Reviewer's report

Title: Plasma leptin and insulin-like growth factor I levels during acute exacerbations of Chronic Obstructive Pulmonary Disease

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Reviewer: Richard Debigare

Reviewer's report:

Overview of the paper

In a group of patients with COPD, leptin and IGF-1 levels were measured at day 1 and day 15 during an exacerbation. In addition, inflammatory cytokines were also measured. Overall, authors found that IGF-1 levels were decreased in patients with COPD compared to healthy subjects. This decrease was still present at day 15. In a similar fashion, leptin levels were increased at day 1 and day 15 in patients with COPD. A relationship between TNF and leptin levels is found at day 1 in COPD. This relationship is lost at day 15. Authors conclude that inappropriately increased circulating leptin levels along with decreased IGF-1 levels occur during acute exacerbations of COPD. Compared to chronic bronchitis, patients with emphysema have lower circulating IGF-1 levels at the onset of the exacerbation but also two weeks later.

1. Is the question posed by authors well defined?

The authors present leptin, TNF and IGF-1 biology in their introduction. The association between these factors and the pulmonary disease is not well connected. As a consequence, the research question is difficult to sort out. The introduction has to be rewritten in order to better link the different concepts and to better define the research question in accordance to the problematic previously exposed in the introduction.

2. Are the methods appropriate and well described?

The methods used to measure inflammatory cytokines, leptin and IGF-1 are appropriate. However, description in the selection of the patient and treatment is incomplete. Is it 52 consecutive patients? Is there any dropout during the study? Is oxygen therapy used during the hospitalization? What is the smoking status of the control subjects? How the control group was recruited? Why they did not measure IGF binding proteins?

Leptin is known to affect energy expenditure. There is no energy expenditure measurement in the study.

3. Are the data sound?

The data presented by the authors are duplicated in table 2 and 3. Table 3
should be deleted. The p column in the table is not necessary. I would suggest the superscript annotation instead. This would also clarify the table 2 where two p columns are presented but not explained. How these values are comparable to what have already been published in patients with COPD. The authors chose to use the median (25-75 percentiles) to present the data. Using this nomenclature, the reader does not know if there were values under the level of detection. This information should be added in results section.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

No comment

5. Are the discussion and conclusions well balanced and adequately supported by the data?

This is a major point in this manuscript. Most of the data presented in this paper are not novel and already known. The discussion is not well focused on the research question. Since the research is not clear, this is probably a reflection of it. It is difficult to follow the rational in their finding and on the interpretation of their data. For instance, on page 12, line 22 we read: “Our data support a role for IGF-1 in acute exacerbations of COPD”. This sentence is not explained and not supported by any argumentation. What kind of role? I am not sure that this study was designed to test this hypothesis.

6. Are the limitations of the work clearly stated?

Authors mentioned fact about IGF-1 level and concurrent biological state that could explain its variation in their cohort.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Reference 20 is incomplete. The relationship between inflammation-leptin and inflammation-IGF-1 is scientifically weak. Literature is abundant and should be carefully reviewed to strengthen the introduction and clearly define the research question.

8. Do the title and abstract accurately convey what has been found?

No comment

9. Is the writing acceptable?

The structure of the introduction has to be carefully revised. Same comment for the discussion.

DISCRETIONARY REVISIONS

Please add page numbering in the manuscript.

Introduction:
Some points in the introduction are unreferenced. For instance, page 3, 4th line starting with:” In a subgroup of COPD….”

Methods:
Why no measure of FFM? The tool to measure FM also measure FFM. This data could be added to the manuscript.

MINOR ESSENTIAL REVISIONS
In addition to the previous comments,

Introduction:
page 3 line 29-30. Increased IGF mRNA levels occur during an acute exacerbation, but you cannot assert causativeness.

page 3 line 32. reference 13 (also in discussion). What is the relevance of hypoxia to COPD in regards to your argument? Yes COPD patients show increased hypoxia and hypoxia in small animals can be used as a model for hypoxia in COPD but without explaining that you cannot introduce this point.

Poor use of terminology in the introduction. Cachexia, weight loss and anorexia are different by their very definition. Pick one and stick with it, if this article is about leptin and regulation of fat mass, use weight loss. If using cachexia, muscle mass should be considered. Also, in a paper about weight loss, leptin and COPD should the obesity paradox not be mentioned/considered?

Methods:
pg6 line 6 ambient air?

pg6 line 18 (and in general) where observers blinded?

Statistical analysis. Why were nonparametric tests used with such a large data pool? Would have thought that the data pool was large enough for the central limit theorem to apply, allowing the assumption of normality.

Results:
Present key results as figures not tables. Show correlations as figures.

pg9 line 17. ‘relationship between’, not ‘relation’.

pg9 line 20. Was the significant correlation positive or negative? Figures would help.

Discussion:
pg11 line 30. ‘limited’, not ‘few’.

pg12 line 27, conclusions that lower IGF levels may lead to “decreased muscle mass loss” do authors mean either “decreased muscle mass” or “muscle mass loss”
MAJOR COMPULSORY REVISIONS

Introduction:

Overall, the introduction doesn’t clearly lead to the research question, doesn’t convince the reader for the case that the authors are trying to present. The introduction is not well constructed in this regard, the writing has to be revised.

Results

While the data from the exacerbation group at D15 is physiological meaningful and interesting it does not provide a reliable internal baseline measure as these values may have been affected by the prior exacerbation (ie is the differences seen between COPD vs control at D15 due to recovery from exacerbation or just normal for COPD?). A control group of stable COPD patients would provide a better comparison than healthy normal disease free adults.

Discussion

pg12 line 27, the reference to cachexia and muscle mass loss seen in COPD is not conclusive in this cohort of patients. No cachexia was seen based on estimates of fat free mass (FFM) of 49.6 vs 51.3 kg (COPD vs control; estimate from authors data, based of body mass – FM, table 1). The relevance of referring to cachexia and muscle mass loss in COPD in the closing sentences of the discussion in a manuscript that does not deal with muscle mass may be incorrect. Muscle mass was not measure in this cohort and was not part of the research question. This incongruence in the concepts (leptin level vs inflammation; leptin level vs muscle mass) has to be reviewed in order to clarify the message of the paper.

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

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