

Format for ANSWERING REVIEWERS



January 25, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (**Physical activity support or weight loss counseling for nonalcoholic fatty liver disease?: 8081-review.doc**).

Title: Physical activity support or weight loss counseling for nonalcoholic fatty liver disease?

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8081

The manuscript has been improved according to the suggestions of reviewers:

- 1) Format has been updated – All changes have been marked in yellow, to expedite revision by Reviewers.
- 2) Revision has been made according to the suggestions of the reviewer

(Reviewer #1-9221)

1- aminotransferase and/or GGT levels were not particularly altered in basal conditions and not in all patients. In addition, it is well known that their levels may change independently on the liver damage and, when fibrosis progress, AST and ALT may decrease. Physical exercise may induce the activation of fibrogenic factors. I think that the reduction of enzyme levels isn't an ameliorative result capable of improve the significance of the study.

Response: The reviewer raises two very important questions, i.e., how much liver enzymes are expression of disease severity and if physical activity may induce additional fibrosis. In the absence of liver biopsy no inference can be made; a few studies point to liver enzymes as a proxy of severity, other did not. Anyway this issue was raised in the discussion. As to the possibility that physical exercise may induce fibrogenic factors, we would like to stress that the psychological support program was intended to stimulate physical activity (not exercise) and that the improvement in liver enzymes was paralleled by decrease liver fat (although measured by proxies). As far as we know, the fibrogenic activity of exercise (strenuous, as in athletes) involves heart and lung. We are not aware of any study involving the exercise-induced fibrosis in the liver.

2- in the discussion the sentence of "liver dysfunction " is wrong. Authors did not study liver function.

Response: Agreed and corrected

3- the majority of enrolled cases was represented by male gender. Females have a different approach to physical exercise. I suggest a different evaluation in relationship to the gender

Response: We agree on possible differences in relation to gender, but the limited sample size prevents a complete analysis. Anyway, a separate analysis in males and females did not produce remarkably different results; the effects of physical activity and diet were both less pronounced in females and in both males and females, most of the significance was lost due to the limited sample size. Data were not reported in the manuscript to facilitate reading, but we added a few words in

the discussion.

4- Even if the results are a good message for clinical practice, the costs and the organization of various teams involved in the treatment and follow-up of NAFLD patients don't consent a large application in different setting.

Response: We agree with the reviewer that our experience cannot be easily transferred to different Liver Units. However, the study confirms that a specific focus on physical activity may help NAFLD patients loose part of their liver fat. The issue is to propose leisure-time physical activities that may be maintained by individuals in the long-term, widening the proposal of gym activities or simple walking, with interaction with sport and other recreational associations. Of note, as previously suggested (see ref. 11), we believe that liver units should refer their patients to diabetes/obesity units, where teams practicing cognitive-behavior therapy and psychological support are more frequently available.

(Reviewer #2-50563)

1. The introduction was missing in the abstract section.

Response: It appears this is the journal policy. Very difficult to summarize background and aims in only 20 words.

2. I want to see longer follow up duration and would recommend the authors to present data on larger number of patients with log follow up duration in the future. May be a prospective RCT.

Response: We totally agree with the reviewer that a longer follow-up and a larger sample size would be needed. As to the comparison by proper RCT, I am definitely suspicious about RCT in the area of behavioral therapy, due to the very large attrition rate they might cause. They may well prove something in countries where patients may be motivated to adhere to the random selection to have treatment for free, not in countries where these treatments are paid by the National Health System and subject want to choose according to their preferences.

3. The data on liver biopsy pre and post treatment should be also helpful in decision-making (if available). 4. It will be interesting to see the data on other factors such as Vitamin E use or coffee drinking (if available) in the 2 groups of patients.

Response: No liver biopsy data are available at follow-up (and very few at entry). This is part of the policy of our Department in the absence of really effective treatments. This policy might soon change, after the publication of the FLINT study. Similarly, patients did not receive vitamin E or other anti-oxidants/hepatoprotective agents in the course of the study.

(Reviewer #3-227342)

1. The outcomes measured (mainly laboratory) in this study might be influenced also by comorbidities (cancer, acute and chronic infections, autoimmune diseases, inflammatory diseases) and concomitant medications (such as anti-inflammatory drugs, statins, etc...), I suggest excluding these patients from the study. Have authors excluded these patients?

Response: We did not exclude these patients from analysis. The majority of cases was being treated with statins or with antihypertensive agents as part of the metabolic syndrome. Removing all these cases would leave very few patients in the analysis of any NAFLD study. During the study period, drug therapy was not changed, except for glucose lowering drugs in case of risk of hypoglycemia

2. Did you calculate the statistical power of study before performing it? Please specify this point in the methods.

Response: As presented, the study was intended to be a feasibility study, based on the clinical audit of the first set of cases enrolled in the psychological support program. No sample size analysis was carried out. This issue was discussed in the present version.

3. Authors did not investigate any possible molecular mechanism underlying their results. This represents a crucial aspect that renders the article mainly as an observational study. Please address these limitations in the discussion.

Response: we totally agree with the reviewer; the study should be intended as an observational study. This issue was raised in the discussion.

4. Several typos are present in the article. Please carefully check English grammar in your revision.

Response: The whole manuscript was checked for typos and English grammar
(Reviewer #4-762087)

The issue, in general terms, is very interesting and have implications in terms of clinical impact. The methods are appropriate. The manuscript is well written and references up to date.

Response: Thanks for appreciation. No comments

3) References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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