Reviewer’s report

Title: Physiological Effects of Ghrelin in Cachectic COPD: substudy of a multicenter, randomized, double-blind, placebo-controlled trial of ghrelin treatment

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Reviewer: Michael Steiner

Reviewer’s report:

This manuscript presents the findings of a small substudy of a larger clinical trial of Ghrelin supplementation. The impact of ghrelin supplementation as an adjunct to aerobic physical training is studied with cardiopulmonary exercise responses the main outcomes measured. The study and its results are interesting and add to the body of knowledge in this area. However, I have some concerns about the presentation and interpretation of the data which would need to be addressed for the paper to be suitable for publication.

Major Compulsory Revisions

1. Why was aerobic rather than resistance training chosen? The rationale for Ghrelin was as an anabolic agent and the population was underweight. The logic would have been to include a resistance training component. Similarly, I was surprised no measure of muscle mass was included. I think these issues should be justified and discussed. On a similar note, the duration of training was short. Please justify.

2. The justification of the sample size is confusing and appears to be predicated on a measurement that wasn’t actually performed (6MWD). I would regard the study as exploratory and as such it’s understood that a formal power calculation may not be possible. I don’t have a problem with this as long as the conclusions are suitably moderated.

3. The data presentation is difficult to follow and needs revision for the impact of Ghrelin supplementation over and above training to be interpreted. I think we need to see the changes in absolute values for exercise performance and physiology following training as well as the values for the changes. The tables appropriately present within and between group changes but I think the graph should be redrawn to depict these absolute values and allow an assessment of the impact of the intervention over and above that of training. For some outcomes (eg endurance time) no absolute baseline values are given and this would correct this omission.

4. There is repetition of the methods in some areas of the results and interpretation of the data in the results which should be restricted to the discussion (P10 para1 “these findings suggest…..).

5. The discussion devotes too much space to a rehash of the results and lacks
depth in its interpretation of the findings. I would like to see it address the following questions:

a. It appears that training alone did not bring about significant improvements in performance. Was this related to the study population (severely impaired with low muscle mass) or inadequate training intensity, progression, volume or duration? What are the implications for the efficacy of Ghrelin? It’s possible that the adjunctive effect of Ghrelin might not be as great when added to a more effective training regime.

b. The limitations to interpretation are not just in the small sample size but also the large number of statistical comparisons made meaning a high chance of a type 1 error. This should be acknowledged or a statistical adjustment made.

c. The correlations are interesting particularly because although not definitive, they suggest a link between the supplementation and the outcome. However, we need to understand the finding more clearly. Does the measurement of “endogenous” Ghrelin reflect the supplemented state (ie reduces with exogenous administration)? How is the correlation with catecholamines explained? I don’t think the discussion is sufficiently clear or incisive.

d. There are alterations in ventilatory efficiency observed in the treatment group. Did the authors consider whether this was related to an increase in respiratory muscle mass and/or strength?

Discretionary Revisions

6. The authors describe the setting as “pulmonary rehabilitation” but only details of physical training are presented and it is unclear whether comprehensive PR (including other components such as disease education) is provided. I would suggest the term “aerobic training” is used.

7. The authors acknowledge that this was a nested study in a larger trial but a brief explanation of the wider objectives of the main trial would help put the current study in context.

8. The authors are to be congratulated on presenting iso time and isoVO2 data which is often missing from training studies but I wonder if both are required as this overcomplicates the data presentation. Unless there is a difference in the Isotime and VO2 responses that offer significant insight I would discard one of these measurements.

9. I don’t think the term “pulmonary cachexia” is particularly helpful or justified here. Cachexia is a clinical syndrome comprising progressive body tissue loss with a metabolic component. The subjects in the study are underweight but no other evidence is presented to support a diagnosis of cachexia. The description should be underweight or (if data on muscle mass can be provided) muscle wasted patients.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

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