Author’s response to reviews

Title: Hormonal aspects of overtraining syndrome: a systematic review

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Hormonal aspects of overtraining syndrome: a systematic review

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Point-by-point response letter

1. As recommended, we corrected the spelling mistakes, but we also decided to require a new extensive language edition for a different language editing service (Oxford Edition Services) that successfully helped us in other papers. Changes are explicit by the comments.

2. We markedly improved the rationale for the statistical analysis and the explanation, as below: “Due to the heterogeneity of the studies that aimed to correlate hormone responses and OTS/NFOR/FOR, our initial plan to perform a meta-analysis was
unfeasible. Moreover, since several variables were taken into account (e.g., type of sports performed, type of tests and stimulus performed, and whether hormones were analyzed basally, and during a resting period or resting after an intensive training load) the analysis of each aspect was performed separately and in several different combinations. Such combinations consisted of studies that performed equivalent methods, although not similar, including all tests stimulated by exercise, regardless of the type of stimulation, tests performed in endurance sports, regardless of the type of sport, and resting combined with basal hormones, regardless of the previous exercise stimulation. Data was also analyzed according to the number of studies investigating each type of sport, the number of athletes with OTS/NFOR/FOR and healthy athletes. The number of studies using each type of test of hormone stimulation was quantified. The study results were analyzed by the percentage of the type of response to each of the tests performed. Since a meta-analysis was not performed, t-tests, one-way ANOVA and non-parametric tests were not employed. Therefore, a statistical analysis program was not necessary.

3. The long sentence at the 3.c.5 section (Joint analysis of resting hormone levels in NFOR/FOR-induced athletes and acute hormone responses to stimulation tests) was edited as recommended, for: “Acute hormone responses to stimulation tests can also be analyzed together with resting hormone levels after an OTP, once both explore capacity to respond to stressful situations. When acute hormones responses were analyzed together with the resting levels of induced NFOR/FOR, the only marker that showed mostly altered levels was aldosterone. However, contradictory findings were observed since half of the altered results were increased whereas half were decreased. Detailed findings are displayed in table 7.”

4. We explicated the limitations of our study, as shown: “In addition to the limitations of the selected studies, this systematic review was also associated with some limitations. First, if the basic PRISMA protocol of the search for systematic reviews was followed, only 12 studies would have been selected. Therefore, an expanded search that went beyond a typical systematic review had to be performed. Second, a more comprehensive analysis to obtain more precise conclusions was unable to be performed due to the unexpected differences in methodology, even when the types of sports or tests were similar. Finally, we found less consistent data than expected, which did not allow for a more complete systematic review of the field.”
5. Due to the long period since the last review, we updated the search.

6. Additionally to the raised points, in order to raise the quality of the paper, we inserted a final discussion paragraph to finish the discussion section with a general explanation that justifies the findings of the systematic review, as below: “Overall, the conflicting findings of the present systematic review reflect the complex relationship between hormones and overtraining syndrome. The main issue regarding the hormone findings in OTS is the causal relationship and the actual underlying mechanism that results in decreased performance. Whenever hormone dysfunction is likely to be the primary cause for the worsened performance, OTS is excluded; this is because OTS requires the exclusion of endocrine disorders to be diagnosed. Conversely, OTS may cause hormone dysregulation, as previously observed (1-39). Thus, identifying whether these dysfunctions are secondary to OTS is challenging. As endocrinologists, we state that generally, whenever a frank and severe hormone dysfunction is found, the diagnosis of OTS is unlikely since OTS tends to induce mild changes in hormone levels, rather than substantial changes. Moreover, since a hormone dysfunction likely explains all the clinical findings, organic etiologies for such dysfunction should be explored. Finally, who defines the diagnosis is the underlying etiology. Whenever hormone dysfunctions do not fully explain the clinical presentation and appear to be a consequence of the OTS, OTS is the diagnosis. In contrast, if the clinical presentation is attributable to hormone dysfunctions, the replacement or suppression of the affected hormone should be approached prior to the diagnosis of OTS.

Finally, it may be too early to claim that GH, ACTH and prolactin responses are undoubtedly blunted in the acute responses of individuals affected by OTS/NFOR/FOR. Since not all of the studies found the same results, some performed slightly different protocols for ME and TBE, and a small number of subjects were included. For practical purposes, whenever an athlete is suspected of OTS/NFOR/FOR, stimulation tests could be performed in order to find the possible relative failure of the adrenals or the pituitary, although only standardized tests by endocrine societies (ITT) are sufficient for these diagnoses.”