Editorial

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Exercise and improvement of NAFLD: Practical recommendations

Rohit Loomba[1,2,3,*,†], Helena Cortez-Pinto[4,*,†]

[1]*Division of Gastroenterology, University of California, San Diego, La Jolla, CA, United States;* [2]*NAFLD Translational Research Unit, Department of Medicine, University of California, San Diego, La Jolla, CA, United States;* [3]*Division of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA, United States;* [4]*Departamento de Gastrenterologia, Hospital Santa Maria, CHLN, Unidade de Nutrição e Metabolismo, Faculdade de Medicina de Lisboa, Portugal*

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Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the Western World [1,2]. There are no approved pharmacologic therapies for the treatment of NAFLD [2,3]. NAFLD is considered the hepatic manifestation of metabolic syndrome and is commonly associated with obesity, and diabetes [4,5]. Lifestyle interventions such as dietary modification to induce weight loss, and exercise have been shown to be beneficial in improving NAFLD as well as improve specific histologic features associated with the progressive form of NAFLD, which is termed as non-alcoholic steatohepatitis (NASH) [6,7]. Therefore, weight loss in obese and overweight patients with NAFLD is commonly the recommended management strategy [2]. Both aerobic and resistance training-based exercise regimen improve liver fat as well as visceral fat [6]. However, the exact role of the amount and the intensity of aerobic exercise that would be needed to reverse or improve NAFLD (or NASH) has not been systematically assessed.

In this issue of the *Journal of Hepatology*, Keating *et al.* aimed to examine the effect of the dose of aerobic exercise training in improving liver and visceral fat in overweight and obese patients with NAFLD who had a sedentary lifestyle [8]. Utilizing a randomized, placebo-controlled clinical trial (RCT) design, the investigators randomized 48 participants into four equal groups (n = 12 in each group) receiving various doses/intensities of exercise training regimen into either; i) low to moderate intensity, high volume aerobic exercise (LO:HI, 50% VO2peak, 60 min, 4 d/wk); ii) high intensity, low volume aerobic exercise (HI:LO, 70% VO2peak, 45 min, 3 d/wk); iii) low to moderate intensity, low volume aerobic exercise (LO:LO, 50% VO2peak, 45 min, 3 d/wk); or iv) placebo (PLA) for an eight week period. The primary end point was the change in liver fat as assessed by magnetic resonance spectroscopy (MRS). The utility of MR-based liver fat assessment has been previously demonstrated and well-accepted in early proof of concept trials in NAFLD [9–11] and is a major strength of this RCT. Authors reported that all three groups irrespective of the dose of the exercise showed improvement in liver fat albeit small compared to the PLA-group independent of weight loss. There were no significant differences between the various aerobic exercise regimens in reducing liver fat over an 8 week period. However, authors conducted additional exploratory analyses and proposed that there was a trend towards greater reduction in liver fat and visceral fat in the two groups that utilized either high intensity with low volume or low intensity with high volume aerobic exercise. This probably suggests that duration of exercise and intensity of exercise are both important and one could perhaps personalize the exercise regimen based upon a participant's choice and still achieve similar results.

The study had several strengths including its randomized-controlled design and the use of MRS to quantify the changes in liver fat. However, there were a few noteworthy limitations. It was underpowered for detecting significant differences in the efficacy of the various exercise regimens in reducing liver fat content. Nonetheless, the fact that they were able to demonstrate that all exercise regimens were able to reduce visceral and liver fat, is an important practical conclusion. Although ^{1}H-MRS is an accurate method of measuring the amount of fat, either in the liver or in the adipose tissue, it does not provide information regarding hepatic necroinflammation. Despite these limitations of current imaging modalities, there is emerging evidence that excess liver fat *per se* (independent of NASH) is associated with increased cardiometabolic risk [12], so the reduction of liver fat may reduce this excess cardiovascular risk. Exercise is shown to improve cardiovascular risk in the general population but the exact mechanisms are unknown. It is plausible that exercise reduces cardiovascular risk by reducing liver fat as shown in this study. Further mechanistic studies are needed to test these hypotheses.

Physical activity may have an important role in the prevention and treatment of NAFLD. Previous studies have shown a

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* Corresponding authors. Addresses: Division of Gastroenterology and Epidemiology, University of California, San Diego, 9500 Gilman Drive, MC 0063, La Jolla, CA 92093, United States. Tel.: +1 858 534 2624; fax: +1 858 534 3338 (R. Loomba). Serviço de Gastrenterologia, Hospital de Santa Maria, Av. Prof. Egas Moniz, 1649-035 Lisbon, Portugal. Tel.: +351 217985187; fax: +351 217985142 (H. Cortez-Pinto).

E-mail addresses: roloomba@ucsd.edu (R. Loomba), hlcortezpinto@netcabo.pt (H. Cortez-Pinto).

† Equal contributors.

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consistent association between lack (or lower level) of physical activity and presence of NAFLD [13,14]. Although the amount of physical activity that is needed to improve NASH is uncertain there is preliminary evidence that vigorous exercise may be associated with a decreased risk of having NASH [15]. The individual, the joint effect of dose and intensity of exercise and their association with improvement in liver fat and other histologic features that are associated with NASH are key research priorities.

The majority of studies conducted in patients with either NAFLD or NASH utilize lifestyle interventions that include both dietary changes and exercise. Therefore, lifestyle intervention although improve NAFLD and NASH, these are seen with accompanying weight loss. In a seminal observation, Johnson *et al.* showed that aerobic exercise was able to reduce liver fat in the absence of weight loss. They utilized MRS of the liver to study 19 sedentary obese individuals for an aerobic exercise intervention trial with a 4 week duration. They found that aerobic exercise alone without any significant weight loss was able to induce a 12% decrease in the visceral adipose tissue volume and a 21% decrease in liver fat content over the 4 week period [16]. Recently, Sullivan and colleagues conducted a RCT to evaluate the weight loss-independent effect of following the physical activity guidelines recommended by the United States Department of Health and Human Services on liver fat content and lipid kinetics in obese persons with NAFLD. They demonstrated that exercise training of moderate intensity for 30–60 min 5 times a week for a 16-week period led to approximately 10% decrease in liver fat content but did not improve triglyceride secretion rate in the absence of weight loss [17]. Many of these studies have assessed the utility of aerobic exercise. However, some patients may not be able to either perform or tolerate aerobic exercise. In those, who are either intolerant or have contraindications for aerobic exercise, resistance training may be considered as either aerobic or resistance training which may induce a reduction in liver fat. In a pilot trial comparing resistance training *vs.* controls, resistance training led to a significant reduction in liver fat content by induction of hepatic fat oxidation and improvement of glucose control through increases in the expression of GLUT4 and glycogen synthase [18]. In a recent trial, Zelber-Sagi and colleagues randomized 62 patients into either resistance training group or control group and demonstrated that resistance training can lead to a reduction in liver fat by using hepatorenal ultrasound index (HRI) [19]. The next question that emerged from the above studies was to assess if one type of exercise regimen is better than another in improving liver fat content. To address some of these issues, Bacchi and colleagues randomized 31 sedentary adults with type 2 diabetes and NAFLD into either aerobic training group or resistance training group for 4 months. They reported either approach to be equally effective [20].

In summary, based upon the review of the available evidence, we offer the following recommendations to the clinicians and the patients suffering from NAFLD or those who are at risk of NAFLD. There is good quality evidence to support that regular exercise is beneficial in reducing the risk of NAFLD. In addition, both aerobic and resistance training regimen are equally effective in reducing liver fat in individuals with NAFLD even in the absence of weight loss. There are no data to support that exercise alone without weight loss can improve or reverse NASH. Hence, lifestyle interventions utilizing both exercise and caloric restriction inducing weight loss (loosing approximately 5–10% of body weight) are needed to improve NASH. The United States Department of Health and Human Services exercise recommendations may lower liver fat but based upon our expert opinion more stringent exercise regimen coupled with dietary interventions may be needed to induce improvement in liver histologic features associated with NASH. Further research is needed to document the dose, intensity, and joint effect of exercise and weight loss in improving liver histology in NASH. Although the minimal effective volume and intensity of exercise are not yet defined it seems that even low intensity and low volume may be beneficial – something is better than nothing.

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Conflict of interest

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Authors' contributions

Rohit Loomba: Editorial concept, interpretation of data, drafting of the manuscript, critical revision of the manuscript, approved final submission. **Helena Cortez-Pinto:** Editorial concept, interpretation of data, drafting of the manuscript, critical revision of the manuscript, approved final submission.

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