Author's response to reviews

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

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Author's response to reviews: see over
Dear editor,

We are pleased to resubmit our manuscript entitled “Plasma leptin and insulin-like growth factor I levels during acute exacerbations of Chronic Obstructive Pulmonary Disease”. The issues raised by the reviewers and our responses are detailed below. The comments from each reviewer are dealt with in turn.

Yours sincerely,

Petros Bakakos
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Reviewer's report
Title: Plasma leptin and insulin-like growth factor I levels during acute exacerbations of Chronic Obstructive Pulmonary Disease
Version: 3 Date: 17 December 2008

Reviewer: Richard Debigare
Reviewer's report:
1. Page 3, line 23. No study are referenced to demonstrate that either Gh or IGF-1 is increased in COPD. Since it is stated in the previous sentence, authors should reference their point.
Answer: A reference (Ref 11), supporting increased GH levels in COPD, has been added.

2. Page 3, last paragraph. Aims are presented without any connection to the previous presentation in the introduction. Please, clearly state your working hypothesis and the subsequent aims in relation to the actual literature.
Answer: Conflicting data has been reported so far regarding IGF-I levels in COPD as mentioned in the introduction. Moreover, a correlation between leptin and TNF-α has been supported by studies as mentioned in the introduction. Accordingly, the aim was to measure leptin and IGF-I levels in COPD exacerbations and examine if these levels are related to systemic cytokine levels (as this applies to leptin according to previous literature).

Answer: “…expressed …” has been replaced by “…had…”

Answer: FFM has been added in tables 1 and 3.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
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'
Reviewer's report
Title: Plasma leptin and insulin-like growth factor I levels during acute exacerbations of Chronic Obstructive Pulmonary Disease
Version: 3 Date: 17 December 2008

Reviewer: Martijn A. Spruit

Reviewer's report:
1) Previously, I have asked how co-morbidities were assessed. The authors answered 'We included in our study COPD patients with no major comorbidities, especially those that could possibly affect leptin and IGF-I levels or those associated with some degree of systemic inflammation, possibly cofounding cytokine levels. Accordingly, patients with diabetes mellitus, congestive heart failure, lung cancer, collagen vascular diseases and disturbances in thyroid function (known to influence leptin levels) were excluded from our study group.' But were comorbidities like diabetes and CHF tested? Rutten et al showed a prevalence of CHF in about 20% of the COPD patients. This should be reported in the revised version of the manuscript.

Answer: We did not test our COPD patients for diabetes or CHF. We relied on their medical history. It is also true that 20% of the COPD patients present CHF (Rutten et al, Am Heart J 2008). Although more than 70% of our COPD patients had been submitted to an echocardiogram during the past year before entering the study, we cannot exclude the possibility that CHF could exist as a comorbidity in few of our COPD patients. A comment has been added to the methods section.

2) The fact that informed consent was obtained not at baseline, but a few days later should be reported in the manuscript.

Answer: The informed consent was obtained in all COPD patients during Day 1 (which is defined as the day of first blood sampling at 8.30-9.30AM of their first morning during hospitalization).

3) Was there a difference in various systemic outcomes between patients with and without oxygen therapy?

Answer: No difference in cytokine, leptin or IGF-I levels was found when comparing patients who received oxygen therapy (n=38) and those who did not (n=14). A comment has been added in the Results section.

4) The authors wrote: All patients received the first steroid dose intravenously inside the hospital and after obtaining the blood sample for Day 1. They have to report this in their manuscript.

Answer: This is mentioned in the discussion section (page 11, line 23). “However, samples on D1 were obtained before corticosteroid administration and on D15 7 days after the last intravenous administration of prednisolone, according to the protocol used”. The word “… the first …” has been added to clearly show that the first steroid dose was given after obtaining the blood sample for Day 1.
5) Previously, I have asked whether the change (the delta) in biomarkers of systemic inflammation and change in IGF-I between D1 and D15 were related.

The authors replied: As mentioned in the correlation analyses in the Results Section (page 9, line 33) IGF-I was not related to any of the biomarkers of systemic inflammation neither on Day 1 nor on Day 15. This however does not answer my question. When the change in systemic inflammatory biomarkers is not related to the changes in leptin then a causal relationship seems less obvious. This should be discussed in the paper.

**Answer:** The author is right. We did not understand properly the question he posed. The changes in cytokines were not related to the changes in IGF-I levels. However, the changes in leptin were related to the changes in TNF-α. A comment in the statistical methods has been added as well as the above finding in the Results (corellations) and its implication in the discussion.

6) The present results are not discussed/compared enough with available literature. For example, Creutzberg et al (ref 7) is not mentioned once in the discussion.

**Answer:** In the study by Creutzberg et al, (Ref 7) they investigated the course of the energy balance in relation to leptin and the soluble TNF receptors, plasma glucose and serum insulin in patients with an acute exacerbation of COPD during the first 7 days of hospitalization.

In our study, we did not evaluate dietary intake and REE (resting energy expenditure).

However, some common findings were observed. Thus, elevated leptin levels were found in COPD patients compared to healthy subjects in both studies that were decreased significantly after 7 days (Creutzberg et al) or 15 days (our study). Moreover, a positive correlation between leptin levels and sTNF receptors on Day 7 was found in the study by Creutzberg. In our study a positive correlation between leptin and TNF-α levels was observed on Day 1.

Two comments regarding the common findings of the two studies were added in the discussion.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**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