Original Article

Effect of a weight lifting training session on leukocyte count and myokine (Interleukin-6) levels

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Abstract:

Exercise is believed as one of the most important stress factors and it can influence the immune system by altering the leukocyte subsets and many cytokines. the main aim of the present study is to monitor the instantaneous effect of weight lifting training session on the leukocyte counts and IL-6 levels in trained weight lifters. Thirteen national-level weightlifters (5 male and 8 female) aged 19 ± 3.09 years with 3.4 ± 2.4 years of training experience were recruited for this study. Blood samples were collected before and after the high-intensity weightlifting training sessions and Leukocyte counts and Interleukin -6 levels are analyzed. Results signify that the weightlifting training elicits a different response on neutrophil and lymphocyte counts. A significant increase ($P < 0.05$) was observed in the absolute neutrophil count after the exercise with a significant reduction in absolute lymphocyte count. Consequently, a significant increase is seen in NLR but no significant change was observed in total leukocyte count after the training session. IL-6 levels are significantly increased ($P < 0.01$) after the training session. It is concluded that the high-intensity weightlifting training could elicit a significant increase in Neutrophil and IL-6 levels immediately after the exercise.

Key Words: Interleukin-6, Cytokine, Neutrophil Lymphocyte Ratio, Weightlifting training.

Introduction:

Hematological parameters are commonly used to assess the nutritional and health status of athletes. Analysis of these parameters would give information about the training-induced adaptations in athletes. In addition to this leukocyte and leukocyte subsets are widely used as the inflammatory markers. Sports training can affect various components and functions of the immune system, heavy exercise is considered as one of the major stress factors that the organism can face. During and after exercise the body system exhibits several alterations in metabolic, endocrine and immune systems to fight against this stress (Shephard & Shek, 2011). From the available literature, it is evident that the type of exercise performed will influence the various subpopulations of the leukocytes differently. It is well-known that moderate-intensity exercise offers protection against infections caused by intracellular organisms by stimulating pro-inflammatory responses, whereas high-intensity exercises encourage the anti-inflammatory responses in order to decrease the post-exercise muscle tissue damage and inflammation but this may increase the vulnerability of athletes to infections. The mode, intensity, and duration of the exercise are the major factors that control the immune system. As per the official guidelines of The International Society of Exercise and Immunology (ISEI), immune dysfunction is largely noticed after prolonged (>1.5 h) and high-intensity exercise. Therefore it has been hypothesized that the athlete's adaptive mechanisms vary in accordance with the type of exercises they perform.

Leukocytes or white blood cells (WBC) protect our body from microorganisms and they also clean up cell debris. By considering the type of granules present their cytoplasm; leukocytes are divided into two types - granular leukocytes (Neutrophils, Eosinophils, and Basophils) and agranular leukocytes (Lymphocytes and Monocytes). Unlike erythrocytes, leukocytes often leave the capillaries and enter the site of inflammation or damaged tissues to perform their defensive functions this phenomenon is called extravasation and it is one of the most distinctive features of leukocytes. The differential leukocyte counts are often used as markers in the diagnosis and prognosis in clinical medicine.

Neutrophils normally comprise 50-70 percent of WBC count. These are granular white blood cells, which contain granules in their cytoplasm that stain light lilac with neutral dyes. They contain a distinct lobed nucleus, the number of lobes of the nucleus increases from two to five with the age of the cell. So neutrophils are also called polymorphonuclear leukocytes (PMNs). Neutrophils mainly work to support innate immunity and protect our body from foreign organisms. In the site of infection, neutrophils act as phagocytes against bacteria. PMNs are also involved in many inflammatory processes.

Lymphocytes are agranular leukocytes, which form around 20–30 percent of leukocytes. All lymphocytes originate from the lymphoid stem cell of bone marrow but their maturation occurs in distinct lymphatic tissues like thymus (T-lymphocytes) and bursa equivalent i.e. gut-associated lymphatic tissue (B-

lymphocytes). The concentrations of all lymphocyte subpopulations are found to increase in the vascular compartment during exercise and decrease after the prolonged exercise. Increased apoptosis of lymphocytes might be a probable reason for this post-exercise decline of lymphocytes (JW, DA, & KS, 2007).

Effect of acute exercise on lymphocyte function: Acute bout of exercise can alter the leukocyte subpopulation counts. The neutrophil count increases during the exercise and it continues to rise even in post-exercise condition, however, the lymphocyte kinetics differs from this. The concentration of lymphocytes increases initially during the exercise but declines below the baseline values after intense long-duration exercise. The initial rise in lymphocyte concentration might be due to the release of all lymphocyte subpopulations into the blood and the decline after intense exercise is considered to be due to the suppression of the functions of NK and B cells. Higher apoptosis percentage of lymphocytes also observed immediately after the high-intensity exercises. (Terra, da Silva, Pinto, & Dutra, 2012).

Interleukin-6/ (IL-6): IL-6 is also known as cytokine gp130 which is being considered as an inflammation responsive cytokine. Cytokines are small glycoproteins that play an essential role in the regulation of immunological responses. They act as an envoy between the cells of hematopoietic, neuroendocrine and immune systems. Based on their method of action cytokines have been categorized into two types; pro-inflammatory and anti-inflammatory cytokines. Because of its pro and anti-inflammatory properties, IL-6 is widely employed as a diagnostic marker in clinical practice. Exercise not only influences the immune-neuroendocrine axis but also brings changes in the circulating levels of metabolites which directly influence the immune cells. Muscle/tissue damage that occurs during the strenuous or prolonged exercise can induce an inflammatory response and this is predominantly mediated by secretion of pro-inflammatory cytokines/chemokines and other mediators of inflammation. Till date, many authors have reported on the exercise-induced cytokine surge into the serum after different types of exercises. Although exercise could increase the plasma concentration of several other cytokines, IL-6 levels mount rapidly than any other cytokine after the exercise. The normal range of plasma IL-6 concentration is ~1pg/ml or even lower in healthy subjects during rest, but it may increase up to 100 folds immediately after the exercise. The extent of increase in IL-6 levels is influenced by the mode, intensity and duration of the exercise. However, the duration of exercise is the most deciding factor to manipulate the IL-6 response. Impaired glucose availability, altered muscle calcium levels, and augmented formation of reactive oxygen species (ROS) that result as a consequence of exercise are the key factors which induce the transcription factors of IL-6 gene expression in contracting skeletal muscle. Some studies have found that the resting basal plasma IL-6 levels in the physically active population are lower than that of the sedentary group. This can be due to the multiple adaptations that take place during the exercise training like the low dependency of trained muscle on plasma glucose and muscle glycogen and increased utilization of intramuscular triglycerides and free fatty acids as a fuel during the exercise.

Weightlifting training: Weightlifting otherwise known as Olympic weightlifting is an athletic discipline in which the athletes attempt to lift weights mounted on barbells to over the head. Weightlifting comprises two types of lifts, the clean and jerk, and the snatch. The clean and jerk is a two-move lift with a close grip and the snatch is a one-move lift with a wide-grip. Bodyweight categories are different for male and female competitors. At present, there are eight weight categories for men and seven for women. Basically, weightlifting exercises engage each and every muscle in the human body and the lifts performed in weightlifting are often used as a favourable tool for developing explosive and functional strength in athletes. Previous researches have shown that the resistance exercises of moderate-intensity may induce a light systemic inflammatory response, which is characterized by increases in the serum levels of inflammatory cytokines, such as IL-1 β and TNF- α (Drenth, Krebbers, Bijzet, & Van Der Meer, 1998; Moldoveanu, Shephard, & Shek, 2017) and this may provide protection against the infection particularly caused by intracellular organisms. Investigations made by Kohm AP et al., 2000; Timmins BW et al., 2008; Shimizu K et al., 2008, have shown that the practice of moderate exercises induces type-1 T helper cells to respond by producing pro-inflammatory cytokines (Kohm & Sanders, 2000; Shimizu et al., 2008; Terra et al., 2012; Timmons & Cieslak, 2008). On the contrary, the high-intensity exercise increases the levels of anti-inflammatory cytokines in order to prevent the inflammatory induced muscle damage and this makes the athletes more vulnerable to infectious diseases.

Weight lifting exercise session: For this study, participants were asked to practice snatch, clean and jerk and back squat exercises with 75% relative intensity. The detailed exercise protocol is as follows.

Gender	Male			Female		
No. of exercises	3			3		
Exercise type	Snatch	Clean & jerk	Back squat	Snatch	Clean & jerk	Back squat
No. reps per set	3-5	3-5	3-5	3-5	3-5	3-5
No. sets	1-6	1-5	1-3	1-4	1-5	1-3
Rest interval (min)	3-5	3-5	2-5	3-5	3-5	2-5
Total Load Volume in kg (Mean $\pm$ SD)	7733 $\pm$ 417	2678 $\pm$ 334	1825 $\pm$ 422	6192 $\pm$ 3078	2706 $\pm$ 1681	1941 $\pm$ 1077
Speed of execution	Medium					

The main objective of our study was to monitor the instantaneous effect of weight lifting training session on the leukocyte counts and IL-6 levels in trained weight lifters.

Material and methods:-

Participants: 13 National level weightlifters (5 male and 8 female) aged 19 ± 3.09 years with 3.4 ± 2.4 years of weight lifting specific training experience were recruited for this study from Sports Authority of India, Bengaluru. The details regarding the health status, history of muscle injuries, hospitalization, medication, and supplementary usage were obtained through the questionnaires. Written informed consent was obtained from all the participants after explaining the procedure and purpose of the study.

Specimen collection and assay: Blood samples were collected before and after the weightlifting training sessions. Samples were collected from the participants in a seated position from the antecubital vein into plain evacuated tubes. All the participants were refrained from training 24 hours prior to the sample collection (Pre-exercise) to avoid acute exercise-induced shifts in plasma volume. After the collection, an aliquot of each sample was immediately mixed with EDTA solution to prevent clotting for hematology. The rest of the sample was collected in a plain tube with a clot activator. Following clotting, the sample is centrifuged at 1000 g for 10 minutes to separate the serum for IL-6 analysis. IL-6 levels were analyzed by using Human IL-6 ELISA kit by Diaclone, France.

Hematological parameter (Complete Blood Count): Anticoagulated whole blood samples collected in EDTA tubes were analyzed in Sysmex –Poch100i^{TM} automated hematology analyzer (Japan) to measure the complete blood cell count and differential leukocyte count and their percentages. The absolute neutrophil count was divided by the absolute lymphocyte count to calculate Neutrophil Lymphocyte ratio (NLR)

Statistical Analysis

The numerical data obtained were analyzed by using SPSS software (version 23.0). All values are expressed in mean $\pm$ standard deviation. The paired t-test was used for the statistical analysis. Statistical significance was set at $P < 0.05$. Hedge's g (unbiased) effect size also calculated between pre and post-tests to measure the magnitude of the effect of the training session.

Table 1: Basic details of Weightlifters

Variable	Mean $\pm$ SD
Age (years)	19.02 ± 3.09
Height (cm)	156.66 ± 12.96
Weight(Kg)	66.96 ± 19.82
Training experience(years)	3.4 ± 2.43

Table 2: Leukocyte differential count and IL-6 levels before and after the weightlifting exercise session

Parameter	Pre-exercise	Post-exercise
WBC (10^9 cells/L)	8.17 ± 2.34	7.87 ± 1.82
Lymphocytes (%)	38.17 ± 9.98	$29.53 \pm 5.95^{**}$
Neutrophil (%)	50.06 ± 12.15	$59.7 \pm 7.8^{**}$
Mixed cells (%)	11.75 ± 4.55	10.76 ± 3.54
Absolute Lymphocytes (10^9 cells/L)	3.06 ± 0.95	$2.29 \pm 0.52^{**}$
Absolute Neutrophils (10^9 cells/L)	4.17 ± 1.77	$4.75 \pm 1.35^*$
Absolute count of Mixed cells (10^9 cells/L)	0.95 ± 0.42	0.83 ± 0.34
Interleukin -6 (pg/ml)	2.99 ± 1.51	$7.51 \pm 4.50^{**}$
NLR	1.46 ± 0.64	$2.15 \pm 0.69^{**}$

Data presented as Mean $\pm$ SD, n=13. *=significant ($P < 0.05$), **=highly Significant ($p < 0.01$) when compared to baseline data.

Table 3: Paired t-test of WBC subsets and interleukin-6

Parameter	95% Confidence Interval of the Difference		T	Df	Sig (2-tailed)	Effect size
	Lower	Upper				
WBC (10^9 cells/L)	-4.751	1.0751	0.843	12	0.416	0.139
Lymphocytes (%)	4.5252	12.7672	4.571	12	0.001**	1.018
Neutrophil (%)	-14.3264	-4.9352	-4.469	12	0.001**	0.914
Mixed cells (%)	-0.6065	2.5758	1.348	12	0.202	0.235
Absolute Lymphocytes(10^9 cells/L)	0.3552	1.1986	4.014	12	0.002**	0.974
Absolute Neutrophils (10^9 cells/L)	-1.1444	-.0094	-2.215	12	0.047*	0.357
Absolute Mixed cells (10^9 cells/L)	-0.0232	0.2693	1.833	12	0.092	0.304
Interleukin -6 (IL-6)	-7.24837	-1.78086	-3.598	12	0.004**	1.304
N/L Ratio	-1.01527	-0.37088	-4.687	12	0.001**	1.004

Data presented as Mean $\pm$ SD, n=13. *=significant ($P < 0.05$), **=highly Significant ($p < 0.01$) when compared to baseline data.

Results:

The mean and standard deviation of age, height, weight and training experience are shown in Table-1. The Mean $\pm$ SD values, Paired t-test results of total leukocyte count, differential leukocyte count, NLR, and IL-6 levels before and after the training session were shown in Table-2 & 3 respectively.

A significant increase was observed in absolute neutrophil count and neutrophil percentage after the training session with a significant reduction in absolute lymphocyte count and percentage. Consequently, a significant increase is seen in NLR but no significant change was observed in total leukocyte count after the training session. IL-6 levels are significantly increased ($P < 0.01$) after the training session.

Figure-1 depicts the leukocyte subset mean values before and after the exercise session.

Pre and post-exercise values of IL-6 and NLR have been depicted in Figure-2 & 3 respectively.

Discussion:

Regular physical exercise may help to boost immunity and to develop resistance against many microbial infections. Many studies have shown that moderate exercise facilitates and enhances immunity. On the contrary, high-intensity exhaustive exercise can lead to reduced immunity with more incidences of infections. ISEI also stated that immune dysfunction is commonly observed after Prolonged, high-intensity exercise (Wesslen et al., 1996). So exercise intensity and volume play an important role in immunological changes that take place after the exercise.

The main findings of our study were 1) high-intensity weight lifting exercise caused a significant rise in neutrophil count and decline in lymphocyte count immediately after exercise 2) As a consequence of this NLR is increased immediately after exercise 3) post-exercise IL-6 levels are higher than the pre-exercise values. Many studies have mentioned the post-exercise neutrophilia earlier, the main cause stated for this is the mobilization of immunocompetent cells into the circulation during intense long-duration exercise. Thus both the neutrophils and all lymphocyte subpopulations are recruited to the blood circulation during the exercise. However, after the strenuous exercise, lymphocyte count starts declining below the base level and the neutrophil count continues to rise. The decline of lymphocytes after intense long-duration exercise might be due to the suppression of functions of Natural killer (NK) and B- cells (Pendersen & Toft, 2000). Another possible cause for decrease lymphocyte concentration during post-exercise might be the increased lymphocyte apoptosis (JW et al., 2007). Wang and Huang have found that the intense exercise could result in a decline in the glutathione concentration (GSH) of lymphocytes; this subsequently induces the apoptosis due to enhanced oxidative stress. According to the study done by Wang and Huang, heavy exercise induces lymphocyte apoptosis by escalating the active caspases like 8, 9 & 3 and by enhancing the DNA fragmentation (Wang & Huang, 2005). However moderate-intensity exercise helps to improve the intracellular anti-oxidative capacity and attenuates the lymphocyte apoptosis.

Catecholamine-mediated leukocytosis: In 1926 Mora et.al, Amtmann, & Hoffmann, have found the effects of psychological states on leukocyte levels. In their study, they noticed a relationship between emotional state and leukocyte count. According to their study report, more prominent leukocytosis was observed in the subjects with strong emotions prior to operation when compared to the patients who can well tolerate the preoperative stress (MORA, AMTMAN, & HOFFMAN, 1926). Later many studies were published regarding the effects of acute psychological stress on the cellular immune system of humans and shown that acute psychological stress could cause a momentary increase in leukocyte count through the mediation of adrenaline. Pronounced leukocytosis after a subcutaneous injection of adrenaline in humans was first illustrated by Loeper and Crouzon. Frey in 1914 reported that the adrenaline injection induces a biphasic response in both animals and humans. The first phase of the leukocytosis that lasts about 30 min was predominantly due to an increase in lymphocyte numbers and in the second phase, an increase in granulocyte count was observed (Walter, 1914). These observations were confirmed later by Hatiegan and Hess. Around the same time, some studies (Grawitz, 1910; Garrey & Butler, 1929) found that the pattern of changes observed in leukocyte levels after physical exercise is almost similar to the changes noticed after adrenaline administration, so it was hypothesized that these exercise-induced effects were due to endogenous adrenaline production (Martin, 1932) (Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996). Adrenaline is known to induce these changes in lymphocyte count via activation of β_2 -adrenoceptors, whereas granulocyte augments involve α -adrenoceptor stimulation.

Interleukin -6: IL-6 is a pleiotropic cytokine produced by a variety of cells that includes T cells, macrophages, fibroblasts and stromal cells in the bone marrow. It acts on a wide range of tissues and mediates a wide variety of biological activities (CONTENT *et al.*, 2005; Donna, 2019). Many studies have shown the augmentation of IL-6 levels after the exercise and this is thought to be due to the increased secretion of IL-6 from skeletal muscle. Bruunsgaard et al compared the concentric and eccentric ergometer bicycle exercise and found that the increase in IL-6 level is related to muscle damage. IL-6 levels are increased more during the eccentric exercise, and a significant association was found between peak IL-6 and peak creatine kinase on the subsequent days ($r = 0.722$; $p = 0.028$). (Bruunsgaard et al., 1997). In our study, post-exercise IL-6 levels are significantly high ($p < 0.01$) compared to the Pre-exercise IL-6 values. This can be probably due to the exercise-

induced release of IL-6 from the muscle cells i.e. mediated through the epinephrine and norepinephrine. Helge et al found that the exercise intensity, arterial adrenaline concentration, and muscle glucose uptake can positively influence the release of IL-6 from human muscle (Helge et al., 2003) and study by Yang et al found that norepinephrine stimulation increases IL-6 protein in human gastric epithelial cells (Yang, Lin, Gao, & Zhang, 2014). IL-6 produced by stromal cells of bone marrow induces the proliferation and differentiation of hematopoietic cells apart from this the IL-6 produced from other sources also can show an intense effect on the production and the kinetics of neutrophils after releasing into the systemic circulation. (HOGG *et al.*, 2013)

Conclusion:

From all our findings it is concluded that the high-intensity weightlifting training could elicit a significant increase in Neutrophil and IL-6 levels immediately after the exercise. However, lymphocyte counts are reduced significantly after the exercise. The increased neutrophil count might be due to the release of catecholamines during the exercise and a decline in lymphocyte count might be due to exercise-induced apoptosis. However further research is required to understand the source of IL-6 production during exercise and whether its expression is mediated through the catecholamines. The accountability of IL-6 in the post-exercise kinetics of leukocyte subsets also needs further understanding.

Figure-1: Pre and Post-exercise Leukocyte counts

Figure-2: Pre and Post-exercise IL-6 levels

Figure-3: Pre and Post-exercise NLR

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