Author’s response to reviews

Title: Hormonal aspects of overtraining syndrome: a systematic review

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Author’s response to reviews:

RESPONSES TO REVIEWERS

Important:

a. Changes in the manuscript are highlighted in bold and marked in yellow.

b. Responses in this file are highlighted in bold.

c. Changes were previously language edited before we sent the revised version of the manuscript.

1) General response to reviewer’s comments:

R. We truly appreciate all the comments. They helped us to improve considerably the quality of the paper.

We performed a wider research, increased the number of searched expressions, and expanded the initially requirements of PRISMA standardization protocol for systematic reviews. Indeed, once we went beyond, several studies that were not originally found have been included, which made us more than double the number of included articles, from twelve to 38 selected studies.

We had to significantly increase the size of the paper once we markedly improved and deepen all the sections, since the methodology of the studies selection until the specification of the results.
We also performed a deeper discussions about the results and the meanings, particularly in regards of the reasons why the alterations were found.

2) Responses to reviewer #1:

a. Majors:

1. “one main limitation of this review relies on the fact that it is mainly a methodological review, discussing methodological aspects rather than the physiological effects of alterations in hormonal status.”

R. Our initial objective was to evaluate hormonal alterations in overtraining syndrome. However, from an endocrinology perspective, validation of hormonal findings lacks once most of the performed tests were not previously standardized. We changed our focus in order to prioritize the hormones alterations and its physiological effects and potential role as OTS/NFOR/FOR markers. We discussed the alterations observed at the studies, we improved and we detailed and deepen the explanations for the hormonal findings.

As can be observed in the manuscript, we markedly increase the level of quality of the review focusing on the found results and clustering in different ways the findings, in order to better understand the possible role of hormones on OTS/NFOR/FOR. Accordingly, the number of tables increased from four to ten.

We are currently performing in our research center a complete assessment of hormonal status, both basal and stimulated, of OTS athletes, comparing to healthy athletes and also to sedentary subjects, in order to better understand the physiological hormonal adaption to sports and then the dysfunctional alterations involved in OTS. In the study that we are performing, we are also concerned on demonstrating causality, not only association, To our best knowledge, this will probably be the first study to perform standardized endocrine gold standard tests in athletes, perhaps due to the previous lack of endocrinology and sports medicine association in previous scientific research groups, and will help to understand whether hormones are markers or inducers of OTS/NFOR/FOR states.
2. Moreover, it is surprising that catecholamine (epinephrine and norepinephrine) were not taken into account in the search of relevant references for this review. Indeed several articles (e.g. from Le Meur et al., Schaal et al., Aubry et al.) have reported significant alterations in catecholamine release in overreached individuals.

R. We increased our search for all hormones, including nocturnal urinary catecholamines, as well as plasma catecholamines, which significantly increased the number of selected papers. We did find the study whose first author was Schaal that demonstrated alterations of catecholamines, but it was performed in amenorrheic athletes, not OTS/NFOR/FOR, and was therefore excluded. In the same study that we are currently performing, we are also analyzing the 12-hour night urinary catecholamines and metanephrines.

3. Statistical analyses are weak, please develop this part by presenting the statistical tests used to analyze your data. Analyses of correlation between hormonal markers and the occurrence of overreaching would be a plus and help the understanding of the results.

R. We specified the statistical tests methods, although the nature of the study does not require more complex levels of statistics, as stated by PRISM gold-standard protocol for systematic reviews and corroborated by the recently published systematic review that we performed on the supposedly existence of “Adrenal Fatigue” (Cadegiani FA et al. Adrenal Fatigue does not exist: a systematic review. BMC Endocr Disord. 2016 Aug 24;16(1):48).

4. In the results section, please present the results of your investigations (what hormones are related to overreaching or overtraining?) rather than just presenting the methods used.

R. The reviewer comments were very helpful, and this comment was specially important, once made us notice that we did not provide the proper attention to the results. We presented in a much deeper way each of the results, and also performed a deeper discussion over the findings.
5. Finally in its current form, this review suffers from this lack of references (only 14 in the reference section). The authors are invited to develop the results and discussion section with relevant references.

R. Although we performed an extensive research along different databases, it was hard to find studies that full-filled criteria for the systematic review, once articles that did not filled the selection criteria were not able to provide reliable information regarding hormonal aspects of OTS/NFOR/FOR. Despite this, we increased the number of references from 14 to 40, which provides a much more base for the proposed review. We defined OTS or FOR as performance reduction, following the latest OTS/NFOR/FOR guidelines. Studies that provided an inappropriate criteria were excluded of the analysis, which decreased the number of selected articles.

Although we importantly raised the number of studies for the systematic review, it is important to point that not always systematic reviews need to provide a large number of studies. Many times systematic reviews may highlight the need for further studies in the field of the reviewed data.

It is also noticeable that we found more reviews (a total of 55) than clinical studies, but none of the previous reviews were systematic.

Also, two types of tests: the previously already diagnosed with FOR/OTF, and the underperformance induced by the tests (previously healthy) were found and differentiated for analysis purposes.

Comparisons were made with control group and also with basal levels (before the stimulation tests, in the same subjects).

Again, by applying the expanded research, we were able to raise the number of included articles from 12 to 38, which has significantly improved the quality of the systematic review. Herein, we have to point that research, even systematic, should go beyond the basic protocol, in order to embrace all the appropriate studies, as most of them did not show up with the basic inclusion criteria.
6. In table 1, The study conducted by LeMeur et al. was conducted in 2014 and not 1985. Catecholamine is not written "cathecolamines", please amend accordingly.

R. Both mistakes were corrected.

7. To sum up, while this paper raises a very interesting and relevant question in exercise physiology, it suffers from his lack of results and references. The authors are encouraged to develop stats, results, discussion and reference sections in order to add a true contribution to scientific literature.

R. As recommended by the reviewer, we delve deepen each of the review aspects and each of the selected studies, which led with an increased from 12 to 38 selected studies, from 14 to 40 references, from 4 to 10 tables (once we also developed other tables in order to show different perspectives of the findings) and doubled the amount of information contained in the systematic review. We believe that now we fully attend to all the requirements.

Reviewer #2:

1. I believe this review highlights the fact that there is limited amount of experimental or observational research in this area.

R. This is exactly the main point of the systematic review. We performed the review systematically, following PRISMA protocol step-by-step, and we were unfortunate to find more than 38 studies (although we significantly increased the number of selected studies). The lack of data is one of the answer to this systematic review.
2. There are some inconsistencies with regard to grammar. 'Despite of' and 'Despite' are used interchangeably. While either term is correct use of language, this should be consistent throughout.

R. Inconsistency was corrected and language was edited again by professional services.

3. There are some spelling and typographical errors throughout the paper and should be revised.

R. Spelling corrections were provided. We are sorry for the mistakes, we changed the configuration of the automatic correction to English USA and resent to the language editing service.

4. The paper refers to a correlation between endocrine responses and overtraining state. Since the authors did not directly correlate markers with any aspect of overtraining state, I would advise on a different choice of word other than 'correlate' to avoid confusion.

R. We improved and deepen the findings in order to provide specific correlations, in order to provide proper “correlations”. However, we changed the “correlate” expression.

5. The introduction categorises overtraining/overreaching and discusses some diagnostic markers but does not provide a rationale for examining endocrine responses.

R. We provided the rationale for the endocrine responses along the introduction and also throughout the discussion, according to the context.
6. The second paragraph of the introduction needs revising as it appears to be one sentence.

R. We revised and split into more than one sentence, in order to become more readable.

7. The methods describe how search strategies were carried out including search terms and databases used. Have the reference lists of each of the 12 selected papers been considered?

R. We reviewed and markedly increased the number of the references to 40, which included 38 selected studies, 1 reference for the current guideline on OTS/NFOR/FOR and 1 reference to explain some hormone alterations.

8. The quality assessment appears to be quite vague. It would be useful to know how many studies were excluded for each criteria.

R. We provided a summary of how many and why each study was excluded (specific section and paragraph in the results section), and provided the summary of the found data at the quality assessment section. Moreover, we clustered the findings in different ways, which led to an increase in the number of tables, from four to ten.

9. It is not clear what was assessed in the review. A list of sports is provided in the results section, including short distance running; however, paragraph 5 of the discussion section explains that only endurance sports were evaluated in the review. It would be worth explaining each event, volume of training to clarify this.

R. We detailed the performed training in different tables (table 1, 2 and 5) with specific results, and after the expansion of the systematic review, we found three studies with resistive exercises, which we discuss in a specific section in the discussion. Therefore, the following sentence did
not provide precise information and was therefore excluded: “Only endurance sports were evaluated in the current review.” (Paragraph 7 of the discussion, first line).

10. Paragraph 6 of the discussion section explains that "Basal hormones could potentially be good markers of OTS/NFOR/FOR" however, this contradicts the findings of the review. The sentence should be revised.

R. Indeed, the sentence did not seem to be clear. We hypothesized that basal hormone levels do not need necessarily have to be out of the normal range in order to provide information about OTS. However, we showed that even differences between healthy and OTS athletes were not found. We rewrote the sentence in order to be clear, as seen below:

“Therefore, regardless of the normal range, whenever athletes with OTS/NFOR/FOR presented significantly different hormone levels than healthy athletes, basal hormones would be able to be good markers or predictors of OTS/NFOR/FOR.”

As seen, we do not mean that basal hormones are confirmedly good markers, but how they could be assessed in order to be considered potentially markers of OTS/NFOR/FOR.

11. In paragraph 7, cortisol responses show conflicting results (50% tests blunted), however, the conclusions state that respond to stress. While it is inconclusive, this should be stated.

R. We modified the conclusion to express more precisely the findings of the review, and actually after the expansion of the review, results slightly changed.

All the comments were very helpful to raise the quality of the paper, and this included the double-check of the findings as well as the coherence of the sentences throughout the manuscript.