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Gender Differences between Elite Men and Women Handball Players in Response to Inflammatory Indices following One Session of Moderate Resistance Exercise

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Abstract

Introduction: Men and women show different responses to exercise stress. Some aspects of gender differences in such situations have not been made clear yet. The aim of this study was to compare gender differences between elite men and women handball players regarding IL-6, TNF-α, cortisol and sex hormones responses to resistance exercise.

Material and Methods: Twenty elite handball players (10 male aged 27.6±1.13, height 183.20± 5.93 cm, body mass 87± 3.31 kg and 10 women aged 26.9± 1.04, height 168± 4.07 cm, body mass 63.71± 7.65 kg) were selected. Resistance exercise program included six separate attempts as: Bench press, Lat pull down, shoulder press, Biceps curl, Knee extension and Knee curl which was done in an alternative method for 3 sets and 10 repetitions at 60 % 1RM. Blood samples were taken before, immediately and 2 hours after exercise regimen. Measurement of IL-6 and TNF-α was done with ELISA method. Also cortisol, Testosterone and human estrogen hormone measurement was done by immunoradiometric assay.

Results: Data analysis showed that there were significant differences in post-exercise IL-6 and testosterone levels between the two groups ($P<0.05$). No significant differences were seen in post-exercise TNF-α, cortisol and esterogen levels when men were compared with women ($P>0.05$).

Discussion and Conclusion: Based on the present study results, one session of moderate resistance exercise as a hypertrophy stimulus caused changes in both gender cytokine levels in which men showed limited inflammatory responses.

Keywords: Resistance exercise, IL- 6, TNF-α, Sex Hormone, Gender, Handball players

Introduction

Men and women show different responses to short term exercise such as exhaustive attempts on treadmill or lifting of heavy weights. Differences in body size and composition, Cardiovascular and respiratory functions, maximum oxygen intake, Endocrine function and metabolism during exercise are the cause of physiological diversity between the two genders [1,2]. Commonly it is sensible when local responses to exercise stress or tissue damage caused cytokine production, which secreted in inflammatory site [3].

Cytokines are small polypeptides that are responsible for immune interventions [4]. Cytokine production may be as a cascade that means the first synthesis of cytokines cause production of second and third respectively [5]. Exercise training and physical activity increases blood levels of cytokines such as IL-6 and TNF-a. These cytokines, along with IL-1, synergistically control infection by regulating the production of acute phase proteins and raising body temperature [6]. Although IL-6 is commonly described as a proinflammatory cytokine, it is more accurate to call it an inflammation-responding cytokine because it increases inhibitory mediators, such as the IL-1 receptor, and stimulates the hypothalamic-pituitary-adrenal axis [7,8]. Some researches indicate that IL-6 produces locally in response to intensive exercise and muscle damage and regulate satellite cells [9]. During resistance exercise IL-6 is released as a cause of hypertrophy, but in response to endurance exercise its release causes atrophic state in muscles [10,11]. Also TNF-α is involved in muscular dystrophy because it is a key cytokine in

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inflammation and increases of this factor, following heavy physical activity, reduce the power and strength of muscle and impairs the muscle contractions [12].

Research reports gender differences in immune system function [2,13] that causes differences in immune system responses during exercise between men and women [14,15]. Many researches showed that women who produce more immune cells have stronger reactions to inflammation and show more resistance to infection, however they suffer more innate immune disorders [2,16]. It appears that high risk of inflammation in women is due to gender effects on the activity of inflammatory cytokines such as TNF-α. However immune response is influenced by exercise and other hormonal factors [17]. Meanwhile sex hormones play an important role in immune system. For example, estrogen increases immune homeral response, and androgen and progesterone restrict intrinsic immune factors [18,2]. Increase of inflammatory state such as high neutrophill activity, and high levels of TNF-α, IL -6 and 8 only lead to inflammatory disease in women [2]. Gender differences certainly can be a limiting and affecting factor on immune function after physical activity. However, because it is not certainly clear whether gender differences can cause changes or not, and also as most researches has been done in the field of long term endurance exercise and little research has been done in the field of resistance exercise, therefore, this research has been designed in response to this question that whether gender differences can be considered as an influencing factor on inflammatory response to one session resistance exercise in elite athletes.

Material and Methods

Participants

A group of 10 male (age 27.60 ± 1.13 years, height 183.20 ± 5.93 cm, body mass 187 ± 3.31 kg) and 10 female (age 26±1.22 years, height168 ± 4.07 cm, body mass 63.71 ± 7.65 kg) volunteers from Iran's national handball team were studied. All the participants were members of the national team for 3 years at least. They met the following selection criteria ascertained using a written questionnaire. They were non-smokers, physically healthy, and had no history of recent infection or other significant health disorders. They had taken no medication within at least 1 week prior to the study. None of the participants had involved in training activities before the pretest blood sampling on the test day. No restriction of diet was required for the study, but participants consumed a higher carbohydrate intake before the test in order to take on a glycogen load. The Ethics Committee of the Urmia University approved the experiment procedures and an informed consent was obtained from the participants.

Exercise protocol

Resistance exercise protocol involved pulley-weight machine exercises which were performed for 40 min. Participants were familiarized with and were instructed how to use the machines appropriately (Nordic Track, Icon Health & Fitness, Inc., China). All exercises were performed as 3 sets of 10 repetitions, involving a 90 s recovery period between the sets [9]. All the participants did warm - up activities including stretching and jogging movements for 10 minutes. Based on the Alternate push exercise (PS) with pull exercise (PL) method, participants performed 6 arranged exercises: Bench press (PS), Lat pull down (PL), shoulder press (PS), Biceps curl (PL), Knee extension (PS) and Knee curl (PL) which was done respectively at 60 percent of one repetition maximum.

Blood sampling

The first stage of blood sampling was taken 10 minutes before the warm - up and after the participants had been in the supine position for at least 15 minutes, to determine basal levels of TNF-α, IL-6 , cortisol, estrogen and testosterone. Immediately and 2 hours after exercise venous blood samples were obtained too. In each phase 5 cc of blood was taken from medial anticubital vein. Plasma samples were separated from venous blood using disodium ethylenediaminetetra-acetic acid (EDTA) as an anticoagulant as soon as possible by centrifuging at 1000×g for 10 min. These samples were stored frozen at -80°C until assayed. They were thawed only once before the analysis.

Cytokine and Hormonal measures

The EDTA plasma samples were used for cytokine determination, which was performed with commercially available ELISA kits according to the manufacturers' instructions. They were carefully checked for specificity, sensitivity and reliability. Plasma concentrations of IL-6 and TNF-α were measured using a series of Ultra Sensitive (US)

ELISA kits developed by BioSource Europe S. A. (Fleurus, Belgium). The absorbance was measured spectrophotometrically using a microplate reader (model 550, Bio-Rad, Hercules, Calif, USA) and the concentration of each cytokine was calculated through comparing the values to a calibration curve established in the same measurement. Each cytokine assay was performed in twice each time. The intraassay coefficient of variation was 4.4%, for the TNF-α assay and 3.0%.for the IL-6 assay. The interassay coefficient of variation was 8.7% for the TNF-α assay and 2.5% for the IL-6 assay. Cortisol concentration was measured using RIA (GammaCoat Cortisol, Incstar Co., Stillwater, Minn., USA). Testosterone and estrogen concentrations were determined using immunoradiometric assay (testosterone and estrogen kit "Daiichi", Daiichi Radioisotope Institute, Tokyo, Japan). The intra- and inter-assay coefficients of variation for cortisol, testosterone and estrogen assay were 4.3%, 5.1%and 6.3%, respectively.

Statistical analysis

All data are reported as Mean ± SD. Within and between protocol and blood measure time-point differences were assessed using two-way repeated measures ANOVA (groups × times). When significant differences were observed, Tukey's pairwise comparisons were employed to assess the source of significance which was set at $P \leq 0.05$. All statistical analyses were performed using SPSS for MS-Windows version 16.0 (Statistical Package for the Social Sciences).

Results

The interactive effects of group and time on variables are summarized in table 1. Results of analysis show that this interaction is significant regarding Serum IL -6 and testosterone changes. Thus neither of the groups trends the same method over time. Time changes were also different in both groups.

Because the effect of group and time on IL – 6 and testosterone changes in both groups was significant, different status in both men and women groups was determined with post hoc Tukey test. Table 2 shows the result of post hoc Tukey test for these variables within and between the groups, before, immediately after and 2 hours after exercise ($P < 0.05$).

As seen in table 2, significant differences were observed in IL-6, cortisol, testosterone and estrogen variables in some interval times within each group and between men and women ($P < 0.05$).

Discussion and Conclusion

1- IL-6 and TNF-α

Our study revealed that there were significant differences in IL-6 and TNF-α rest levels between men and women. Greater inflammatory risk profile in women at rest time is thought to be due to sex differences in the activity of proinflammatory cytokines such as IL-6, which is associated with a wide spectrum of inflammatory and autoimmune disorders. Autonomic mechanisms play a role in the regulation of IL-6 production [19]; hence, sex differences in autonomic activity might also contribute to differences in proinflammatory cytokine production. Increases in sympathetic activity along with β-adrenergic receptor activation suppress stimulated production of proinflammatory cytokines [20,21]. Substantial evidence indicates that autonomic nervous system activity differs between men and women, and that men show higher levels of sympathetic balance than women [22,23,13]. On the other hand some studies showed dichotomous effects of sex hormones: Estrogen and metabolites stabilized or increased cytokine secretion whereas testosterone inhibited this secretion. This dual role of estrogens and testosterone on cytokine secretion has been described in the literature and it was thought that this phenomenon could explain the well-known female-to-male preponderance in acquiring autoimmune diseases, particularly when TNF and IFN-γ play a dominant disease perpetuating role [24, 25].

Our study replicated results of several other studies showing an exercise-induced increase in IL-6 production [10,12]; however, our observation of a moderate but non-significant increase in TNF-α production is in contrast with the findings of some other studies [26,27]. Timmons et al. revealed that TNF-α level did not change after exercise in men which is in line with our results [28]. The reason may be that generally TNF-α level is increased only with long, intense, exercise that involves using a large muscle mass. On the other hand, some studies indicated that physiological concentrations of IL-6 inhibit the production of the TNF-α [6]. Other

studies suggested that production of TNF-α was enhanced after exercise tasks that is likely to be related to an inflammatory response to exercise [29,12]. IL-6 also has an anti-inflammatory action (e.g., it induces acute-phase proteins and stimulates the hypothalamic-pituitaryadrenal axis) and therefore controls the inflammatory response and contributes to the maintenance of homeostasis [30]. It seems that an additional mechanism is involved. IL-6 increases after the psychological and physical challenges. Given that IL-6 is rather an inflammation-responsive cytokine, a potent anti-inflammatory and an immunosuppressive mediator, these findings might refer to its role in maintaining homeostasis during stress. On the other hand, TNF-α production observed after a heavy exercise task is likely to be related to an inflammatory response to exercise. Therefore, our moderate resistance exercise is considered to be a model of limited inflammatory response; so such exercise also affects the number of circulating leukocytes, predominantly natural killer cells, which corresponds to their β_2-receptor expression [31]. These changes are thought to be a short-term enhancement of immune function [32,33].

Table 1: Analysis of variance with repeated size in relation to changes in IL - 6, TNF-α, cortisol, testosterone and estrogen in elite men and women handball players.

Source	F value	P value	Effect size (PES)
Interactions effect of groups and time on IL – 6 changes	53.02	0.001	0.841
Interactions effect of groups and time on cortisol changes	6.92	0.69	0.036
Interactions effect of groups and time on testosterone changes	5.82	0.01	0.409
Interactions effect of groups and time on estrogen changes	6.643	0.25	0.012
Interactions effect of groups and time on TNF-α changes	2.21	0.54	0.01

Table 2: Evaluation of IL-6, TNF-α, cortisol, testosterone and estrogen's significant status in relation to the period of time in elite men and women handball players

Variables	groups	T1	T2	T3
IL-6	Men	1.58±0.53 *	2.83±0.75 *¥	6.17±0.61*¥+
(Pg/ml)	women	2.87±0.82	2.44±0.14	3.16±0.82 ¥+
TNF-α	Men	3.84±1.00 *	3.86±1.36 *	3.86±1.26 *
(Pg/ml)	women	5.08±1.23	5.21±1.22	5.20±1.71
Cortisol	Men	163.49±41.93 *	151.86±39.06 *	80.89±10.73*¥+
(Mg/L)	women	77.24±11.08	74.54±10.95	54.72±4.84 +
Testosterone	Men	5.09±0.99 *	5.58±0.88 *¥	5.65±1.08 *¥
(Pg/ml)	women	0.27±0.06	0.3±0.05	0.23±0.07¥+
Estrogen	Men	27.24±7.36 *	22.38±6.41*	20.59±4.50 *¥
(Pg/ml)	women	112.13±35.65	103.98±38.73 ¥	74.44±12.90¥+

Values were expressed as Mean±SD. T1: before; T2: immediately; T3: 2 hours after exercise. *: significant difference between men and women in the same variable. ¥: Significant difference in time T1 at 0.05 levels in the same row. +: Significant difference in time T2 at 0.05 levels in the same row.

The next finding of our research was that immediately after a moderate resistance exercise IL-6 increase in men was significantly greater comparing to its increase in women. Recent research indicated that the main source of IL-6 release in response to exercise is recruitment skeletal muscle [26, 34]. It appears that the main reason for the plasma IL-6 increase after resistance exercise is that in this type of exercise greater muscle mass is involved. [35]While in women because of a smaller muscular mass, such an increase was not observed. According to our data regarding an increase in IL-6 in response to psychological stress, it seems that enhanced IL-6 production is not solely a result of a mechanical event. Testosterone may also affect IL-6 secretion. Testosterone can increase synthesis of cytokines [18,2,5]. Thus, increasing testosterone concentrations in men after resistance exercise may lead to an increase in such cytokines levels. In women testosterone levels were lower and did not have a significant enhancement after resistance exercise; so testosterone did not affect anti-inflammatory IL-6 levels in women. Another effective factor is the recruitment type of muscle fiber. Gene expression of IL-6 Secretion in type I muscle fibers has been reported [11]. Due to higher training pressure in women, more type II muscle fibers are involved and that could be a possible reason of restricted IL-6 secretion in women.

Finally, our data analysis showed that, two hours after exercise IL-6 secretion developed in both women and men. Researchers believed that this phenomenon is related to muscle damage [36]. On the other hand, exercise induced muscle injury has been regarded to be the primary stimulus for the IL-6 response. Recent studies suggest that exercised muscle is stimulated by complex intra muscular signals and releases IL-6, disregarding muscle damage. Subsequently, muscle damage induces a repair response, including macrophage entrance into the muscle, causing further IL-6 production. This injury persuaded IL-6 response is delayed and smaller than the IL-6 production related to muscle contraction [37,12].

2- Cortisol

We found a gender difference in rest adrenocortical levels in which males showed higher cortisol levels compared to females. In search of biological variables, corticosteroid binding globulin (CBG) could be considered a candidate for explaining this gender difference. It may be speculated that the reported effect is due to higher levels of the binding protein. Upon stimulation, cortisol molecules released from the adrenal cortex may then more readily be bound to CBG, resulting in lower free cortisol concentration measured in females compared to males. Alternatively, differences in psychological variables may be considered responsible for the enhanced cortisol secretion observed in men [38,12].

Research data indicates that there was no significant difference in serum cortisol levels immediately and two hours after exercise between men and women. Even though physical activity and psychological stress affect neuroendocrine and immunological parameters differently, both are potent activators of the central nervous system and alter the immune response [8]. Both stressors increase intracellular production of cAMP through stimulation of β-receptors on immune- competent cells [39]. The beneficial effects of moderate exercise are well documented [40]. Thus, immunological performance is continuously trained and might therefore protect the person effectively against infections [41,27]. This may be applicable to limited psychological stressors, but chronic stress is thought to suppress immune function (42). It seems that our moderate resistance exercise as a limited inflammatory response improves immune function. One the other hand evidence from the literature strongly supports the concept that estrogens enhance and androgens diminish the glucocorticoid response to a variety of stimuli. Although the mechanisms for these interactions are not fully elucidated, there is strong evidence that sex steroids affect the expression of glucocorticoid receptors in the central nervous system and modulate the negative feedback exerted by cortisol at the hypothalamus [1,2]. These observations led us to hypothesize that cortisol interacts with testosterone or estrogens on the cellular level [15]. In this study testosterone levels were higher in men compared to women immediately and two hours after exercise, while estrogen did not show such a profile. Some studies also corroborated the results of this research, among which are David and colleagues' (2001) who studied 2 hours of Marathon run and Brain and mark's (2006) who investigated a 90 minute practice on an ergometer bike but did not report any significant difference in

cortisol levels between male and females[43,15].

3- Estrogen and testosterone

Sex steroid hormones are mainly secreted by the ovary and testis. Levels of estrogen in plasma are higher in females while testosterone levels are higher in males [44]. These gender differences contribute to physiological characteristics [1,45], including differences in energy metabolism, muscular strength, and body composition. Rest levels of these hormones, as observed in this research, corroborated this fact. Also data showed that significant differences were observed in serum testosterone levels immediately after exercise between men and women; in which, immediately after exercise, testosterone levels were higher in men. Some other researches also, reported significant differences in testosterone levels immediately after exercise between men and women [1,46]. Sex hormones are synthesized through the esteroidogenesis process and with the cooperation of 17β-HSD, 3β-HAD P-450arom enzyme. Research showed that exercise increased, the expression of these three enzymes in males while in females, the expression of 17β-HSD increased , 3β-HSD did not change, and P450arom decreased [1,2]. Thus a session of resistance exercise may cause specific gender-related changes in steroidogenesis enzyme expression and this factor could be one of the effective factors in gender-related differences in testosterone levels [1]. Above-normal testosterone levels immediately after exercise in men compared to women was also attributed to the greater muscle mass in men [47]. In fact women have less fat free mass compared to men and consequently have lower percentage of testosterone levels than men. Another affecting factor can be the intensity of exercise. Exercise with 60 percent intensity is a hypertrophy stimulant and this factor can stimulate testosterone production in men who have previous strength training [48]. In fact, the intensity of exercise stimulated hypertrophy mechanisms an adaptation effect that may increase testosterone levels. On the other hand recent data showed Endurance exercise causes gene expression of estrogens whereas resistance training causes androgens gene expression [1].

Conclusion: in brief our research revealed that doing one session of moderate resistance exercise creates different cytokine responses between men and women, in which men show limited inflammatory responses.

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