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FAS RESPTOR AND FAS LIGAND EXPRESSION IN BLOOD LYMPHOCYTES ARE INFLUENCED BY EAROBIC AND CONCURRENT EXERCISE

ZEENAT EBRAHIMI[*1], ALI JALIL[2], PARYVASH PIRAKI[3], KAMAL AZIZBAIGI[4], MOZAFAR YEKTAYAR[4], BAHAREH RAHIMIAN ZARIF[5]

1: Lectureship in Department of Physical Education, Sanandaj branch, Islamic Azad University, Sanandaj, Iran. Zin368@gmail.com

2: Associate Professor in Department of Immunology and Hematology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran.

3: Lectureship inDepartment of Physical Education,Darehshahr branch, Islamic Azad University, Ilam, Iran

4-Assistant Professor in Department of Physical Education, Sanandaj branch, Islamic Azad University, Sanandaj, Iran

5- Assistant Professor in Department of Biology, Sanandaj branch, Islamic Azad University, Sanandaj, Iran

***Corresponding Author: E Mail: zin368@gmail.com; Mob: +98 9183336007**

ABSTRACT

Fas receptor (CD95) & Fas ligand (CD178) polymorphisms in the promoter regions influence transcriptional activities. The interaction of these two genes plays a crucial role in apoptotic cell death regulation. We aim to study the effect of 8-weeksadaptive aerobic and concurrent exercise CD95and CD178 Expression in healthy women Lymphocyte. 36 healthy inactive women with 19.58± 0.9 average age were divided into 3 groups, the experience groups were performed 8-wk adaptive aerobic and concurrent exercise completed a moderate exercise consists 30 minutes training in day and control group were inactive in duration. Blood was collected before and after 8-wk, after strenuous exercise, and 24h after strenuous test to determine CD95 and CD178 expression on lymphocyte cells that was determined by employing flow cytometry.Result

shown there was statistically significant difference in the CD95 and CD178 expression after 8-weeks in experimental groups athwart control group. We found that the level of CD95 and CD178 were significantly decreased after 8-weeks in experimental groups. Also, CD95 and CD178 expression changed after exhausting exercise in all groups. But CD95 did not significant difference in CT group. CD178 have significant decrease in CT and AT group and increase in CG group 24 H later, while CD95 increased 24h later but, this change were not significant in all groups. In conclusion, our data show that CT and AT exercise reduces CD95 and CD178 expression on lymphocytes, indicating that health activity might lead to decrease apoptosis of peripheral lymphocyte cells from active person in compare with inactive person.

Keywords: Apoptosis, Aerobic exercise, Concurrent exercise, CD95 and CD178 expression, Exercise intensity

INTRODUCTION

Fas (CD95 or APO-1) is a 36-kDa cell surface protein that belongs to a large family of TNFreceptors. Fas Ligand (FasL or CD178) is a type II membrane protein of 40 kDa that binds to Fas. Activation of Fas with FasL induces apoptosis in normal and tumorcells [1]. A major signaling pathway for the extrinsic induction of apoptosis is the Fas receptor (FasR)/Fas ligand (FasL) pathway. After binding of FasL to FasR, the receptor is trimerized[2]. Fas and Fas ligand (FasL) polymorphisms in the promoter regions influence transcriptional activities. The interaction of these two genes plays a crucial role in apoptotic cell death regulation [3]. The apoptosis-inducing death receptor CD95 (APO-1/Fas) controls the homeostasis of many tissues [4].By expression of the apoptosis-inducing protein CD95L (FasL, APO-1L, CD178), tumors may eliminate tumor-infiltrating lymphocytes and suppress anti-tumor immune responses [5].

Surface receptor Fas and its ligand (FasL) are illustrated as mediator of apoptosis to act in the immune system:(1) to limit over-expression of an immune response via deleting unwanted lymphocytes incidentally, (2) to remove auto-reactive T cellsduring thymus selection. Ascertainments byscientist show that Fas/FasL (CD95/CD95L) interaction is straight away responsible for activation induced cell death along with the fact that activated lymphocytes express the receptor protein Fas and its ligand FasL [6]. Exercise training prevented hypertension-enhanced cardiac Fas-dependent and mitochondria-dependent apoptotic pathways and enhanced

cardiac pro-survival pathway in rat models [7].

Apoptosis is of fundamental importance to guarantee a balance between the generation of new cells and removal of damaged or aged cells. Thereby, apoptosis is a complex process of cell death that allows cells to die in a well-controlled fashion [2]. Apoptosis can be pathological, a sign of disease and damage, or physiologic, a process essential for normal health. Inappropriate or excessive apoptosis has been implicated in several types of neurodegenerative disorders, including stroke [8]. This pathological deregulation of cell death can be characterized by either too much loss of essential cells in the heart, brain, and other tissues with little regenerative capacity or too little cell turnover in self-renewing tissues, giving rise to cancer and other maladies [9]. Nowadays, the response of immune system to exercise and sport has evolved into a topic which is attracted by health care and sport professional. Alternations in immune system parameters are often seen in many athletics [10,11]. Apoptosis produced in B cells through Fas (APO-1, CD95) triggering is regulated by signals derived from other surface receptors [12].Therefore, a better understanding immune system response to exercise and sports may help both athletic and heath professional.

Exercise is a type of physiological stress which has a substantial effect on leukocyte life span [2]. Studies have represented that intensive and strenuous exercises activate lymphocytes and finally lead to apoptosis of these activated cells. Accumulating evidence imply that adaptive exercise not only have various beneficial effects on skeletal, muscle and heart but also it may enhance the function of immune system [13,14]. Regular training promote resistant to upper respiratory infection, whereas intensive training increase the risk of infection[15]. Accordingly regular training protect against malignancy, but strenuous exercise is somehow associated with cancer risk [16]. Overall, mounting evidence indicate that regular training have many advantages on immune system. However, its mechanism at least partially, remains to be explored.

Strenuous exercise modulates several factors that may alter apoptosis [17]. For example, glucocorticoids, reactive oxygen species (ROS) [18, 19]. Some studies have represented that only the number of lymphocytes and not neutrophils declined below the corresponding pre-exercise value 2 hours after physical activity [20].

furthermore, many reports have shown that the number of lymphocytes decreases following Strenuous exercise, which could be as the result of induction of apoptosis in these cells[21]. These studies suggest that the decline in leukocyte number after exercise occurs due to the induction of leukocyte death [20]. Moreover, the increase in DNA fragmentation depends on the intensity and duration of the exercise [22, 23].

Combining aerobic exercise and resistance training in the same workout session, a technique referred to as concurrent training, can be a time-efficient training method[24]. Current public health recommendations for physical activity combine aerobic exercise with resistance training [25].The benefits of regular physical exercise are well documented. Similarly to endurance exercise, an increased rate of apoptosis was mainly related to the intensity of resistance exercise. In this regard, intensity means weight loads of 75% of the one repetition maximum or above, while rest-interval length seemed to have only minimal effects [2].However, there are few studies that approach the benefits of concurrent training (aerobic plus strength) in the lymphocyte apoptosis. There is less information available that this training can help to lymphocyte apoptosis or no. The aims of the present study, therefore, were to investigate the effect of adaptive training on immune function especially on Fas receptor (CD95) and Fas ligand (CD178). For this purpose use of Aerobic and concurrent exercise as adaptive training for 8-weeks, for 3 d_wk. Measures of blood sample were made before and after the adaptive training intervention to survey impacts of adaptive training, after strenuous exercise to evaluate the harmful effects of intensive training and 24 h later to determine the back rest. If changes after strenuous exercise are low compared to the control group, it can be concluded that adaptive exercise has positive effects on the immune system. As well as the impact of the training is more if, the return to its original state after 24 hours was closer to the values of rest

MATERIAL AND METHODS

Volunteers

36 healthy inactive women with 19.58± 0.9 average ages were divided into 3 groups: aerobic training (AT), concurrent training (CT) and control group (CG).They had not any physical activity for the previous 6 months. Before beginning testing, all the subjects completed 1-repetition maximum (1RM) assessments on the resistance

exercises to be performed in the study, to establish the precise workout intensity to be used. In addition, they performed a maximal aerobic capacity (VO_2max) test to establish the appropriate the intensity for the aerobic sessions. Also, participants are assumed the descriptive variables include of height, weight, age, body fat percentage. The heart rate during exercise was measured to ensure that same intension training program by marking gauge using Polar heart rate. The characteristic of volunteers is shown in table 1.In both training protocols (AT, CT), the participants were subjected to 24 sessions of 60 minutes each, with the same progressive intensity of 50–75% monitored by the Borg scale (Table 1). Each training session was divided into five minutes of initial warm-up, 50 minutes main workout, and five minutes of stretching. AT and CT were performed three days per week and CG don't have any training in 24 session. After this duration all group performed one session strenuous exercise.

Exercise protocol

Aerobic protocol: Each subject ran for 50 minutes on a treadmill at a stride pace of 70% VO_2max.

Concurrent protocol: The subjects performed a 25-minute run at 70% VO_2max, as in the aerobic protocol. Five minutes after completing the run, they completed 3 sets of 10 repetitions at 70% of their 1RM, with a 105-second rest between sets and exercises. Each subject performed the following seven exercises in this order: (1) bench press, (2) leg press, (3) barbell biceps curl, (4) triceps extension, (5) hamstring curl, (6) latissimus pull-down and (7) knee extension. (24).

Strenuous exercise: Our strenuous exercise consisted of treadmill running, just at the end of the dark cycle one session strenuous exercise were performed at 80% maximal oxygen uptake on treadmill for 10 min in all of them according to the previous study (26).

Simple collection and processing

Blood sample were taken before, after 8-weeksof adaptive exercise, immediately after strenuous exercise and 24 h later. All samples were taken in special tubes containing EDTA as anticoagulant. Blood samples were stained with 10 µ l of either anti-human CD95-PE or isotype antibody (both from Biolegend, CA) for 30 min on ice and kept in dark. Then washed with FCM buffer (PBS containing 1% BSA) and analyzed by flow cytometry (FACS Cali bur, Becton-Dickinson). Data were analyzed by FCS Express software. Lymphocytes were gated based on their forward and side scatters and then Fas receptor (CD95) and

Fas ligand (CD178) expression was analyzed on them.

Data Analyses

To calculate measures of central tendency and dispersion data were analyzed using descriptive statistics. Data were statistically analyzed by ANOVA with repeated measure and benferonyhoctest for four different time points (before exercise, after two months, almost immediately after strenuous activity after 24 hours of intense sports activity) in the two groups.SPSS19 software used to analyze the data and the significant level was considered for all data α=0/05.

RESULTS

Data were analyzed by FCS Express software. Lymphocytes were gated based on their forward and side scatters and then Fas receptor (CD95) and Fas ligand (CD178) expression was analyzed on them. Descriptive measurement was present in table 2. Result shown there was no statistically significant difference in the CD95 and CD178 expression after 8-weeks in control group. While, that was significant in experimental groups. We found that the level of CD95 and CD178 were significantly decreased after 8-weeks in experimental groups. Also, CD95 and CD178 expression changed after exhausting exercise in all groups. But CD95 did not significant difference in CT group. CD178 have significant decrease in CT and AT group and increase in CG group 24 H later, while CD95 increased 24h later but, this change were not significant in all groups. In conclusion, our data show that CT and AT exercise reduces CD95 and CD178 expression on lymphocytes, indicating that health activity might lead to decrease apoptosis of peripheral lymphocyte cells from active person in compare with inactive person table3.

DISCUSSION

The Fas and Fas-L expiration was assessed in healthy women who underwent two type of adaptive exercise. In order to gate the lymphocyte population, samples were fan by flow cytometry and lymphocytes were gated based on their forward and side scatter. Interestingly, we found that Fas and Fas-L expiration reduced after 8-weeksexercise session in CT and AT groups, however, there was no change after 8-weeks in control group. Mooren et al. (2002) reported that two treadmill exercise tests, the first (strenuous exercise) and the second (moderate exercise), Immediately after the strenuous exercise, the percentage of apoptotic cells increased significantly, whereas it remained unchanged after the moderate exercise [27]. This result is partly

consistent with our result, the effect of moderate exercise in this research was against our finding.

Exercise intensity is assumed to be main effectors of exercise induced lymphocyteapoptosis [2]. We could explain this discrepancy as we used a moderate protocol for adaptive exercise and this protocol may have some beneficial effects on immune system by reducing CD95 and Cd178 expression on lymphocytes. CD95 has been shown to be associated with apoptosis and is a signal of initiating of apoptosis [28].Exercise mobilizes peripheral immune cells and the magnitude of this effect reflects the intensity and duration of the effort [20].While numbers of circulating lymphocytes significantly increase during exercise, it is followed by a post-exercise lymphopenia. It is believed that lymphopenia is the result of at least two different processes. On the one hand lymphocytes are redistributed into various tissues and organs and cells die by apoptosis [2]. However, another study conducted by Simpson et al. (2007) have recently showing that apoptosis of peripheral lymphocytes doesn't appear to contribute to exercise-mediated lymphocytopenia [21].

Thus, reduction in the level of CD95 expression implies that adaptive light training apoptosis might strength the immune system against pathogens. Supporting of this notion, a previous report has demonstrated that regular training reduces the chance of occurring malignancy [16]. Besides, the results of this study are not in agreement with a previous report showing that expression of CD95 is influenced by acute exercise in healthy children and adolescents[29]. We have to note that the type and duration of the training protocols as well as the gender and race of the participants may influences on the level of CD95 and CD178 expression and apoptosis of lymphocyte. Our result is agreed with Okolow et al. (2007). They examined the influence of regular training on apoptosis in sedentary rats and rats that were trained for8-weeks. In untrained animals, the acute exercise resulted in increased apoptosis. While, in the rats exposed to the 8-week regular training, there were no changes in apoptosis in compared to the sedentary animals[30]. Chaeand Kim, (2009). Forty-five male rats were divided into the following three groups to performed exercise 5 days a week for 8 weeks. The results show that forced moderate-intensity treadmill exercise increases the level of nerve growth factor and activates P-PI3-K to induce PAkt in order to suppress apoptotic

cell death in the hippocampus of induced aging rats[31].

Acute exercise has been reported to induce injury, including apoptosis, not only in skeletal muscles but also in the heart and in thymocytes [32]. A wide variety of research was measured in the apoptosis or in related compartments in response to acute exercise and training[12, 17, 27].But the aim of this research was comprehensive effect of the strenuous exercise bout after tow type adaptive training, to measure CD95 and CD178 expression changes. On the other hand, it is well known that regular physical activity is associated with beneficial changes in aerodynamic, hormonal, and metabolic functions of many organs[32]. Recently, we have illustrate that applied strenuous exercise resulted in CD95 and CD178 expression significantly up regulation lymphocytes immediately after strenuous exercise in control group. This finding was similar to AT group but this difference was significantly decreased while CD95 in CT group increased however this change was not significant. Also, CD178 expression was significantly increased in all groups. These findings suggested that the strenuous exercise-induced apoptosis in lymphocyte cells could involve action of CD95 and CD178 receptors as well as oxidative stress, while the regular training was shown to prevent apoptosis.

Survey results were not similar with extraction outcomes by Mooren et al. (2002). They found an up regulation of CD178 after both exercise tests. As regards, only after strenuous exercise a characteristic shift in CD95 expression profile toward cells with a high receptor density was observed, Expression of the CD178 remained unchanged after both strenuous and moderate exercise [27]. This finding suggests the duration (or intensity) of exercise influences apoptosis response. Strenuous exercise increases apoptosis in the lymphocytes and neutrophils of athletes (20).This research use strenuous exercise as stress while Mooren et al. use it as protocol training. Physical exercise can be categorized as a “stressor”, which is accompanied by increased concentration of catecholamine, corticosteroids, etc.

Exercise induces several different types of physiological stress yet, paradoxically, is known to confer protection against diseases such as cardiovascular disease and cancer [33].Consequently, we were recently able to indicate that human blood lymphocytes express increased levels of Fas and FasL following intensive exercise. Our results approve that adaptive exercise can regulates

Fas/FasL expression of cells lymphatic. Enhanced expression of CD95 and CD178 in control group after strenuous exercise match with assail of apoptosis. These results are coherent with the finding that strenuous exercise as stress affect apoptosis. This result is in line with thestudy of Tanimura et al. (2010).They show that intense exercise affects the immune system. Reduce lymphocyte apoptosis might prevent the decrease of lymphocytes in endurance-trained [34].Similar results were found by Hovanloo et al. 2013 and Jahromi et al. 2014.This result is partly consistent with Tanimura et al. (2009) Displays short-term high-intensity exercise induced a decrease in the T lymphocyte counts without increasing in CD95 expression. However, our study is not consistent with the study of Lagranha et al. (2004) as for showed an increase in the apoptosis of lymphocytes obtained after a single session of exercise [39]. Blood samples collected atresting time in noon to reduce effect of cortisol hormone. Thereby, this finding may be influenced by not only the effect of strenuous exercises but also the effect of the adaptive exercise duration.

However, the duration of the exercise-induced apoptosis but, this effect is unknown since multiple post-exercise times are needed to determine it completely, we measures it 24 h after of strenuous exercise. The result shown CD178 have significant difference in all group in compare with CD95.CD178 have significant decrease in CT and AT group and increase in CG group 24 H later, while CD95 increased 24h later but, this change were not significant in all groups. Whilst we though the expression of CD95 on lymphocytes reduced 24h latter, but it did not reach to the steady-state (figure 2). Our data are in the line with other studies demonstrating that CD95 expression on lymphocytes increased during and just after the intensive exercise and then resorted to the steady-state 24h latter[29,40]. On the other hand, CD95 expression on lymphocytes of experimental group did not significantly enhance 24h after strenuous exercise implying that adaptive exercise may prevent of CD95 up regulation on lymphocytes (figure 2). Accumulating evidence indicate that light and regular training enhance immune system function [10,41], whereas Strenuous exercise suppress the immune system and increase lymphocytes apoptosis [29,42].The difference in CD178 result show that adaptive exercise was more effective in CD178 in compare with Cd95. So, adaptive exercise can reduces CD95 expression on lymphocytes of healthily individual. Thus,

light and regular training may prevent induction of apoptosis in lymphocyte cells. Although previous studies [43, 44] suggested that Ligands such as TRAIL, FasL and TNF can, however, be produced as recombinant proteins and used for anticancer therapy the mechanism of the apoptosis remains to be investigated. There is fundamental evidence delineated that Fas/FasL are present in the lymphocyte cells and their expression are important for immune function. This result, in agreement with [40, 45, 46,47] indicate that strenuous exercise enhance the Fas and FasL expression. Both Fas receptor and ligand were increased after the marathon with different kinetics. Whereas the Fas receptor peaked at 1 h, Fas ligand was increased 3 h after the run. After the treadmill tests Fas receptor expression was enhanced in both groups, whereas Fas ligand increased only after the strenuous treadmill test [40]. Based on previous studies [2] post-exercise lymphopeniais one of the most events that occur after Exercise particularly in intensive exercise. It is believed that lymphopenia is the result of at least two different processes. On the one hand lymphocytes are redistributed into various tissues and organs [48]. On the other hand cells die by apoptosis. These processes are thought to run in parallel and their relative magnitude seems to depend on the mode of exercise [2]. Our result was not confirmed only with a study by Friedman et al. (2012).They use repeated high-intensity "Wingate cycle bouts influence markers of lymphocyte migration but not apoptosis.

In conclusion, it is considered that this study examine the effects of adaptive exercise on apoptotic situation. However, these studies concentrated on the role of adaptive exercise on the positive and negative effect of strenuous exercise on Fas/FasL-mediated apoptosis. Results obtained in this study are in good agreement with other studies exhibit that active person have more resistant in the pressure of exercise. Finally, our data show that adaptive exercise may reduce apoptosis-related molecules, CD95. However, we have to consider that other makers and molecules associated with apoptosis such as Bcl-2, mitochondrial membrane potential need to be examine after 8-weeks of adaptive exercise.

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