

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 non-alcoholic fatty liver disease

Reviewer's code: 02539817

Reviewer's country: United States

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"/> Grade A: Excellent	<input 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 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		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] 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. 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



BAISHIDENG PUBLISHING GROUP INC

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>

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. 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?

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 non-alcoholic fatty liver disease

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 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		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

- 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. 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. - Methods section: why the Author perform liver biopsy and not transient elastography to evaluate the patients? Please report the country of Ethics Committes. - Discussion section: please define on the basis of the data, the potential better training for overweight patients with NAFLD. I suggest also to report that the major limit of the study is the small simple size.

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 non-alcoholic fatty liver disease

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 checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" 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		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

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

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 non-alcoholic fatty liver disease

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 checked="" 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 checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Life style modification is a potent strategy for ameliorating NAFLD. This study introduces an interest story that ER and EX improve NAFLD from different mechanisms. However, according to my knowledge, although the plasma 3- β -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- β -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.

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 non-alcoholic fatty liver disease

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 checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" 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		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] 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!

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 non-alcoholic fatty liver disease

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 type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

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 increase 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. 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. The analysis of the two patients who had an increase in



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8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>

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. 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.