Available online at www.worldscientificnews.com

World Scientific News

WSN 50 (2016) 239-249 EISSN 2392-2192

Changes in selected neuroendocrine and immunological markers during exercise

Natalia Grzebisz

Department of Physiological Sciences-Medical, Department of Biochemistry,
Faculty of Physical Education, The Jerzy Kukuczka Academy of Physical Education in Katowice,
72A Mikolowska Street, 40-065 Katowice, Poland

E-mail address: n.grzebisz@gmail.com

ABSTRACT

Physical exercise has multidirectional impact on the mechanisms of neuroendocrine responses. The regular and moderate stimulates the immune mechanism, whereas the interval may lead to increased susceptibility to infections. In recent years there has been increased interest in the issues of the impact of exercise on the efficiency of the immune mechanisms. In practice, such knowledge may be used to prevent infections in athletes and possible states of overtraining. Among the signaling molecules involved in the immune response of the body to exercise mentioned markers hormonal balance (testosterone, cortisol, estradiol, hormones, pituitary and hypothalamus), the metabolism of proteins and amino acids (balance nitrogen, glutamine, increase in creatine kinase). Review of the current state of knowledge about the change of levels of markers of hormonal system during exercise and suggestions direction of future research in the area of these issues have been taken in this paper. This is a translation of a part of my authorship the original source in Polish „Zarządzanie zmianami poziomu wybranych markerów neuroendokrynnych oraz immunologicznych podczas wysiłku fizycznego". The text was published in an edition of the Scientific Publishing Sophia in 2015.

***Keywords*:** cortisol; catecholamines; estradiol; exercise

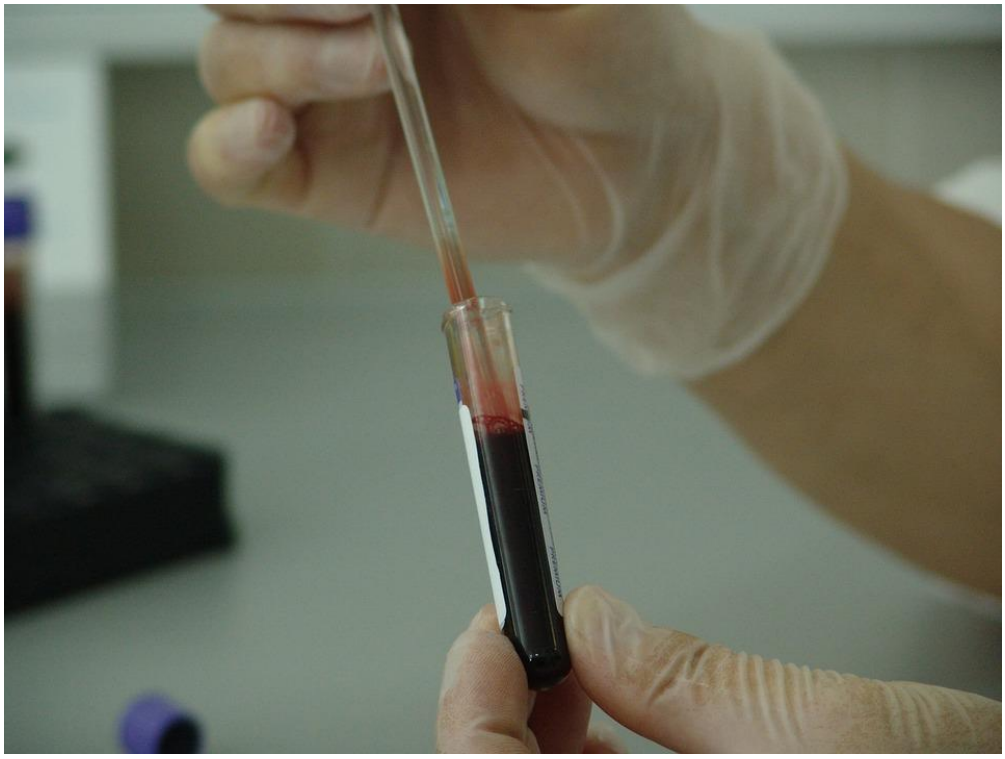
1. INTRODUCTION

Physical exercise in its competitive aspect and a high intensity training may contribute to a significant disruption of homeostasis of the organism, leading to an injury or a disease. An improper use of training loads and inadequate rest together with mental stress lead to fatigue and, consequently, overtraining with all the health consequences. Verification of selected metabolites, hormones, enzymes and immune factors in the blood may help to plan exercise and prevent the states mentioned above.

The immune and neuroendocrine systems coordinate the body response to a physical effort. This integration was observed as early as in 1855, when it was discovered that reducing the level of adrenaline was accompanied by an increase in the number of circulating lymphocytes. These observations were confirmed in 1924 when the anterior pituitary gland in mice was removed, which resulted in the atrophy of the thymus, where the maturation of T lymphocytes takes place. Therefore, the role of hormones in the immune system seems to play a significant role. An important aspect, in this case, is a mechanism for communicating with the immunological neuroendocrine system [Wojtaszek 2016, p. 8-10].

As has already been stated above, among the signaling molecules involved in the body immune response to exercise there are: hormone balance markers(testosterone, cortisol, estradiol,pituitary and hypothalamus hormones), the metabolism of proteins and amino acids (nitrogen balance, glutamine, an increase in creatine kinase) and immunological markers (e.g. immunologlobins A and leukocytes).

This paper tries to provide some information on the current state of knowledge about the change of immune markers levels and neuroendocrine during exercise as well as make some suggestions concerning the future research in this area of science.



2. CORTISOL

Glucocorticoid cortisol is released from the adrenal cortex in response to the increased supply of ACTH and stress exercise. The nature of the effort is critical for activation of the secretion of this hormone.

Intensive resistance training that generates high amounts of lactate has a greater effect on the release of cortisol [Peeters et al. 2008 p. 673-82]. The volume of effort is also important in a hormone response, especially during short intervals, which was confirmed by tests on a group of basketball players [Moreira et al. 2011 p. 166-172]. During cardio exercise, the lowest cortisol values are recorded at a maximum intensity of 50% VO2 max, and the highest in submaximal and maximal zones [Allgrove et al. 2008 p. 653-661].

Table 1. The effect of exercise intensity on salivary cortisol (n ¼ 10; mean values with standard errors in parentheses). [Allgrove et al. 2008 p. 653-661].

Cortisol ($nmol*l^{-1}$)	Pre exercise	Post exercise	1h post exercise
50%	13.7 (1.2)	13.1 (1.0)	10.8 (1.0)
75%	13.7 (1.0)	14.6 (1.2)	14.4 (1.1 *)
Exhaustion	14.0 (1.6)	14.3 (1.6)	16.4 (1.7 *)

*Significantly higher than 50% V_ O2max at that instant, P50.01

High levels of this hormone in the blood correlate with maintaining a high CK (keratin kinase), up to 24 hours after the end of exercise, which may cause a fall of the immune system [Moreira et al. 2011p. 166–172]. Time has also an impact on the level of cortisol. The largest amount of cortisol is released with a two hour delay. The values measured after one hour of rest are significantly higher than in-effort parameters [Allgrove and wsp.2008 p. 653-661]. In such a situation, the lymphocyte reaction to an antigen is significantly reduced. It is possible that the effects of exercise on the immune system is small and temporary, but if the trainaing leads to a state of overtraining, it may weaken the immune system.

3. CATECHOLAMINES

Catecholamines are organic chemicals produced in the body as a result of tyrosine changes (amino acid). 50% circulate in the blood bound to plasma proteins. Intense resistance training increases the concentration of the major catecholamines (epinephrine, norepinephrine and dopamine). This will depend on the strength of muscle contraction-stimulated by the volume of training and the length of interval pauses [Kraemer et al., 2003 p. 361-86]. In addition, the release of catecholamines is conditioned by the response from the nervous system. These hormones determine the rate of muscle contraction by controlling the availability of energy as well as the release of other hormones. This process also depends on psychological factors (fear, physical discomfort, the state of arousal and exercise stress.

Research confirms the existence of the interaction of catecholamines with β2-adrenergic receptors in the mobilization of immune cells by an indirect impact of physical activity, but the mechanism is not fully understood. Research has shown a time interaction between plasma adrenaline and noradrenaline, and expression of β2-adrenergic receptors on circulating

leukocytes in response to a heavy resistance training in men and women [Fragala et al. 2011 p. 156-64]. The expression of β2-adrenergic receptors on monocytes increases during the estimated exercise, and reduces on the monocytes and granulocytes while its duration. Similarly, adrenaline and noradrenaline rise during exercise and return to the baseline during rest [Smith T. et al. 2011 p. 469-484]. Practically, there were no apparent differences in the level of adrenaline and receptor expression between men and women. Further research in this direction is required with a particular emphasis on cellular responses in different types of exercise and populations [Wiegers G.J. et al. 2001 p. 2293-301].

4. TESTOSTERONE AND ESTRADIOL

Sex hormones (testosterone and estradiol) interact in a bidirectional system, separately for men and women [Tarnopolsky 2008 p. 648-654]. Also, due to dimorphism, one can notice some differences in concentration of secretion of these hormones and their effect on the immune system, as well as the adaptation to effort and regeneration.

Estradiol is a steroid hormone synthesized primarily in the gonads and in the adipose tissue. The concentration of circulating estrogen in males does not differ from that in women who are in the follicular phase of the menstrual cycle when estrogen levels are the lowest. In women, periodically,one can observe an increase in estrogen levels during the ovulatory cycle and chronically higher during pregnancy. It turns out that estradiol plays a protective role in muscle damage in response to an increase of creatine kinase. Little is known about its response to intense exercise. There are reports of growth of circulating estradiol during resistance training [Kraemer et al., 1995 p. 809-17]. It also acts as an antioxidant and stabilizer of muscle membranes.

The impact on the immune function is slightly ambiguous. Animal studies have demonstrated that estrogen stimulates the production of antibodies, but also mediates in reducing the level of T cells involved in a delayed-type hypersensitivity reaction, mediated by inflammatory processes in the granulocyte, NK cell cytotoxicity. Sex hormones, including estrogen are involved in a typical control to maintain a balance in the production of lymphocytes T and B (Lymphopoiesis). The specific steps are negatively regulated by estradiol, and the process of B lymphopoiesis is increased when we deal with the estrogen deficit. [Zembroń-Łacny et al. 2008 p. 526-528]. There is a synergistic effect between estrogen and glucocorticoids. The sensitivity of glucocorticoids increases when there is a high concentration of estradiol. With respect to testosterone, estradiol stabilizes or increases the secretion of certain immunomodulatory cytokines (TNF, IL-2, IL-4, IL-6, IL-10 and IFN-ɣ) in peripheral blood leukocytes of healthy males in the presence of cortisol [Janele and et al. 2006p. 168-82]. Estrogens can play an important role in inflammatory processes during exercise. This finding requires confirmation in further studies.

Moreover, testosterone levels have been observed to be changing in response to physical effort. Testosterone is an important anabolic hormone affecting significantly the muscle adaptations to resistance training in men. The increased concentration of endogenous testosterone enhances androgen receptor response to resistance training primarily by stimulating a protein synthesis pathway [Spiering et al. 2009 p. 195-9]. In men, resistance training causes an increase in the concentration of endogenous testosterone. Its level goes back to the rest value after two hours after the exercise. Many reports also confirm a

testosterone increase in women in response to a resistance training. It is, however, significantly lower than in men.

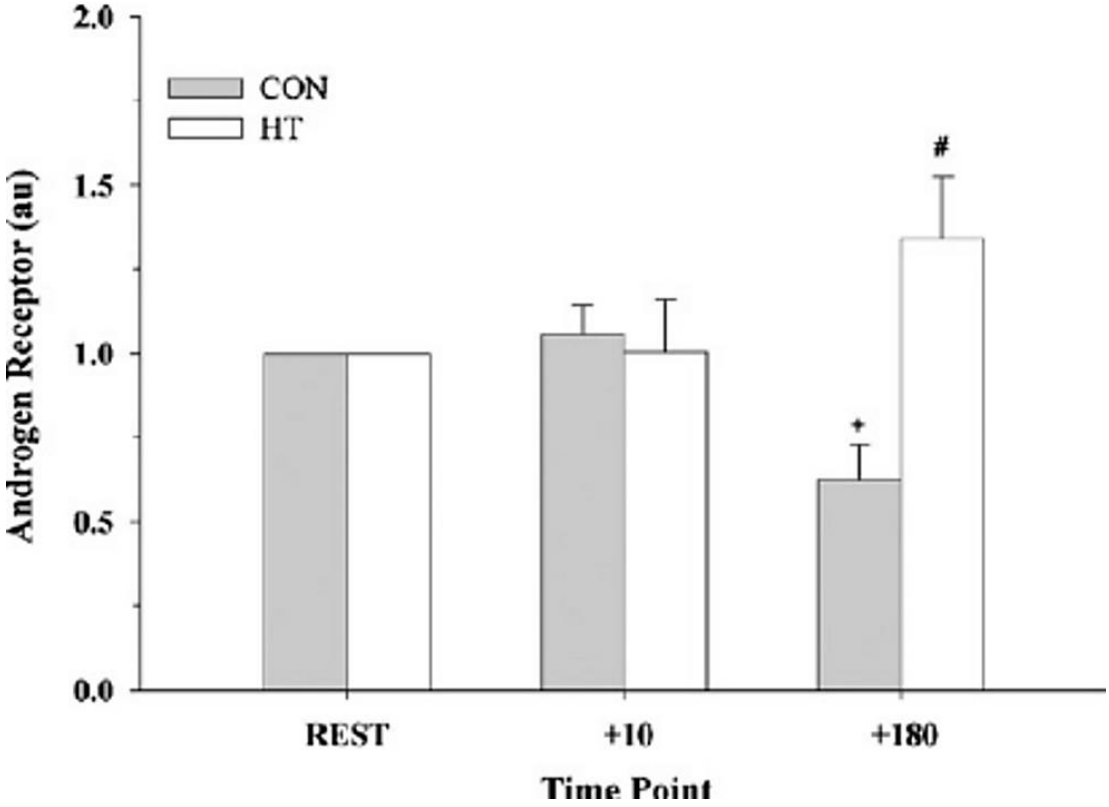


Figure 1. Muscle androgen receptor (AR) responses (mean ± S.E.) to the control (CON) and high-testosterone (HT) trials. # = significantly ($p \leq 0.05$) different than correlation [Spiering et al. 2009 p. 195-9].

Testosterone also affects the immune functions through a system of macrophages, lymphocytes and smooth muscle cells with adrenergic receptors. The interaction is shown in a biological feedback loop in which the specific cytokine impair the synthesis and release of testosterone [Mealy et al. 1990 p. 470-5]. At the same time it inhibits the secretion of type-specific cytokines IL-2, IL-4, IL-19, TNF, IFNɣ [Janele et al. 2006 p. 168-82]. This interaction primarily affects cellular immunity but does not affect IL-2 and the production of IFNɣ lymphocytes (POS et al., 2004). In contrast to estradiol, testosterone inhibits the production of cytokines (IL-2, IL-4, IL-10 secretion (TNF INFɣ) in peripheral blood leukocytes in healthy men [Janele et al. 2006 p. 168-82]. The results showed that the expression of steroid hormone receptors correlates with some infectious processes during the infection [Butts et al. 2011 p. 1000-7]. In parallel, testosterone is involved in muscle regeneration.

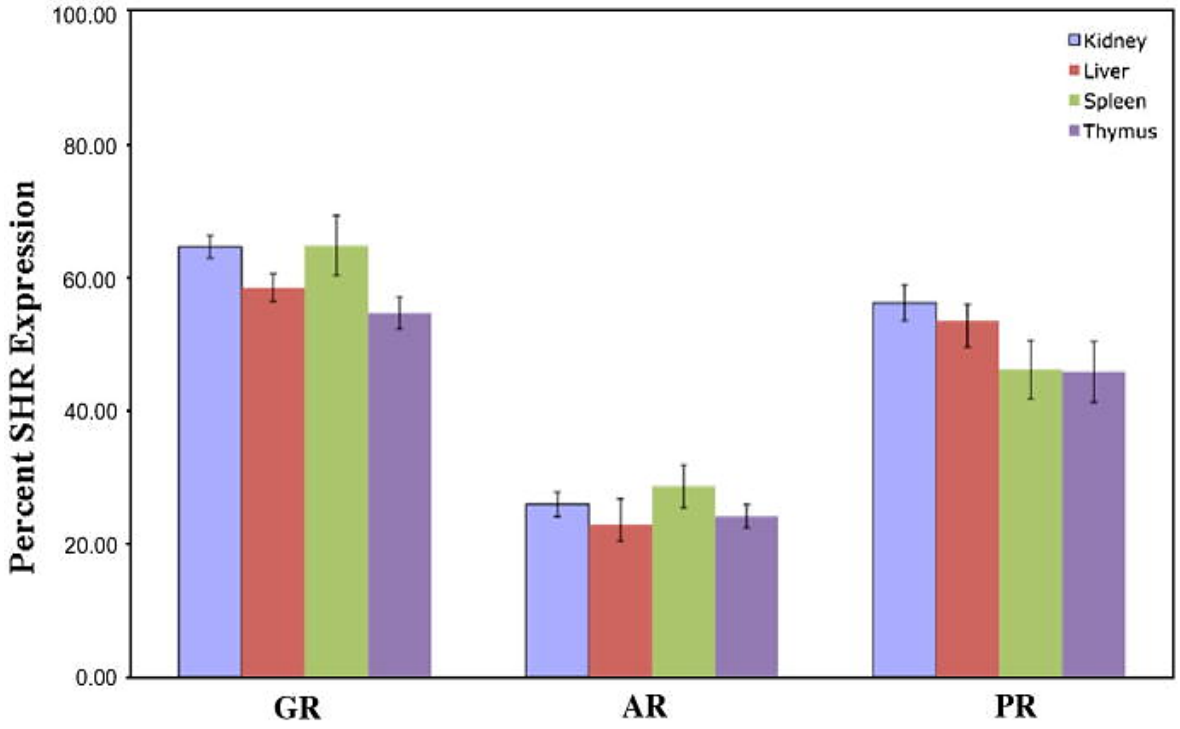


Figure 2. Steroid hormone receptor expression in T lymphocytes from lymphoid and non-lymphoid tissues [Butts et al. 2011 p. 1000-7].

Changes in the levels of testosterone as well as cortisol (a stress hormone) equalize after 48 h [McLean et al. 2010 p. 367-383].

5. IMMUNE INDICATORS

Similarly to the endocrine system, the immune system is also sensitive to physical strain. Additional factors that stimulate its activation may include: medical conditions, infections or cancer. During the exercise, in saliva and blood, there is a change in the concentration of immunologlobinA (S-IgA), NK (natural killers) and the production of proinflammatory cytokines by specific lymphocytes.

The immunoglobulin is responsible for: the neutralization of viruses and toxins, a delay in mucosal bacteria reproduction, absorption of antigens and an increase in non-specific immune components, such as lactoferrin or lactoperoxidase. Their reduction after physical effort was found in the study of a group of basketball players, rowers and swimmers [Morgado et al. 2014 p. 708-714, Orysiak et al. 2012 p. 311-315]. Its decline was correlated with s decreased immunity [Moreira et al. 2011p. 166-172]. These results have not been clearly confirmed in subsequent studies. According to D.Koch, there were no changes to the IGA after exercise [Koch et al. 2007 p. 86-90]. This may be due to individual conditions in this response [Orysiak et al. 2012 p. 311-315].

Table 2. Mean and SEM of SIgAabs, SIgArate and salivary cortisol before and after the investigated training period [Moreira et al. 2011, p. 166-172].

	Before training period	**After training period**
Salivary cortisol	17.6 (1.8)	26.8 (4.9)
SIgAabs	587 (94)	720 (153)
SigArate	106 (20)	92 (21)

Before training period: before commencement of the investigated training period; after training period: 1 week after the investigated training period; SIgAabs: absolute SIgA concentration; SIgArate: SIgA secretion rate.

* Significant difference between before and after training period ($p < 0.05$).

Next results were presented by Judith E. Allgrove. During the exercise of an intensity of about 50%, the concentration of immunoglobulins A in saliva increased, but at higher intensities the parameter was observed to decrease [Allgrove and wsp. 2008 p. 653-661].

No specific indication concerning the impact of this marker on the possibility of developing URTI - Under Respiratory Track Infection has been made so far. [Gleeson et al. 2013 p. 451-457]. These changes can, therefore, have an individual character.

Background information on the release of immunoglobulins A in response to exercise is slightly ambiguous and, thus, requires further research.

6. LEUKOCYTES

Intensive resistance effort causes changes in circulating leukocytes (primarily lymphocytes and neutrophils). The concentration of neutrophils in the blood increases as a result of intense exercise and stays elevated a few hours after the training. On the other hand, the level of lymphocytes during the exercise increases and then, within two to six hours after the exercise can even fall below the baseline [Król et al. 2007 p. 78-82]. The magnitude of these changes is determined by the intensity and duration of exercise [Gleeson 2007 p. 693-9]. This effect is especially visible during endurance exercises with a duration longer than one hour and a half nd the intensity of 55-75% VO2 max. Changes in the number of circulating leukocytes return to the base 3-24 hours after the endurance activity [Gleeson 2007 p. 693-9].

However, this type of effort may temporarily affect the immune function, and basic immune functions in athletes are no different from those in untrained people [Gleeson et al. 2013 p. 451-457]. Studies have shown that the resistance and endurance training almost uniformly increase the level of circulating leukocytes [Miles et al. 1998 p. 1604-9]. On the other hand, long-term resistance training reduces the basic level of cytokines and decreases the extent of inflammation [Calle et al. 2010 p. , Mathur et al. 2009 p.].

Other compounds circulating in blood such as pro- and anti-inflammatory cytokines change the functions of leukocytes and generally increase their level in response to exercise [Gleeson et al. 2013 p. 451-457].

Exertional leukocytosis is significantly activated in men. In women, there was no significant change [Morgado et al. 2014 p. 708-714]. The reason may be psychological and emotional conditions [Orysiak et al. 2012 p. 311-315].

7. CONCLUSIONS

Physical exercise has a multidirectional impact on the mechanisms of immune and neuroendocrine responses. The regular and moderate exercise stimulates the immune mechanism, whereas the interval one may lead to an increased susceptibility to infections. In recent years there has been an increased interest in the issues of the impact of exercise on the efficiency of the immune mechanisms. In practice, such knowledge may be used to prevent infections in athletes and possible states of overtraining.

Among the signaling molecules involved in the body immune response to exercise there are: hormone balance markers(testosterone, cortisol, estradiol,pituitary and hypothalamus hormones), the metabolism of proteins and amino acids (nitrogen balance, glutamine, an increase in creatine kinase) and immunological markers (e.g. immunologlobins A and leukocytes).

The level of cortisol and free testosterone are considered by some researchers to be important markers of immune response and hormonal training. The relationship between these hormones was once considered an indicator of the catabolic and anabolic balance as well as a tool to evaluate a possible overtraining in athletes. Today, it is known that research on these markers can give even more answers about the body's response to exercise. It is closely associated with the impact on hormone levels and their influence on the immune system (eg. an increase in testosterone, hGH hormone, cortisol, epinephrine and norepinephrine).

The release of cortisol, especially after the exercise, and catecholamines during it, stimulates the production of immune cells (neutrophils and natural killers cells). This effect is differentiated by lymphocytes and monocytes having receptors for specific proteins and neuroendocrine hormones. The size of these changes depends on the type of activity and the gender. It was shown that both interval training and strength training significantly stimulate this system to work. In men, testosterone levels increase some immunological functions through a system of macrophages, lymphocytes and smooth muscle cells with adrenergic receptors. In women, who are less sensitive to changes in testosterone, estrogen seems to play a key role in post-workout regeneration and immune response. Yet, this knowledge is not clear and requires further research.

Current research results on changes in biochemical markers under the influence of physical activity have not been confirmed in subsequent publications. It is not possible to determine how certain hormonal and immunological indicators such as cytokines or immunoglobulins behave. This knowledge should be consolidated and confirmed in subsequent studies.

References

[1] J.E. Allgrove, E. Gomes, J. Hough, M. Glesson, Effects of exercise intensity on salivary antimicrobial proteins and markers of stress in active men. *Sports Sci.* 26 (2008) 653-661.

[2] C.L. Butts, Y.L. Jones, J.K. Lim et al., Tissue expression of steroid hormone receptors is associated with differential immune responsiveness. *Brain Behav Immun*, 25(5) (2011) 1000-7.

[3] M.C. Calle, M.L. Fernandez, Effects of resistance training on the inflammatory response. *Nutr Res Pract* 4(4) (2010) 259-69.

[4] M.S. Fragala, W.J. Kraemer, A.M. Mastro et al., Glucocorticoid receptor expression on human B-cells in response to acute heavy resistance exercise. *Neuroimmunomodulat* 18(3) (2011) 156-64.

[5] M. Gleeson, Immune function in sport and exercise. *J Appl Physiol* 103(2) (2007) 693-9.

[6] M. Gleeson, N. Bishop, M. Oliveira, P. Tauler Influence of training load on upper respiratory tract infection incidence and antigen-stimulated cytokine production. *Scand J Med Sci Sports* 23 (2013) 451-457.

[7] D. Janele, T. Lang, S. Capelino et al. Effects of testosterone, 17beta-estradiol, and downstream estrogens on cytokine secretion from human leukocytes in the presence and absence of cortisol. *Ann N Y Acad Sci.* 1069 (2006) 168-82.

[8] J.A. Koch, A.D Wherry, M.C. Petersen, J.C. Johnson, M.K. Stuart, W.L. Sexton Salivary immunoglobulin a response to a collegiate rugby game. *Journal of Strength and Conditioning Research* 21(1) (2007) 86-90.

[9] R.R. Kraemer, R.J. Heleniak, J.L. Tryniecki et al. Follicular and luteal phase hormonal responses to low-volume resistive exercise. Med Sci Sports Exerc 27 (6) (1995) 809-17.

[10] W.J. Kraemer, N.A. Ratamess Endocrine responses and adaptations to strength and power training. w: Strength and power in sports. Blackwell Scientific Publications (2003) 361-86.

[11] K. Król, K. Grocholewicz Wybrane białka śliny jako biomarkery miejscowych i ogólnych procesów chorobowych- przegląd piśmiennictwa. *Roczniki Pomorskiej Akademii Medycznej w Szczecinie* 53(1) (2007) 78-82.

[12] N. Mathur, B.K. Pedersen Exercise as a mean to control low-grade systemic inflammation. *Mediators Inflamm Epub* (2009) 11.

[13] B. McLean, J. Aaron, V. Kelly, M.R. McGuigan, S.J. Cormack Neuromuscular, Endocrine, and Perceptual Fatigue Responses During Different Length Between-Match Microcycles in Professional Rugby League Players International. *Journal of Sports Physiology and Performance* 5 (2010) 367-383.

[14] K. Mealy, B. Robinson, C.F. Millette et al The testicular effects of tumor necrosis factor. *Ann Surg* 211(4) (1990) 470-5.

[15] M.P. Miles, S.K. Leach, W.J. Kraemer et al Leukocyte adhesion molecule expression during intense resistance exercise. *J Appl Physiol;* 84(5) (1998) 1604-9.

[16] Moreira et al Monitoring Stress Tolerance and Occurrences of Upper Respiratory Illness in Basketball Players by Means of Psychometric Tools and Salivary Biomarker. *Stress and Health* 27 (2011) 166-172.

[17] J.P. Morgado, C.P. Monteiro, C.N. Matias, F. Alves, P. Pessoa, J. Reis, F. Martins, T. Seixas, M.J. Laires Sex-Based Effects on Immune Changes Induced by a Maximal Incremental Exercise Test in Well-Trained Swimmers. *Journal of Sports Science and Medicine* 13 (2014) 708-714.

[18] J. Orysiak, J. Malczewska-Lenczowska, Z. Szyguła, A Pokrywka The role of salivary immunologlobulin a In the prevention of the Upper respiratory tract infections In athletes- an overview. *Biol Sport.* 29 (2012) 311-315.

[19] G.M. Peeters, N.M. van Schoor, E.F. van Rossum et al. The relationship between cortisol, muscle mass and muscle strength in older persons and the role of genetic variations in the glucocorticoid receptor. *Clin Endocrinol* 69(4) (2008) 673-82.

[20] E. Posma, H. Moes, M.J. Heineman et al The effect of testosterone on cytokine production in the specific and nonspecific immune response. *Am J Reprod Immunol* 52(4) (2004) 237-43.

[21] T.B. Smith, W.G. Hopkins, T.E. Lowe Are There Useful Physiological or Psychological Markers for Monitoring Overload Training in Elite Rowers? *International Journal of Sports Physiology and Performance* 6 (2011) 469-484.

[22] B.A. Spiering, W.J. Kraemer, J.L. Vingren et al Elevated endogenous testosterone concentrations potentiate muscle androgen receptor responses to resistance exercise. *J Steroid Biochem Mol Biol* 114(3-5) (2009) 195-9.

[23] M.A. Tarnopolsky Sex differences in exercise metabolism and the role of 17-beta estradiol Med Sci Sports Exerc,. 40(4) (2008) 648-654.

[24] H.Wojtaszek, Selected aspects of innovative motivation, World Scientific News, 44 (2016) 8-12.

[25] G.J. Wiegers, M. Knohach, G. Bock et al CD4(-H)CD8(+)- TCR(low) thymocytes express low levels of glucocorticoid receptors while being sensitive to glucocorticoid-induced apoptosis. *Eur J Immunol.* 31(8) (2001) 2293-301.

[26] Zembroń-Łacny, J. Ostapiuk-Karolczuk Udział cytokin w metabolizmie mięśni szkieletowych. *Sport Wyczynowy* (10-12) (2008) 526-528.

(Received 12 June 2016; accepted 28 June 2016)