



Editorial

The independent effect of exercise on biopsy proven non-alcoholic fatty liver disease: A systematic review

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Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver diseases from non-alcoholic fatty liver to non-alcoholic steatohepatitis (NASH), leading to fibrosis, cirrhosis, and even to hepatocellular carcinoma.¹ The overall global prevalence of NAFLD is about 25% and steadily rising.²⁻⁵ However, to date, no drug has been approved drug for the treatment of NAFLD. Lifestyle modification, including exercise, weight reduction, and diet control is known to be the only accepted treatment for NAFLD.⁶⁻⁸ However, the independent effect of exercise on biopsy-proven NAFLD remains controversial.

This issue of the *Clinical and Molecular Hepatology* carried the first systemic review of published literature by Chen et al.⁹ for evidence on the independent effects of exercise on histological or non-invasive test (NIT) outcomes in patients with biopsy-proven NAFLD. The systemic review⁹ includes seven interventional and two observational studies. In this review, histologic endpoints were evaluated in six studies in-

cluding two randomized controlled trials (RCTs), one non-RCT, one uncontrolled study, and two cross-sectional studies. Two RCTs^{10,11} failed to demonstrate the independent impact of exercise on histological improvement in the absence of weight reduction or diet intervention. On the other hand, the non-randomized interventional studies showed that exercise could reduce hepatocyte ballooning and liver fibrosis.¹²⁻¹⁵ However, these studies were limited by the absence of separate NASH-related data and by the uncontrolled study design. Moreover, Chen et al.⁹ did not analyze the difference between the effects of aerobic and anaerobic exercise on NAFLD. In the previous RCT involving subjects with clinically defined NAFLD, Hallsworth et al.¹⁶, showed that resistance exercise improves NAFLD regardless of changes in body weight. Therefore, the results would have been more meaningful if Chen et al.⁹ had also confirmed an independent effect according to the type of exercise on biopsy-proven NAFLD.

With regard to NIT, three RCTs and two non-RCTs assessed the independent effect of exercise on biopsy-proven NAFLD for hepatic steatosis, steatohepatitis, and liver fibrosis.^{12,13,17-19}

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One RCT published by Rezende et al.¹⁷ used transient elastography as an NIT for the evaluation of the benefits of exercise in NAFLD patients with hepatic steatosis and fibrosis. Although this study is the only RCT to use transient elastography to assess the independent benefit of exercise on biopsy-proven NAFLD, aerobic exercise failed to demonstrate significant improvement of hepatic steatosis or fibrosis severity in this study.¹⁷ On the other hand, interestingly, other studies using magnetic resonance imaging-proton density fat fraction (MRI-PDFF) to measure outcomes have demonstrated improvement in hepatic steatosis due to exercise.^{18,19} However, there were no significant changes of the serum biomarkers for liver fibrosis and steatohepatitis.^{12,18,19} Given that MRI-PDFF is an accurate diagnostic method for hepatic fat over the entire liver and that it is a repeatable and reproducible quantitative examination method,²⁰⁻²³ this result is clinically significant.

To analyze the independent role of exercise, it is important to strictly control potential bias associated with the intensity, frequency, and type of exercise between eligible studies. However, it is not easy to completely control these variables. This would inevitably be a limitation of this study.⁹ It is also regrettable that a meta-analysis was not included in this systematic review.⁹ This is an area that needs to be supplemented through further research in the future.

Nonetheless, this study⁹ highlights the need for additional research to assess the independent role of exercise in the improvement of histologic and clinical biomarkers in patients with biopsy-proven NAFLD.

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Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NIT, non-invasive test; RCT, randomized controlled trials; MRI-PDFF, magnetic resonance imaging-proton density fat fraction

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