Reviewer's report

Title: Extremely short duration high intensity training substantially improves insulin action in young healthy males

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Reviewer: LABROS S SIDOSSIS

Reviewer's report:

Major Compulsory Revisions
In the title, abstract, and everywhere else in the manuscript, the authors should make clear that they refer to “interval” exercise.

Abstract, P2
l.11: A second time trial? When was the first done? Refer to that along with the baseline VO2max test.
l.17: low case p-value
Do the authors really believe that this high-intensity exercise regime could be applied to sedentary populations or the obese and insulin-resistant subjects? I mean, 4-6 Wingate tests with 4 min of rest in between?

Introduction
P3, l.10-12: “Furthermore, as we do not understand the precise mechanisms which link physical activity and a reduced risk of developing CVD or T2D the scientific basis for current health guides can be challenged[4].” – First, add a space between the end of the sentence and the reference and delete the space in between the reference and the period. My main concern with this sentence is that it is not necessary to understand the mechanisms linking exercise to reduced disease risk for making recommendations; knowing how much exercise, what kind, what frequency, etc., affects morbidity and mortality usually suffices. The mechanisms between these relationships are good to know, but certainly not a prerequisite.

P3, 1.20: ref.7 does not compare different intensities, ref.8 found what the authors assert only in obese but not in diabetic patients, ref.9 did find what the authors assert, but it should be taken into account here that the higher intensity training was also of higher energy expenditure than the low intensity training. Braun (J Appl Physiol 1995;78:300) found no effect of intensity provided that total energy expenditure of training be the same. Hence only the study by Kang (ref.6) and only in obese subjects supports a key role for intensity independently of duration/energy expenditure. The authors need to revise this sentence.

Methods
P4, subjects: how did you randomize subjects in a group of 16 and a group of 9, instead of two approximately equal groups? Where there any dropouts from the control group? Please explain.

P6, time trials: why did you choose the fastest time out of the two trials, and not the mean of the two which would be more accurate anyway?

P7, post-training assessment: why was the second OGGT performed either 2 or 3 days later? How many subjects in each case?

P7, post-training assessment: why did the authors not perform a post-training VO2max test? This would inform about the efficacy of training much better than the self-selected time trials.

P7, Calculations and statistical analysis: did the authors consider the possibility that OGGTT-derived indices of insulin sensitivity are not optimized for higher-than-normal values? See Niakaris (J Sports Sci 2005;23:1065) and references therein.

P7, Calculations and statistical analysis: the authors should analyze their data with two way ANOVA for repeated measures, to include the between-subject factor (training vs control). Unless they assume that responses in the training and control groups were different (i.e. significant interaction) a priori and thus only use paired analysis?

Results

P7-9, glucose, insulin and NEFA responses: include a statement that fasting plasma glucose and insulin concentrations were not affected by training (from what I can tell from Figure 1, at least), like you do for NEFA. Also, report insulin response to OGGT for the control group. And, since fasting NEFA were different, calculate the “incremental” (“decremental” in this case) AUC and compare this pre and post to document whether NEFA were reduced “to a greater extent” after training.

P9, physiological considerations: what about insulin response 2 vs 3 days after training? By “improvement” you mean reduction? In this sense, it is interesting that the responses after 3 days were somewhat further improved than after 2 days.

Table 1: Height for the training group is 1.3 meters?

Legend to Figure 1: use just one symbol for differences between time-points and one for differences between pre/post, P<0.05.

Figure 1: Shouldn’t the units for AUC (all three subpanels) be mol x min / liter? Also, y-axis on top panels says “concentration” while the other two don’t. The legend to bottom panel doesn’t show the “pre/post” indication (probably covered under the AUC subpanel).

I would like to see the same figure with data from the control group – add Figure
2. Discussion

P10, first half of second paragraph: A single bout of exercise affects insulin sensitivity for at least 48 hours into recovery (see the review by Magkos & Sidossis. European Endocrinology 2008;4:22-25). Hence it is not clear what the contribution of the last bout of training is in this study, where OGTT was performed 2 and 3 days after the last bout. And, your ref. 32 (Hughes) found a reduction in glucose (but not insulin) response to OGTT given 72 hours after the last bout of training, so your statement that glucose AUC is reduced in previous studies only when assessed within 24 hours is not entirely correct. The authors should modify this section accordingly, and perhaps consider subject characteristics (e.g. lean or obese or insulin-resistant, etc.) in these comparisons.

P10, second half of second paragraph: How did you calculate the energy expenditure of the training program? It seems to me that 45 + 55 = 100 kcal for a total of 30 Wingate tests, i.e., ~3 kcal per Wingate test (!), is extremely low.

P11, last line of second paragraph: what other mechanisms relevant to HIT may be responsible? You speculate on this in the following paragraph (glycogen etc.), but the study by Hughes (ref. 32) involves continuous aerobic exercise, not HIT, and they just failed to find a correlation between the increase in GLUT4 and the increase in insulin-mediated glucose disposal; yet both increased.

P12, second paragraph: The authors suggest that the lowering of fasting plasma NEFA from 350 to 290 umol/l in this study could be mediating the observed responses to the OGTT, and cite studies with exogenously-induced suppression (acipimox) or increase (intralipid) in plasma NEFA concentration to support their assertion. However in the latter cases, changes in NEFA were extreme (e.g., ~75% decrease in ref. 40, and 5-fold increase in ref. 41) and thus not comparable to the 17% decrease in fasting plasma NEFA concentration in this study. Also, along with ref. 42, the authors should consider many other studies (e.g., Horowitz, Am J Physiol Endocrinol Metab 2000;279:E348 - Sial, Am J Physiol 1998;274:E785) that found no significant changes in fasting NEFA concentration and rate of appearance in plasma 36-72 hours after the last training session. The authors should revise this paragraph to reflect these uncertainties.

Minor Essential Revisions

Abstract, P2
l.17: low case p-value

Introduction

P4, l.2: change “aimed” to “aiming”

Discussion

P10, l.3: delete “the” before “low compliance”
P11, l.1: change “observe” to “observed”

References

1 & 10 – Association AD is American Diabetes Association? (Insert a comma after “American Diabetes Association” in your reference manager software so that it formats correctly!)
2 – Association AH is American Heart Association? “In” where?
4 – citation details are missing.
15 – JAMA, not Jama
16 – Abbreviate journal name.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests