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RESEARCH ARTICLE

The Effect of an Ultradistance Foot Race on Thyroid, Stress Hormone Levels and the Immune System

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Abstract

Background: The aim of the present research is to investigate the effect of an ultra-marathon race on the levels of thyroid, immune and stress system hormones. Moreover, to explore a potential correlation of the above-mentioned hormones with stress hormones.

Methodology: 30 out of the 40 participants who took part in the race, finished the 246 km in less than 36 hours, and were included in the study. There were 3 different sampling times: prior, after and 48 hours after the race. Blood samples were taken to identify stress and inflammation markers, such as CRP, IL-6 NTproBNP, MBL, troponin, leptin, cortisole and thyroid hormones.

Results: CRP, IL-6, SAA, NTproBNP and cortisol showed a dramatic increase after the race, much higher than their initial values, but returned to their initial equilibrium after 48 hours, except SAA which increased further. The behavior of mannose binding lectin with a similar growth trend was similar. Small fluctuations in all the thyroid hormones were observed with initially an increase in the levels, then a downward trend, reaching the initial values again. The only case where the concentration decreased after the race is that of leptin, while troponin concentrations were not detectable.

Conclusions: An ultra marathon can be a very stressful event for the body, often elevating hormone levels beyond their normal rate. A significant correlation was observed in the way cortisol changes with CRP, IL-6 and NTroBNP, which reveals the close relationship of the endocrine-immune system in extreme cases of exercise such as that of Spartathlon.

Keywords

Exercise, Marathon, Hormones, Thyroid, Immune system, Oxidative stress, Overtraining syndrome, Stress

Introduction

Spartathlon is one of the most difficult and longest running races in the world. It takes place every year starting from the Acropolis, usually every last Friday of September at 7 in the morning and ends in Sparta in front of the statue of Leonidas at 19:00 of the next day, which is the maximum time limit for the race to be completed (< 36 hours). Athletes run on muddy roads and climb on mountains of 1,200 meters altitude without being allowed to rest or sleep, even at night. It is a super-marathon with a fixed distance of 246 km where athletes compete for the best possible time. Various studies that measured biological indicators after the end of the race suggested what one would

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logically assume, that the race causes a prolonged and very intense overexertion and overwork of the body at all levels, physical and mental [1].

Researchers are demonstrating an increasing interest in the former as they want to further explore how the human body reacts in the face of an extremely stressful situation, as is to carry out a marathon race e.g. Spartathlon. In addition, the "exercise and stress" standard can easily be used in research protocols and allows the study of the interactions of 3 systems of the human body simultaneously: the nervous, the immune and the endocrine system.

Overtraining can cause ischemic hyperemia, tissue damage, acidosis and oxidation caused by catecholamines, resulting in reduced performance and severe muscle fatigue. Many of these are the main symptoms of the overtraining syndrome. From the literature it is clear that overtraining is associated with hypothalamic-pituitary dysfunction. According to Selye's (1956), the body responds to what is perceived as a threat of homeostasis and adapts accordingly. The human body is made so that any stimulus (stressor) regardless of source and nature (environmental stressors such as rain, psychological stressors, e.g. loss, or in the case of this research, exercise) can automatically activate the autonomic nervous system to deal with it [2]. The autonomic nervous system in turn commands the neuroendocrine system and more specifically the hypothalamic-pituitary-adrenal axis (HPA axis) for its activation and cortisol production. Although the body's response to the stimulus will be the same, the nature and duration of stress can change the sensitivity of the cortisol's feedback mechanism for production volume, concentration, and duration of production [3]. The role of CRH is also to regulate the activity of the sympathetic nervous system and in part its behavior during exercise. It is produced by neurons in the microcellular part of the Para Ventricular Nucleus (PVN) in the anterior pituitary gland and the way it stimulates the release of ACTH is to induce the transcription of the proopiomelanocortin gene (POMC, proopiomelanocortin). The activity of the HPA axis as a result of the whole above biochemical process can be inhibited by the endogenous opioid peptide, β-endorphin, produced both at rest and during exercise [4].

The intensity, the duration as well as the type of the activity can have a huge impact on the reaction of the stress system and therefore also on the immune and endocrine system of the human body.

Methods

Procedure

Three blood samplings were performed, before, after and 48 after the end of the race. The duration of the race in order to consider the participation of the athletes valid has to be less than 36 hours. After the collection of all the samples, the analysis of the blood samples was carried out in the Biochemical Department, GNP Athens "The Hagia Sophia". The race took place with a daily temperature ranging from 5 °C to 36 °C and relative humidity of 60-85%.

The study protocol was approved from the Bioethics Committee of the Harokopio University, Laboratory of Nutrition and Clinical Dietetics. All experimental procedures conformed to the National Health and Medical Research Council guidelines for experimentation with human subjects.

Sampling and analysis

In each blood draw, 10 ml of blood was taken from the participants from the vein while they were sitting. Samples were taken at 3 different times, before (pre), immediately after (within 15 minutes) and 48 hours later during the post recovery period in exactly the same way. Venous blood samples were taken with sterile plastic syringes and immediately transferred to tubes containing the appropriate anticoagulant (citrate, EDTA, heparin). A quantity of plasma and serum was collected after centrifugation at 1500 g at 4 °C for 10 min and stored frozen at -80 °C for maintenance until analysis.

Serum levels of the hormones T3, T4, FT3, FT4, TSH, cortisol, as well as the cardiac markers D-pro-BNP and Troponin-T were measured using enhanced electro ChemiLuminescence, with the immunological analyzer Roche Cobas e 411 (Roche Diagnostics Mannheim, Germany). The serum Amyloid A (SAA) and C-Reactive Protein (CRP) inflammation proteins were measured by immunofluorescence method with BN Prospec nephelometer (Siemens Siemens Healthineers, Liederbach, Germany) Leptin, Interleukin-6 (IL-6) and Mannose-Binding Lectin (MBL) concentrations were performed by immunoenzymatic methods (R&D Systems USA, Minneapolis).

Statistical analyses

In order to investigate the primary objectives of the study, the analysis of repeated measures ANOVA was conducted. To examine the correlation between the quantitative variables of the study, an analysis was performed using the Pearson correlation coefficient, in case the normality criteria based on asymmetry and curvature was met, while in the cases of the analysis was violated, it was carried out through the Spearman correlation coefficient. The statistical analysis of the data was performed through SPSS, vol.22 for Windows (SPSS INC., Chicago, IL). The significance score was set at 0.05 for all analyzes.

Results

Table 1 summarizes the main results of the study. All the levels before the race where between the normal range of any healthy human being. Right after the end

Table 1: Indicator levels pre, post and 48 hours the race.

	pre	Post	48h-post
Inflammation			
SAA (mg/L)	3.2 ± 0.56	340.8 ± 62.2	444.6 ± 77.3
CRP (mg/L)	0.65 ± 0.2	97.3 ± 17.4	63.8 ± 12.1
IL-6 (ng/L)	0.9 ± 0.1	7781.0 ± 2017.0	0.7 ± 0.1
Thyroid Function			
TSH (mU/L)	1.9 ± 0.2	3.4 ± 0.5	2.0 ± 0.2
T4 (nmol/L)	98.4 ± 3.8	106.8 ± 3.8	97.6 ± 2.9
FT4 (pmol/L)	17.3 ± 0.4	20.6 ± 0.6	18.3 ± 0.4
T3 (nmol/L)	1.5 ± 0.1	1.7 ± 0.1	1.4 ± 0.0
FT3 (pmol/L)	4.8 ± 0.1	5.4 ± 0.3	4.5 ± 0.1
Immune Function			
MBL (mg/L)	1.63 ± 0.13	1.88 ± 0.11	2.00 ± 0.16
Leptin (g/L)	1.41 ± 0.14	0.19 ± 0.03	0.86 ± 0.44
Stress			
Cortisol (nmol/L)	13.9 ± 4.3	31.1 ± 9.9	12.2 ± 5.6
Cardiac Stress			
NT pro-BNP (ng/L)	40.1 ± 9.6	964.6 ± 153.9	82.1 ± 12.1
Troponin T (g/L)	Non detected	Non detected	Non detected

of the race the levels of SAA, CRP and IL-6 changed dramatically with an upward trend, reaching levels hundreds of times higher than the initial ones. However, MBL increased slightly, but remained at normal levels, while leptin decreased from 1.41 mg/ml to 0.19 mg/ml, which is quite high to the point where the value is much lower than the normal limit. Thyroid hormone levels have all been on the rise, but still remain normal. The biggest changes were observed in cortisol levels, whose level tripled after the race from the original price as the increase in cardiac stress and more specifically NTproBNP was extreme, where levels reached the number of 964.6 ± 153.9 pg/ml with a limit in healthy people < 120 pg/ml.

After 48 hours, SAA increased even more, reaching a value of 444.6 ± 77.3 mg/L. However, the CRP decreased significantly, but remained at high levels, as did the SAA to a point much higher than the maximum normal range and much higher than the original measurement. The IL-6, despite its huge increase immediately after the race, returned to completely normal levels at the 3rd time. The MBL rose slightly from the previous measurement, still staying within normal values. Similar was the behavior of leptin, which increased significantly from the previous measurement and tends to approach its original value before the race. There was a slight difference in thyroid hormone levels, with a slight decrease and a tendency to return to the original measurement values. The course of cortisol was also decisive, which after tripled in the measurement immediately after the race, decreased 48 hours later but not statistically significant. The drop in NT pro BNP was also large, but it remained exactly double the price compared to the measurement of the first moment. Finally, troponin concentrations at all 3 times were below the lowest detectable values and therefore undetectable.

Discussion

The immune system's reactions to exercise depends on the nature, extent, and duration of physical activity and directly depends on the ability of leukocytes to migrate through the blood to neighboring tissues [5,6]. Prolonged intense exercise causes systemic inflammatory changes and possible organ damage, as indicated by the dramatic increase in IL-6, CRP, SAA, and other indicators of endothelial dysfunction and specific muscle damage enzymes as reported in the Goussetis study, 2009 [7]. However, it is one of the best models that could be used in research because it offers the opportunity to study the physiological mechanisms (regardless of whether it is followed by successful repair of the damage) as any change or damage that may occur in the body at any level is reversible [8-10]. In order to be able to maintain its homeostasis intact, the body treats this condition by making a huge defense effort [3,11,12]. Especially in the category of professional athletes, where training programs are very intense and inconsistent with small recovery times, there is rhabdomyolysis and increased oxidative stress, factors confirming the severe inflammation in which the athlete's body is located [13-15], a fact which also justifies the extreme values observed in the second phase of the study, immediately after the end of the race.

The most significant changes in this study were observed in inflammatory hormones with a huge increase in levels after the race but also their stay at

high levels and after 48 hours of recovery especially SAA which increased even more in the 3rd time. The fluctuations in thyroid hormones were relatively small. Particularly increasing was the course of NTproBNP, where levels after the race reached or far exceeded normal human limits.

A similar course but of lesser intensity was the increase in cortisol, which tripled at the 2nd phase but returned to lower values than the initial measurement after the recovery window. The leptin course was reversed where the levels reached a drop of 80% while remaining much lower than the initial measurement after 48 hours. Interesting are the relationships 48 hours before the end of the race between the thyroid hormones FT3 and FT4 and MBL, suggesting a possible close interaction between the immune system and the endocrine system. Changes in MBL concentration have previously been associated with thyroid function in Graves' disease, where elevated MBL levels have affected the concentration of thyroid hormones themselves [16].

In our study, the increasing course of MBL values at all three point in time shows a steady increase caused by exercise, which can make MBL an indirect indicator of muscle tissue damage and inflammation after exercise. Leptin is a major endocrine mediator with multiple roles in various endocrine pathways, including thyroid function [17,18]. In this study, leptin levels immediately after the race were associated with TSH 48 hours before the race, further enhancing the case).

Margelis A and co (2005) in a similar study reports that IL-6, CRP, SAA and free plasma DNA levels increased significantly (by 8000-, 152- 108- and 10 times, respectively) from the initial reference values, in end of the race [19]. However, IL-6 levels returned to normal for 48 hours, while CRP protein, SAA A and free plasma DNA remained elevated. An indisputable consequence of a marathon is the cellular damage to which athletes are subjected [20-22]. More specifically, myocardial damage has been assessed through imaging techniques such as cardiovascular magnetic resonance imaging and ultrasound, as well as serum markers such as troponin and NT pro-BNP [13,23]. Heart damage is due to inflammation of the myocardium and heart fatigue caused by exercise and not necrosis, while reports of abdominal function are rather contradictory [24].

Determination of the concentration of acute phase proteins and especially those metabolized very rapidly, such as CRP and SAA, can confirm or rule out inflammation or tissue necrosis in emergency differential diagnosis [25,26]. Prices after the second blood draw of CRP, SAA and IL-6 confirm the acute inflammation in which the body is located immediately after the race as they are a hundred times higher than the initial ones. C-reactive protein (CRP) as well as other acute phase proteins such as SAA, fibrinogen and MBL are produced by hepatocytes in response to the secretion of cytokines or other mediators in various conditions (including acute inflammation) or cells, but also in autoimmune or malignant diseases [27-29]. Interleukin-6, which belongs to the pro-inflammatory cytokines, is considered a potent stimulant of CRH, resulting in hyperactivity on the HPA axis [30-33]. This hyperactivity results in increased production of ACTH and cortisol, as evidenced by the comparison of values in 2nd and 3rd blood sampling.

The acute inflammatory response leading to cytokine production is often involved in the pathogenesis of type 2 SD. Several studies in recently diagnosed patients with type 2 SD indicate that inflammatory markers, such as CRP and interleukin-6, are quite high [34,35]. Cortisol is also involved in the above process, which at high levels, weakens the management of glucose and makes it impossible for the body to react to insulin [36]. And in the case of thyroid in people with type 2 diabetes, high levels of cortisol in the body, prevent the conversion of inactive thyroxine (T4) to the active hormone triiodothyronine (T3), which must travel throughout the body and activate each cell of the organism [37-39]. During stressful situations, the conversion of T4 hormone to reverse T3 (RT3 or Reverse T3) increases, which is an inactive type of T3 and competes with cell receptors with active T3, preventing it from reaching the first cells.

Conclusions

Numerous studies in marathon runners confirm that intense and prolonged exercise causes debilitating rhabdomyolysis, which remains asymptomatic and is often unrelated to the clinical symptoms often seen in these athletes. However, it is characterized as the only model for the study of acute inflammation because any damage that can be caused is reversible. As far as we know, no study has looked at muscle and not just exercise-induced damage combining so many different biomarkers like this. As well as very few studies are concerned with the overall stress of the body and not just with oxidant.

This study confirms once again that types of exercise such as the Spartathlon marathon lead the body to extreme biological states. A similarity was observed in cortisol behavior with CRP, IL-6 and NT-proBNP as there was a dramatic increase in the above values immediately after the end of the race and their almost complete return to normal after the 48-hour recovery window, a fact which enhances the interaction of the systems of the human body and especially in our case of the endocrine with the immune system.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Ethical Statement

The study protocol was approved from the Bioethics Committee of the Harokopio University, Laboratory of Nutrition and Clinical Dietetics. All experimental procedures conformed to the National Health and Medical Research Council guidelines for experimentation with human subjects.

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