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July 13, 2016

Dear Professor Fang-Fang Ji

Science Editor

World Journal of Hepatology

Thank you for your correspondence regarding our manuscript entitled "**Independent effects of diet and exercise training on fat oxidation in NAFLD**" indicating that our manuscript is of interest.

We are grateful for the referees' comments. We have responded point-by-point to all comments and believe the amendments have improved the overall quality of the manuscript. The responses to each comment are listed below. Where appropriate we have amended the manuscript text (in track changes) and in the responses we have detailed where the modifications have been made.

Thank you for your consideration.

Sincerely,

Dr. Ilaria Croci
Prof. Nuala M Byrne
Dr. Veronique S Chachay
Prof. Andrew P Hills
A/Prof. Andrew D Clouston

Dr. Trisha M O'Moore-Sullivan
Assoc. Prof. Graeme A Macdonald
Prof. Johannes B Prins
Dr. Ingrid J Hickman

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 26954

Title: Independent effects of diet and exercise training on fat oxidation in NAFLD.

Reviewer's code: 02539817

Reviewer's country: 0

Science editor: Fang-Fang Ji

Date sent for review: 2016-05-03 14:15

Date reviewed: 2016-05-03 22:45

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Y] Grade A: Excellent	<input type="checkbox"/> Y] Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Y] Accept
<input type="checkbox"/>] Grade B: Very good	<input type="checkbox"/>] Grade B: Minor language polishing	<input type="checkbox"/>] The same title	<input type="checkbox"/>] High priority for publication
<input type="checkbox"/>] Grade C: Good	<input type="checkbox"/>] Grade C: A great deal of language polishing	<input type="checkbox"/>] Duplicate publication	<input type="checkbox"/>] Rejection
<input type="checkbox"/>] Grade D: Fair	<input type="checkbox"/>] Grade D: Rejected	<input type="checkbox"/>] Plagiarism	<input type="checkbox"/>] Minor revision
<input type="checkbox"/>] Grade E: Poor		<input type="checkbox"/>] No	<input type="checkbox"/>] Major revision
		BPG Search:	
		<input type="checkbox"/>] The same title	
		<input type="checkbox"/>] Duplicate publication	
		<input type="checkbox"/>] Plagiarism	
		<input type="checkbox"/>] No	

COMMENTS TO AUTHORS

The authors conducted a randomized comparative intervention (starting with 21 subjects, and retaining 16 through the end of 16 months) trial of energy (calorie) restriction and exercise training on non-alcoholic fatty liver disease. The phenotyping of subjects was very detailed, and included careful measurements of numerous parameters, including the (sometimes) technically challenging beta-hydroxybutyrate. Liver biopsy at the conclusion of the study, which otherwise relied on state-of-the-art respiratory indices, was also quite compelling. The authors find that the two interventions have different effects on NAFLD as well as on basal and insulin-stimulated substrate utilization. The data are presented in attractive tables and figures-I see no point in restating them here. The discussion is balanced in its review of the clinical literature, and shows how the new results fit in a broader physiological and pathophysiological framework. The authors rightly stresses that the sample size was small, arguing to me that a larger replicate study is warranted. 1) One piece of missing data I'd like to see are the clamp parameters:

was Rd increased in the exercise training group to a greater degree than in the energy restricted group? If the authors have additional supervised fasting data, it would be quite interesting to see whether serum amino acids, particularly leucine and lysine-a major but neglected source of ketogenic carbon atoms. Also, Rd (rate of glucose disposal) would be informative in that skeletal muscle and adipose clearly change in these two interventions. **2)** The other area that might merit discussion is the molecular changes that transpire in the energy restricted vs. "exercised" livers. Is redox (NAD⁺ and sirtuin) metabolism and signaling altered? Likewise, why are fibrates (PPARA-agonist, inducing beta oxidation) not effective therapy but pioglitazone (whole-body insulin sensitizer) is?

RESPONSE TO REVIEWER (02539817)

1) RESPONSE: We agree with the reviewer that clamp parameters including the rate of glucose disposal are informative. This data is indeed already presented in the submitted version of the manuscript. The M-value, representing the whole-body glucose disposal rate in the steady-state of the hyperinsulinemic-euglycemic clamp is presented in Table 1. The M-value increased in response to EX while it did not change significantly in response to ER. Serum amino acids were not assessed.

2) RESPONSE: We agree with the reviewer that analysis of redox metabolism and signalling, as well as comparisons at the molecular level of the mechanisms of benefit of exercise, diet and pharmacological interventions, would be of interest. **ACTION:** We added to the discussion that analysing redox metabolism and gene expression in response to these two interventions would be of interest. The paragraph now reads: "Future studies assessing the effect of lifestyle intervention in NAFLD on rates of hepatic fatty acid uptake, oxidation, and storage using a newly validated method combining ¹¹C-palmitate imaging by positron emission tomography with compartmental modelling^[1], would be of interest. Studies including assessment of redox metabolism and gene expression are also warranted."

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 26954

Title: Independent effects of diet and exercise training on fat oxidation in NAFLD.

Reviewer's code: 01136482

Reviewer's country: Italy

Science editor: Fang-Fang Ji

Date sent for review: 2016-05-03 14:15

Date reviewed: 2016-05-07 16:17

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
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		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

- **1)** Introduction section: NAFLD is strictly linked with overweight/obesity, in particular with visceral fat deposition (i.e. Clujul Med. 2015;88(4):489-93). I suggest to report this data.
- **2)** In this section the Author report also that lifestyle interventions is mandatory in the treatment of NAFLD. However, last international guidelines and several papers, showed the pivotal role of the diet (i.e. Mediterranean diet) to treat NAFLD patients (i.e. EASL guidelines. J Hepatol 2016; World J Gastroenterol. 2014;20(45):16831-40). Please improve this part. -
- **3)** Methods section: why the Author perform liver biopsy and not transient elastography to evaluate the patients? Please report the country of Ethics Committes. -
- **4)** Discussion section: please define on the basis of the data, the potential better training for overweight patients with NAFLD.

- 5) I suggest also to report that the major limit of the study is the small sample size.

RESPONSE TO REVIEWER (01136482)

1) **RESPONSE:** We agree with the reviewer that NAFLD is strictly linked with overweight/obesity, in particular with visceral fat deposition. **ACTION:** We now modified the relevant section in the introduction which now reads: "Development and progression of NAFLD are linked with a number of factors including genetic predisposition^[2], physical inactivity, obesity, visceral adiposity and insulin resistance (IR)^[3]."

2) **RESPONSE:** We agree with the reviewer that dietary modification is an essential component of NAFLD treatment and that diet therapy (e.g. Mediterranean diet) can be effective without weight loss.

ACTION: The relevant section in the introduction has been reworded to achieve greater clarity. It now reads: "Lifestyle interventions consisting of diet (improved diet quality with or without energy restriction (ER)) or diet in conjunction with exercise training (EX) are currently the most commonly advocated therapies for NAFLD management^[4-6]".

3) **RESPONSE:** Liver biopsy was chosen because it is the gold standard technique for the assessment of NASH and determination of disease severity^[7,8].

Elastography (FibroScan) measures the elasticity or stiffness of the liver to estimate fibrosis^[9], however it cannot precisely distinguish between the intermediate stages of liver fibrosis and features of NASH; and its reliability as a longitudinal measure after a lifestyle intervention in obese patients is suboptimal^[10].

ACTION: As requested by the reviewer, it has been specified in the methods section that the country of the ethics committee that approved the study is Australia.

4) **RESPONSE:** To determine the ideal type of training for the management of a given disease, studies comparing multiple training regimes are needed. This was beyond the scope of the present study. In the discussion we acknowledge this and speculate about the ideal training for NAFLD: "Future research is required to investigate the impact of different doses and types of exercise programs on the severity of steatosis as well as on hepatic and whole-body substrate metabolism. Dose and type of exercise are likely to be crucial factors impacting on the clinical benefits of an exercise intervention^[11,12]. To date, the beneficial effects of exercise training on NAFLD have been mostly seen in response to aerobic exercise training^[13-19] or with an aerobic

component^[20]. It is possible that aerobic exercise training has a greater impact on hepatic steatosis and hepatic Fat_{ox} than other training regimes because during aerobic exercise substrate availability is more closely matched with substrate oxidation and energy deficit is greater than during other training regimes."

- 5) **RESPONSE:** We agree with the reviewer that the sample size of this study is relatively small. This has been acknowledged in several points throughout the manuscript including: Discussion, page 16, second paragraph; and Discussion, page 17, second paragraph.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 26954

Title: Independent effects of diet and exercise training on fat oxidation in NAFLD.

Reviewer's code: 00160163

Reviewer's country: China

Science editor: Fang-Fang Ji

Date sent for review: 2016-05-03 14:15

Date reviewed: 2016-05-11 10:14

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
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COMMENTS TO AUTHORS

Lifestyle modification is a potent strategy for ameliorating NAFLD. This study introduces an interesting story that ER and EX improve NAFLD from different mechanisms. However, according to my knowledge, although the plasma 3-B-hydroxybutyrate levels do correlate with hepatic oxidation, it is not enough for the authors to draw a conclusion that the hepatic fatty acid oxidation increased just based on a little change in circulation 3-B-hydroxybutyrate. So, the authors should either do not mention the concept of hepatic fatty acid oxidation, or need to add more convincing data to show that the hepatic beta-oxidation did increase.

RESPONSE TO REVIEWER (00160163)

RESPONSE: We agree with the reviewer that β -hydroxybutyrate concentrations are not a direct measure of hepatic fat oxidation, but rather a common used marker of hepatic



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fat oxidation. This is explained in the methods section and acknowledged in the discussion: “Finally, it must be acknowledged that β -hydroxybutyrate concentrations, while being a commonly used marker of hepatic Fat_{ox} ^[21], do not represent a direct measure of hepatic Fat_{ox} .” For greater clarity, wording throughout the manuscript has been modified, substituting the wording “hepatic fat oxidation” with β -hydroxybutyrate concentrations when necessary.

ACTION: In a number of points throughout the manuscript the wording “hepatic fat oxidation” has been substituted with “ β -hydroxybutyrate concentrations”.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 26954

Title: Independent effects of diet and exercise training on fat oxidation in NAFLD.

Reviewer's code: 00503443

Reviewer's country: Italy

Science editor: Fang-Fang Ji

Date sent for review: 2016-05-03 14:15

Date reviewed: 2016-05-11 18:51

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Y] Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The work entitled: "Independent effects of diet and exercise training on fat oxidation in NAFLD", by Ilaria Croci et al., aims to investigate the different effects of energy restriction (i.e. diet with weight loss and exercise training (i.e. physical activity without weight loss) in a group of patients suffering from NAFLD. As the same authors state (Discussion section page 17 line 12) the sample size of this work is small, but it is in line with other similar papers. Indeed, this is a good paper, well conceived and well written (sometimes a bit prolix), equilibrated in the various sections. Their findings stress the different, but complementary, benefits on the management of NAFLD, and that the ER inducing weight loss is more efficacious in improving the severity of liver disease than EX. Therefore in the opinion of this reviewer, the paper deserves publication in World Journal of Hepatology. However, just a little correction is recommended on page 9, Body composition section, line 3: "In the NAFLD group" may be omitted. There is no another group of patients!



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RESPONSE TO REVIEWER (00503443):

REPONSE: We thank the reviewer for pointing out this oversight.

ACTION: The suggested modification has been made.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 26954

Title: Independent effects of diet and exercise training on fat oxidation in NAFLD.

Reviewer's code: 02528832

Reviewer's country: Spain

Science editor: Fang-Fang Ji

Date sent for review: 2016-05-03 14:15

Date reviewed: 2016-05-13 04:41

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> [Y] Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> [] The same title	<input type="checkbox"/> [] High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> [] Duplicate publication	<input type="checkbox"/> [] Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> [] Plagiarism	<input type="checkbox"/> [] Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> [] No	<input type="checkbox"/> [] Major revision
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		<input type="checkbox"/> [] The same title	
		<input type="checkbox"/> [] Duplicate publication	
		<input type="checkbox"/> [] Plagiarism	
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COMMENTS TO AUTHORS

Authors comment adequately the only problem of this study, which is the short number of individuals who completed the study. Results are interesting and the study is well conducted

RESPONSE TO REVIEWER (02528832):

We thank the reviewer for the positive feedback.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 26954

Title: Independent effects of diet and exercise training on fat oxidation in NAFLD.

Reviewer's code: 00005350

Reviewer's country: Italy

Science editor: Fang-Fang Ji

Date sent for review: 2016-05-03 14:15

Date reviewed: 2016-05-19 00:59

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
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		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
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COMMENTS TO AUTHORS

The paper by Ilaria Croci et al reports hepatic fat oxidation (Fatox) and whole-body substrate oxidation under basal, insulin-stimulated and exercise conditions before and after 6 months of exercise training (EX) or energy restriction (ER) in patients with NAFLD. ER was found to increased hepatic Fatox estimated by the increase in beta-hydroxybutyrate and reduced severity of steatosis, but did not change substrate oxidation rates during acute exercise. EX improved substrate oxidation under basal, insulin-stimulated and exercise conditions, but not hepatic Fatox and severity of disease. Increase in hepatic Fatox was associated with decrease in hepatic steatosis and this could be one of the mechanisms through which the ER group achieved reduction in steatosis. The paper, which is clear and well written, is relevant, since it provides pathophysiological insight into the mechanism produced by two commonly used procedures to treat obesity and NAFLD. **1)** Major criticism The use of $p > 0.05$ to state that total energy expenditure in the basal state remains unchanged (page 12, line two from bottom) is incorrect.

Probability can be used to reject the null hypothesis of equality, not to prove the null hypothesis. **2)** The analysis of the two patients who had an increase in beta-hydroxybutyrate plasma level while on exercise treatment, and of the two patients who had a reduction in beta-hydroxybutyrate plasma level might reveal some interesting mechanism and should not be simply considered as outliers or atypical patients. **3)** Minor criticism If some indexes of inflammation were recorded, they should be considered, because of the metabolic effect that they may have or, vice versa, the modulation of microinflammation that can be obtained by metabolic change.

RESPONSE TO REVIEWER (00005350):

1) RESPONSE: We agree with the reviewer that statistics can be used to reject the null hypothesis of equality, not to prove the null hypothesis.

ACTION: We corrected the relevant section (results, page 12), which now reads: "Total energy expenditure in the basal state did not significantly change in response to both interventions ($P>0.05$)."

2) RESPONSE: We agree with the reviewer that the inter-individual variability observed in response to treatment is an interesting result in itself. On the results section, page 13, the word outlier is used because correct in statistical terms; and because we reported results of one additional analysis that has been performed to ensure that the main message of that section (unchanged β -hydroxybutyrate concentrations in response to EX) was not driven by the response of one individual. We agree that further research on the intra-individual variability in response to treatment is crucial.

ACTION: In the discussion it has been added that: "Inclusion of genetic and molecular parameters in future investigations, might provide insights on the mechanisms responsible for the inter-individual variability observed in response to the treatments. "

3) RESPONSE: We agree that adding data about inflammation is relevant. C-reactive protein (hsCRP), a biomarker of inflammation, did not significantly change post-intervention in response to either intervention.

ACTION: hsCRP data has been added to Table 1.

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