

May 18, 2016

Ze-Mao Gong  
Science Editor  
World Journal of Gastroenterology  
Baishideng Publishing Group

Dear Dr. Gong,

We are re-submitting our manuscript "Effectiveness of Exercise in Hepatic Fat Mobilization in Non-Alcoholic Fatty Liver Disease" to World Journal of Gastroenterology for publication consideration. We would like to express our deepest appreciations to the reviewers for their excellent suggestions. We have addressed the issues raised by the reviewers but could not access to the file that reviewer 3 had attached and mentioned in his/her commend.

Again, please accept our appreciations for the suggestions and looking forward to hearing from you.

Sincerely,

Zobair Younossi, M.D., M.P.H.

Vice President of Research, Inova Health System

Chairman, Department of Medicine

## **Reviewer 1**

The review is interesting, for the topic and for the adopted style of presentation. Please, address some limitation of this overview: Yes, "Exercise is different from activity. Activity refers to any movement requiring energy, that is, not resting. Exercise refers to planned and/or structured movement of a specific intensity, frequency and duration": but it is likely that exercise prescription contribute to modify current, previous physical activity. Moreover, if exercise is a drug, at least for fatty liver, also physical activity conceivably is medicine. Probably some comment should be methodologically appropriate. RE or AE is quite a general itemization: exercise performed open air or not should be defined and this may be a very critical discrimination. Seemingly, not all the reported studies describe overall effect on BMI. The number of dropouts is quite great, and also information on adherence are quite vague, apart the lack of nutritional information at baseline and with some interventional change. Looking at most of the original articles the profiles (physical activity, diet) of these subjects – pre-intervention – seems quite incomplete for allowing any straightforward conclusion. Was physical exercise prescription done with any criterion and preliminary assessment? The point is of interest for MDs, also considering the conclusion: "An exercise intervention of moderate intensity is effective for the mobilization of IHTG. The findings support the view that exercise is effective in reducing IHTG in patients with NAFLD independent of weight loss or dietary manipulation". Low cardiorespiratory fitness is a prominent behavioral risk factor for cardiovascular disease (CVD) morbidity and mortality, so that a preliminary assessment and a well targeted monitoring is needed when prescribing physical exercise. Check, please, the spelling of few words in Fig. 1

## **Comment 1:**

We have addressed the concerns in Reviewer 1's comment. We have elaborated on the differences between exercise and activity in the introduction section. In summary, exercise and physical activity are not synonymous; exercise is a subcategory of physical activity, which is planned, structured, repetitive and purposive with a specific intensity, frequency and duration. We have also addressed the issues brought up about what is meant by exercise as medicine in the discussion section. We agree this is an important point. Another important point mentioned by the reviewer is about the specifics of the exercise. Our comment that moderate intensity exercise is associated with a positive effect on fat mobilization is based on the data reported in the review. Even when the exercise prescription targeted a heart rate below 80% VO<sub>2</sub> maximum, and the frequency/duration did not exceed 150 minutes/week (both accepted as definitions of moderate intensity), benefit was achieved.

Finally, we have corrected the spelling errors in the Figure 1.

## **Reviewer 2**

Introduction section: diet, in association with exercise is the cornerstone in the treatment of NAFLD. recently, many data have been reported in this way the efficacy of Mediterranean diet (i.e. Abenavoli et al. World J Gastroenterol 2014). please improve this point. I suggest also, to briefly include data on NAFLD worldwide prevalence (i.e. Msarone et al. Rev Recent Clin Trials 2014) - Discussion section: exercise effectively reduce liver fat. The choice of training should be tailored based on patients preferences to be maintained in the long-term. This point is essential, and was now highlight in the recent EASL guidelines (Hepatology 2016 in press). Please include it and this reference in order to improve your work.

## **Comment 2:**

We would like to thank Reviewer 2 for these great recommendations. We have added a section regarding the Mediterranean diet and its beneficial effects on patients with NAFLD. We have also included recent data about the global prevalence of NAFLD and cited the recommended references. Although studies have focused on different exercise/diet combinations and give recommendations according to those findings, exercise interventions should be personalized in patients with NAFLD, given the cardiologic and metabolic risk factors. This point is clearly stated in the EASL guidelines and we have improved our review by adding this reference.

## **Reviewer 3**

Golabi et al. presented a review paper entitled "Effectiveness of Exercise in Hepatic Fat Mobilization in Non-Alcoholic Fatty Liver Disease". The aim of the review paper was to investigate the efficacy of exercise interventions on hepatic fat mobilization in NAFLD patients using a systematic review approach. The authors reported that exercise is effective in reducing IHTG in patients with NAFLD independent of weight loss or dietary manipulation and that combining exercise with dietary interventions augments the reduction in IHTG. I enjoyed serving as a reviewer of this manuscript and think it is a very interesting topic. The authors pose a research question that is not really new, yet they use strict selection criteria regarding the assessment of intrahepatic triglycerides (IHTG), together with the description of the interventions. This may add useful

information regarding the choice for a specific intervention and may aim to contribute to more healthy, physiological, financial and time efficient clinical practice/intervention in the specific sub-population possibly enhancing the patients' outcome. Nevertheless, after reading the paper, I found several overlooked aspects that need to be addressed. I think this paper needs a throughout revision. Please find detailed comments on the attached file.

**Comment 3:**

We would like to thank Reviewer 3 for consideration but as we could not access the file, we cannot comment on this.