218/JCTH.2022.00103.

For over a century, fatty liver has been associated with inadequate physical activity. 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 non-alcoholic 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, which together with the above-mentioned conditions, could have implications for the capacity and enjoyment of exercise. In 2015, Peng and colleagues 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 non-dentical 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 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 these 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. 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). It is plausible that reduction 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, these factors will worsen pulmonary function.

Patients with MAFLD may be 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). 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). In contrast, SGLT2 inhibitors not only improve insulin sensitivity, systemic endothelial function, and reduce systemic inflammation, but also reduce...
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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 colleagues4 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.

Funding
None to declare.

Conflict of interest
OTA has been an editorial board member of Journal of Clinical and Translational Hepatology since 2021. DMvR has no conflict of interests related to this publication.

Author contributions
Manuscript preparation, revision, and approval of final version of submitted manuscript (DMvR, OTA), guarantor of manuscript (OTA).

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