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Growth hormone (GH) and prolactin responses to a non-exercise stress test in athletes with overtraining syndrome: results from the Endocrine and metabolic Responses on Overtraining Syndrome (EROS) — EROS-STRESS

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ABSTRACT

Objectives: Overtraining syndrome (OTS) leads to worsened sports performance and fatigue. The pathophysiology of OTS has not been entirely elucidated, and there is a lack of accurate markers for its diagnosis. Changes in hormonal responses implicated in OTS were stimulated by exercise, which has limited their interpretation. Hence, we aimed to evaluate growth hormone (GH) and prolactin responses to a gold-standard and exercise-independent stimulation test, the insulin tolerance test (ITT).
Design: Volunteers were recruited and divided into OTS-affected athletes (OTS), healthy athletes (ATL), and healthy non-active subjects (NCS) groups, after general and specific inclusion and exclusion criteria.
Methods: We evaluated the responses of growth hormone (GH) and prolactin to the ITT, and compared between groups.
Results: A total of 51 subjects were included (OTS, n = 14, ATL, n = 25, and NCS, n = 12). OTS disclosed significantly lower basal levels of GH ($p = 0.003$) and prolactin ($p = 0.048$), and GH ($p = 0.001$) and prolactin ($p < 0.001$) responses to ITT ($p = 0.001$), compared to ATL, but similar to NCS. OTS showed a later rise in GH levels in response to hypoglycemia, compared to ATL, but not to NCS. We suggest cutoffs for GH and prolactin levels to aid in the diagnosis of OTS.
Conclusions: OTS-affected athletes show reduced GH and prolactin basal levels and responses to a non-exercise stress test compared to healthy athletes, but not to sedentary subjects.

1. Introduction

Imbalance between training load and recovery may induce a state of sport-specific underperformance associated with intense fatigue. Such overtraining states include functional overreaching (FOR), non-functional overreaching (NFOR), and overtraining syndrome (OTS),[1,2] depending on the duration of the decrease in performance and improvement after recovery.

OTS may be triggered by a shorter resting period compared to the intensity and duration of the training sessions, poor sleep quality, and a low calorie intake[1–3]; however, the precise pathophysiology of OTS remains unclear. The crucial aspect leading to OTS and its related states is probably a long exposure to an environment depleted of energy, which forces the exposed tissues to adapt in order to survive. However, studies indicate the resulting inflammatory, immunologic, neurological, metabolic, and hormonal adaptions are actually dysfunctional (maladaptions).[1,3]

So far, there are no definitive and accurate biochemical markers of OTS, although some inflammatory[4–6] and biochemical[5,7] markers have been suggested. In addition, blunted hormonal responses to exercise stress, such as prolactin, growth hormone (GH), adrenocorticotropic hormone (ACTH), and cortisol, may explain a hallmark of OTS (i.e., early time-to-fatigue).[8–10] Hormones are physiologically elevated during the first bout of exercise, but are unable to be released again during subsequent exercise stress within a short period of time.[8,9] This seems to be due to either a reduced hormone reserve or an induced hyposensitivity of the hypothalamus or the pituitary after the first exercise stress.[11–13] This decrease in hormone response does not necessarily indicate there is a dysfunction within the glands or hormones of the endocrine system. Indeed, the lack of hormone response may instead be attributed to a diminished

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signaling response to stress originating from the musculoskeletal and cardiovascular systems.

Despite the lack of studies evaluating GH and prolactin responses to stress, particularly to stimulation tests that are not dependent on exercise performance (which could confound the actual origin of the impairment, as described above), the current findings show that GH and prolactin tend to disclose blunted responses to stimulation tests.[11,14] However, from an endocrinology perspective, it is unclear the exact underlying reasons that would induce the lack of proper response to stress. While prolactin release is likely related to stressful situations, the role of prolactin in the stress response, and its possible role in OTS symptoms/signs, remain unknown. Likewise, it is not entirely clear the acute metabolic and muscular effects of physiological GH release in response to exercise, and whether GH plays a role in performance during training and/or in the recovery process. Moreover, whether dysfunctional responses to GH and prolactin are due to a reduction of external signaling (i.e., from systems other than the endocrine system), or result from an intrinsic alteration of the hormonal axis, has not yet been evaluated.

As part of the Endocrinology and metabolic Responses on Overtraining Syndrome (EROS) study, this arm of the study aimed to evaluate whether the dysfunctional GH and prolactin responses still occur during an insulin tolerance test (ITT), a gold standard and non-exercise stress test, regardless of subjects exercise conditioning. This removes differences in exercise capacity and signaling to the brain. In particular, we evaluated GH and prolactin responses in OTS-affected athletes (OTS group) compared to physically active (healthy athletes, ATL group) and non-physically active control subjects (sedentary normal control subjects, NCS group).

2. Methods

The full design, materials, methods is disclosed elsewhere.[15] This study recruited participants through social media (Facebook and Instagram). Candidates were requested to contact the main researcher (FAC) with information regarding baseline characteristics (age, gender, estimated weight, and height) and proposed group he intended to participate (overtraining syndrome — OTS, healthy athletes — ATL, or healthy non-active subjects (normal control subjects) — NCS).

Initial inclusion criteria for all groups (athletes suspected for OTS, healthy athletes and healthy sedentary subjects) were: male gender; aged between 18 and 50 years; body mass index (BMI) between 20.0 kg/m^2 and 32.9 kg/m^2 (athletes) and between 20.0 kg/m^2 and 30.0 kg/m^2 (non-athletes), absence of psychiatric disorders, use of centrally-acting drugs or hormone therapy.

Non-active control subjects (NCS) fulfilled the initial inclusion criteria, were considered sedentary (i.e., without any physical activity including walking, tracking, and cycling) for at least three years, and were without a history of exercise that would fulfill the athlete criteria below.

For all athletes (OTS and ATL), additional inclusion criteria regarding training level were required, including: 1. trained at least four times and >300 min per week; 2. with moderate-to-intense training intensity; 3. for at least six months of regular training the current sport(s) without interruption for more than 30 days.

For OTS candidates, the following criteria was required, as stated by the latest guidelines[1]: underperformance, persistent fatigue, increased sense of effort during training and worsened sleep quality, and excluded of eating disorders, hypocaloric diet, emotional and social problems, and absence of infection or inflammation.

Subjects that fulfilled the above criteria (height and weight were self reported at the first contact, BMI was then calculated, and if previously included, data was confirmed by us at the clinic using high precision weight and height scales; age was self reported and further confirmed by verification of an identity card) and were the underwent initial blood exams (phase two), 36–48 h after exercise (if athlete), and normal levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine, hematocrit, neutrophils, creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin, vitamin B12, fasting glucose, total testosterone and thyroid-stimulating hormone (TSH) were required in order to be included.

The selected subjects signed a term of consent approved by the ethics committee of the Federal University of São Paulo. NCS were then referred directly to the tests, whereas all athletes underwent an initial questionnaire (used for all arms of the EROS study), with regards to mean training intensity, amount of training per week, and number of resting days per week. OTS were also asked for details regarding their level of recovery of performance and time to recover from fatigue.

All subjects underwent an insulin tolerance test (ITT), as detailed in the EROS—Study methods manuscript.[15] In brief, after a baseline blood was collected (time zero), 0.1 IU/kg of regular insulin was administered intravenously in the semi-recumbent subjects, and blood was then collected at the time of hypoglycemia (time one) and 30 min after (time two). For all times, GH, prolactin, and glucose samples were measured, whereas IGF-1 was determined basally (at time zero). Hypoglycemia at time one was defined as: 1. Capillary glucose was <30 mg/dL without symptoms; 2. Patients classified symptoms as moderate to severe (a score of 5–10, on a scale from zero to ten) regarding either adrenergic (shakiness, cold sweating, heart palpitations, or pallor) or neuroglycopenic (sleepiness, mood changes, or unrest) symptoms, or both; or if capillary glucose was <45 mg/dL in the presence of any symptom. Time-to-hypoglycemia, in minutes, and intensity of adrenergic and neuroglycopenic symptoms were evaluated during the ITT, self-referred, from zero to ten, regarding intensity.

Serum GH and serum prolactin were evaluated by commercially available electrochemiluminescence assay kit at a laboratory. We compared basal levels and hypoglycemia-induced GH and prolactin responses, and changes in prolactin levels along the ITT, between the three groups.

Statistical analyses procedures were the same as employed at all the arms of the EROS study. In summary, Nonparametric ANOVA tests (Kruskal–Wallis Test) and one-way ANOVA tests were performed according to data characteristics; for all cases, post-hoc tests were performed (level of significance was established when $p < 0.05$). Normality distribution was evaluated by the Kolgomogorov–Sminorv test.

3. Results

Among 146 subjects initially recruited, including 87 athletes suspected for OTS, 46 healthy athletes and 13 sedentary subjects, a total of 51 were selected (34.2%).

All three groups presented similar age (OTS = 30.6 years, ATL = 32.7 years, and NCS = 33.2 years) and BMI (OTS = 26.7 kg/m^2, ATL = 24.9 kg/m^2, and NCS = 33.2 kg/m^2). Athletes (OTS and ATL) presented a similar number of minutes of training per week (OTS = 574.3 min and ATL = 550.0 min), number of training days a week (OTS = 5.36 days and ATL = 5.46 days), and training intensity (OTS = 8.79, and ATL = 8.76, on a scale from zero to ten). CrossFit was professionally practiced at least part-time by 89.7% of the subjects, whereas others practiced other sports, always including resistive and endurance exercises.

As shown in Table 1, GH levels were consistently and significantly higher at all times in ATL than OTS and NCS, whose

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