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Original Article

The Combined Effects of Eccentric Resistance Training and Blood Flow Restriction on the Level of Interleukin 15 and Tumor necrosis factor-alpha on Non-Athletes

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Abstract

Background: The present study aimed to determine the effect of a session eccentric resistance exercise with and without blood flow restriction on Interleukin 15 and Tumor necrosis factor-alpha in nonathlete People.

Methods: In a crossover research design, 36 male non-athletes (with an average mean of 25± 2.9 age, 22± 1.39 kg/m2 mass body index) were asked to participate in the study randomly. The exercise consisted of one lower limb resistance session and one set until exhaustion. The exercise consisted of one lower limb resistance session and one set until exhaustion. The exercise intensity in each group was 30% of One Repetition Maximum Respectively. The blood flow Restriction was done by the proximal pressure gauge on the thigh. The blood samples were taken 48 hours before the test. The blood samples were analyzed to determine Interleukin 15 and Tumor necrosis factor-alpha. The statistical analysis was examined based on the study's objectives through descriptive statistics, correlative, and independent tests(P=0.05).

Results: The result showed there is a meaningful increase in Interleukin 15 after one session of eccentric resistance exercise accompanied by blood flow(P=0.000), but in comparison to the control group, the Tumor necrosis factor-alpha in the experiment group showed a meaningful decrease (P=0.000).

Conclusion: It seems low-intensity eccentric resistance exercise for one session accompanied by blood flow Restriction could have an appropriate effect on the discharge rate of muscle growth factor and a decrease in inflammatory factors derived from physical activity.

Keywords: Eccentric resistance exercise, Interleukin 15, Training with Blood Flow restriction, Tumor necrosis factor.

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Introduction

Resistance training has experienced a surge in popularity, particularly over the last two decades. These exercises help improve the performance of athletes by increasing strength, potency, speed, endurance, hypertrophy, balance, and coordination(1). Resistance training with high intensity significantly increases muscle strength and muscle mass. As per recommendations from the American College of Sports Medicine (ACSM), achieving an increase in muscle mass and strength necessitates performing exercises at an intensity of at least. 70% of one repetition maximum (1RM), with training below this threshold seldom resulting in notable muscle growth(2).Moreover, resistance training conducted at lower intensities (20- 50%), can also foster muscle development and strength when combined with blood flow restriction(2). katsu method effectively enhances athletes' performance by constricting blood flow using suitable occlusion devices during resistance, endurance, or a combination of training sessions. This training method is performed with low. This blocker is usually created by tying a light, flexible elastic above the upper arm or thigh. Numerous mechanisms have been proposed to elucidate muscle adaptations following the Katsu method, including increased recruitment of Fast-twitch muscle fibers in hypoxia conditions(2, 3), generation of Reactive oxygen species (ROS) such as Nitric oxide(4), heightened release of catecholamine and Growth hormones due to anaerobic metabolism and lactate accumulation (5, 6), elevation in protein synthesis leading to hypertrophy(3), augmentation of heat shock protein levels (7), Muscle cell swelling, and intricate Cell signaling pathways (8, 9). Despite the resistance training with blood flow restriction, diminished blood flow induces peripheral and ischemic hypoxia, amplifying the impact of exercise on the targeted muscle and ultimately contributing to enhanced muscle mass and strength (10, 11). Two pivotal factors influencing muscle growth are metabolic stress and mechanical tension. Muscle growth is achieved by activating Autocrine (stimulation of protein synthesis via signaling pathways of anabolic increase or catabolic decrease) and Paracrine (for example, increased activation, satellite cell Proliferation, and satellite cell fusion). It is thought that these two primary mechanisms can affect secondary mechanisms, and by stimulation of protein synthesis (autocrine) Along with satellite-cell activation (paracrine), they can be the cause of muscle hypertrophy(12). One of the mediators released by immune cells and muscle cells are cytokines, which play an important role in regulating the development and behavior of their target cells. Cytokines are glycosylated polypeptides that are released by many cells in the body (13). One of the effects of cytokines is the activation and proliferation of satellite cells following exercise (14). Interleukin 15 is a cytokine highly expressed in skeletal muscle tissue and can cause muscle hypertrophy as an anabolic factor(15). Studies have found that during muscle hypertrophy, mRNA expresses interleukin 15 in skeletal muscles and interleukin-15 protein is produced and secreted in these muscles, which helps to increase muscle. Glycogen through mechanisms such as (Myosin heavy chain (MHC) accumulation and Adhesion, stimulation of protein synthesis and protein degradation rates, Glucose transfer into muscle fibers by increasing the glucose transporter(GLUT4) activity in the membrane of these cells.) and also , preventing the apoptosis process in muscle fibers causes muscle hypertrophy (16, 17). Bezgir et al.(17) investigated the impact of eccentric and concentric exercises with emphasis on strength exercises on the Serum levels of interleukin-15 and their correlation with Inflammatory indicators (CRP & TNFα) in both athletes an non-athletes. The findings revealed a significant disparity in interleukin-15 levels among non-athletes before and after each exercise type; but in athletes, it showed a significant increase only after eccentric exercises. The interesting thing is that at the highest serum level of interleukin-15 , the level of CRP has significantly decreased in athletes and The levels of CRP and TNF-α have significantly decreased after eccentric exercises in non-athletes. The results show that the level of preparation of people in resistance training can balancing blood circulation and also it can have a potential effect on indicator of anti inflammatory during resistance training. however The regulatory role of muscle contraction in relation to interleukin15 as a Myokine has not been fully defined yet(18). While numerous cytokines exist , certain ones may offer a more precise assessment of muscle damage induced by physical activity in response to resistance training with blood flow restriction (19). inflammatory Markers serve as direct indicators of this phenomenon (17). Although some studies have reported that low-intensity resistance training with blood flow restriction causes a gradual increase in tumor necrosis factor alpha (TNF-α). However, the magnitude of this effect appears minimal. But maybe the resulting values suggest that only training with high mechanical stress can cause enough muscle damage to produce cytokines and thereafter create compensatory muscle growth. Therefore, Inresistance exercise with blood flow restriction , muscle damage may not happen, which is due to the low intensity of this type of resistance exercises (10). Thiebaud et al. (20) investigated the impact of low-intensity concentric and eccentric exercises with blood flow restriction of exercise-induced muscle damage and pain. Contrary to the prevailing notion of significant muscle fiber enlargement following low-intensity exercise with blood flow restriction; but with the violation that the amount of muscle damage during these exercises was low and this issue is not compatible with studies that consider muscle damage as one of the important and effective responses in resistance exercises. The results obtained are summarized as follows: The maximum voluntary contraction force for concentric exercise with blood flow restriction decreased by 36% and for eccentric exercise with blood flow restriction by 12% immediately after the exercise, However, these changes were transient, with no significant alterations observed one to four days post-exercise. Additionally, Only concentric exercises with blood flow restriction, demonstrated an immediate increase in muscle thickness, while muscle pain persisted up to two days post-eccentric exercise, possibly indicative of injury resulting from such workouts. In the research carried out by Eisuke et al. (20) they investigated the effect of muscle hypertrophy and changes in the production of cytokines after Eccentric exercises in mouse skeletal muscle, With the isokinetic device .The results revealed a significant increase in interleukin-6 levels across both groups, while TNF-α and interleukin-10 remained unchanged. Net muscle weight increased significantly after 10-Eccentric exercise sessions (4Sets and 5- Reps); While in the first five training sessions, with the same program, no significant effect was observed. Probably, decreases the levels of TNF-α is related to the increased levels of interleukin-6 produced by muscles. More studies are needed to investigate the unknown effects of this training method. In this regard, This research seeks to answer the question that, Is there a difference between resistance training with blood flow restriction and without blood flow restriction on growth factors and muscle damage in terms of mechanical stress caused by training.

Material and method

This research was semi-experimental, and the research design used pre-tests and post-tests. After the Confirmation of the research plan by the postgraduate education committee, the participants in this research were selected from physical education students with an age range of 25±5 years, and 36 subjects were randomly selected in two groups of 18 people; they extroverted resistance training with blood flow restriction, and The other group was exposed to extroverted resistance training without restrictions. The subjects were healthy and free of any infectious and immune diseases, neuromuscular diseases (such as dystrophy, cachexia), inflammatory diseases, cardiovascular diseases, hormonal diseases, obesity, and blood pressure, and none of them were treated with medicine such as anabolic hormones, nutritional supplements (acid amines, creatine, antioxidants, multivitamins, and anti-inflammatory medicine, muscle damage, and colds). After providing the necessary information to the subjects about the research steps, the health and satisfaction questionnaire form was taken from them. In addition, the subjects' anthropometric characteristics, including height, weight, body mass index, and body fat mass, were measured. After familiarizing myself with the exercise program and ensuring that there were no muscle cramps, a maximum repetition was performed for all subjects in the knee extension movement to determine the intensity of the exercise. Also, blood was taken 48 hours before the test and fasting, and immediately after the test, blood was taken from the medial vein in the amount of five cc. After about 20-30 minutes at room temperature, the samples were separated from their serum and plasma by a centrifuge for 15 minutes at a speed of 3500 rpm and then kept in a freezer with a temperature of minus 80 degrees until the measurement time.

Measurement of interleukin 15 was carried out with a Korea Koma ELISA kit, using the ELISA method, and in picograms per milliliter (pg/ml). The measurement of TNF-α was done with the China Biotech kit and by the ELISA method and in picograms (pg/ml) in the laboratory. An extrovert resistance training session involved performing the knee extension movement up to the limit using the ISO Kinetic device with an intensity of 30% maximum repetition and a speed of 30 degrees per second. The specifications of the training program are presented in table 1.

Table number one - specifications of eccentric resistance training program

	Number of sessions	Number of sets	Number of repetitions	Exercise pressure	Execution speed	Limit pressure
Experimental group	A meeting	a set	70 repetitions	30% of 1RM	30 degrees per second	120 millimeters of mercury
control group	A meeting	a set	70 repetitions	30% of 1RM	30 degrees per second	

The blood flow was blocked using an air sphygmomanometer with a tape greater than five centimeters thick and a pressure of about 110-120 mm Hg in the proximal part of the thigh. After collecting the data, appropriate statistical methods were used based on the goals and research questions. Data analysis was used to compare between groups from descriptive statistics (mean and standard deviation) for the central indicators related to the subjects' general characteristics and from inferential statistics (correlated t-test and independent t-test) for intra-group comparison of the correlated t-test and independent t-test. Kolmogorov-Smirnov test was used to determine the normality of data distribution, and SPSS21 software was used for data analysis.

Results

In Table number two, the Central tendency related to the General characteristics of the study subjects, the experimental group (eccentric resistance exercise with blood flow restriction) and the control group (eccentric resistance exercise), including age, height, weight, fat percentage, and body mass index are presented Table 2.

Table number two - the results of the descriptive statistics of the anthropometric variables of the subjects

Variable	Group	Average	The standard deviation
age (years)	Experimental group	26/6	2/9
	control group	26/9	2/9
height (cm)	Experimental group	174/16	5/22
	control group	175/50	5/01
weight (kg)	Experimental group	67/31	3/04
	control group	73/08	5/28
body mass index (kg/m2)	Experimental group	22/27	1/39
	control group	23/70	0/86
fat percentage	Experimental group	9/92	1/38
	control group	11/87	2/51

Table number two - the results of the descriptive statistics of the anthropometric variables of the subjects

Variable	**group**	**pre-exam**		**After the test**		**t statistic**	**Degrees of freedom**	**probability value**
		average	standard deviation	average	standard deviation			
IL-15 (picograms per milliliter)	Experimental	12/45	1/01	13/83	1/16	-13/59	17	0/000
	Control	12/29	1/59	12/70	1/66	-10/06	17	0/000
TNFα (picograms per milliliter)	Experimental	24/22	0/79	22/39	0/94	11/32	17	0/00
	Control	24/31	0/79	25/15	0/78	-11/73	17	0/00

Descriptive statistics results of anthropometric variables of subjects in table number three, the results of the correlated t-test are presented in order to compare the average level of interleukin 15 and TNF-α before and after the test in the groups.

According to the P-value observed in the intra-group, the level of interleukin-15 in the experimental and control groups (P=0.00) is lower than the value (P=0.05), so the difference between the average level of interleukin-15 in the pre-test and post-test in both groups is significant. Also, the p-value that observed intra-group level of TNF-α in the experimental and control groups (P=0.00) is lower than (P=0.05), so the difference in the mean level of TNF-α in the pre-test and post-test of both experimental and control groups is significant.

Inter-group comparison of IL-15 and TNFα levels in subjects of two groups According to the comparison of the average difference between the pre-test and post-test interleukin 15 levels between the two experimental and control groups and the lower P-value observed (P=0.000), The difference between the two experimental and control groups is significant, and it can be said that the average level of interleukin 15 is not the same between the two experimental and control groups. Therefore, an eccentric resistance training session with blood flow restriction affects the level of interleukin 15 in non-athletes immediately after training and increases the level of interleukin 15. Also, comparing the average difference between the pre-test and post-test levels of TNF-α between the two experimental and control groups and the lower P-value observed (P=0.000), the difference between the two experimental and control groups is significant, and it can be said that the average level of

TNF-α between the two groups Experimental and control are not the same. Therefore, an eccentric resistance training session with blood flow restriction affects the level of TNF-α in non-athletes immediately after training and causes a decrease in the level of TNF-α.

Discussion

This study aims to determine the simultaneous effect of an eccentric resistance training session with blood flow restriction on changes in the concentration of interleukin 15 and tumor necrosis factor-alpha in non-athletic men. The tension applied to the motor units during eccentric contractions causes increased damage to Z lines and sarcomeric structure. This damage is caused by increased stress on the motor units due to reduced call during eccentric contractions(21). Fluids and plasma proteins and the proliferation of inflammatory cells in the injured area initiate inflammatory responses. The plethora of these cells increases muscle damage by releasing reactive oxygen species, xenophagy, and proteolytic enzymes. On the other hand, they accelerate repairing damaged tissue(21). A series of events known as the inflammatory response occurs in response to tissue damage or infection. The short-term inflammatory response is activated in the early stages of injury and initiates a pathway leading to damaged tissue repair (22). Inflammatory cytokines TNF-α balance the function of immune cells and their migration. During local inflammatory responses, all three of these cytokines increase vascular permeability, which also causes swelling and redness in inflammation. Consequently, mediators of inflammation and chemokines act as a set; This causes physiological responses to a set of stimuli. Acute inflammatory responses develop and increase rapidly and remain for a short period. TNF-α can initiate and strengthen acute phase reactions and stress and cause heat generation. Therefore, they are released at the site of inflammation caused by pathogens or tissue damage and facilitate the entry of neutrophils, monocytes, and other cells involved in antigen purification and cause tissue healing(23). It has been found that muscular exercise increases the level of some plasma cytokines(24). It can be said that the effect of low-intensity resistance training and blood flow restriction on the level of TNF-α immediately after the training showed a significant decrease, which was considerably different compared to the control group. Also, the average level of TNF-α is not the same between the two experimental and control groups, and as a result, an eccentric resistance training session with blood flow restriction immediately after exercise reduces TNF-α levels in non-athletes. This is consistent with the results of some studies and ineffective with others. Isuke et al. (21) used an isokinetic device to study the effect of muscle hypertrophy and the changes in cytokine production after eccentric exercises in the skeletal muscle of mice. The results showed that net muscle weight increased significantly after 10 eccentric exercise sessions (4-Sets and 5-Reps), while no significant effect was observed in the first five training sessions with the same program. Interleukin 6 was significantly increased in both groups, while TNF-α and interleukin-10 remained unchanged. An increase in the level of interleukin-6 and exercise stress can reduce TNF-α. In a research study, researchers investigated the effect of eccentric and concentric exercises with emphasis on strength exercises on the serum Serum interleukin-15 levels and its relationship with inflammatory indices (CRP and TNF_α) in athletes and non-athletes. The results showed a significant difference in the amount of interleukin 15 in non-athletes, which was obvious before and after each type of exercise, but in athletes, it increased only after eccentric exercises. Interesting point is that at the highest Serum interleukin-15 levels , the level of CRP has significantly decreased in athletes. The amount of CRP and TNF-α decreased significantly in non-athletes after eccentric exercises. The results show that the level of preparation of people in resistance training can modulate circulating levels of interleukin 15 in blood and have a potential effect on anti-inflammatory indicators during resistance training (17). A study conducted by Toufighi et al. (25) investigated the effect of resistance training sessions on the hormonal and inflammatory responses of men and women. The samples were taken immediately and two hours after training. As a result, interleukin 6 and testosterone significantly differed in both groups. However, no significant difference was seen in TNF_α and cortisol. Probably, the increase in the amount of interleukin-6 that production from muscle tissue caused TNF-α suppression, and it also justifies the effectiveness of exercise, Stimulation, and the production of cytokines that cause muscle growth. Most of these proteins have anti-inflammatory properties (25). Interleukin-6 directly restrains the expression of TNF-α. This antagonist performs its antiinflammatory activity by restraining the interleukin-1 receptor, preventing the transmission of pro-inflammatory interleukin (IL)-1 message. Also, the increase of interleukin-15 that occurs through macrophages suppresses TNF-α. However, less muscle damage occurs due to the nature of low-intensity resistance training with blood flow restriction, low stress, and high metabolism. This significant decrease in this research can also follow this occurrence. So, if the increase in TNF-α level in training without blood flow restriction can be directly related to the nature of eccentric resistance training and muscle damage; As a result, it is suggested that the Mechanisms involved and previous contradictions, which are the result of the type, intensity, and duration of the sports activity used and the time of blood sampling, should be further investigated. One of the effects of mechanical and metabolic stress of resistance training with blood flow limitation is the production of cytokines by muscle (myokines), which have autocrine and paracrine roles(25) (14). One of the effects of myokines is the activation and proliferation of satellite cells after training(14). Myokines facilitate cellular responses to exercise, such as suppressing Proteolytic, angiogenesis, and regulation of muscle glycogen. Identifying skeletal muscle as a cytokine-producing organ led to the discovery that cytokines released from muscle are not only related to exercise-related changes but also mediators for metabolic changes related to exercise and metabolic changes following training adaptations. Another significant point recently noticed about myokines is their effects on skeletal muscle hypertrophy following resistance training. Interleukin-15 is a cytokine highly expressed in skeletal muscle tissue, which can cause muscle hypertrophy as an anabolic factor(15). Like an endocrine gland, skeletal muscle produces and releases myokines in response to muscle contraction, which can affect metabolism and other organs. Scientific evidence shows that interleukin-15 plays an important role in muscle hypertrophy and has been introduced as a factor in the growth and hypertrophy of skeletal muscles. In relation to the effect of low-intensity resistance training with blood flow restriction on the level of interleukin-15 immediately after training, it can be said that its level showed a significant increase ($P=0.000$) compared to the control group, this is consistent with the results of some studies and ineffective with others. In a study, Bezgir et al. (17). investigated the effect of eccentric and concentric exercises with emphasis on strength exercises on the Serum interleukin-15 levels and its relationship with inflammatory indices (CRP and TNF-α) in athletes and non-athletes. The results showed a significant difference in the level of interleukin 15 in nonathletes, which was evident before and after both types of training, but in athletes, it increased only after eccentric training. Interestingly, at the highest serum interleukin 15 in athletes, the level of CRP decreased significantly. In non-athletes, the amount of CRP and TNF-α decreased significantly after eccentric exercises.The results show that levels of preparation in resistance training can modulate the circulating levels of interleukin 15 in the blood and potentially affect anti-inflammatory indicators during resistance training. Nielson et al. (26) investigated the effect of heavy and high-intensity resistance training on interleukin 15 in young men. The data reveals that, within a 24-hour timeframe post-training and during the reversion to the initial state, there was a twofold escalation in interleukin 15 mRNA levels. The mechanism of this increase probably explains the body's immune system's response to waste and inflammatory substances. Muscle damage caused by exercise is higher in the first 24 hours after exercise, and the immune system tries to remove waste and inflammatory substances; therefore, This cytokine is increased for changes in the immune system to eliminate inflammatory agents. On the other hand, after exercise, Due to the elimination of inflammatory factors and reduction of inflammation, it has been adjusted to the pre-exercise amount. Riechman et al.(27) conducted research with 153 participants who had no history of illness and received a normal diet. They did weight training for ten weeks. The results showed that the plasma concentration of interleukin 15 after the first session was significantly higher than in the last. The difference between the present research and Richman et al.'s research is probably due to the individual characteristics of the subjects, nutrition, type of exercise program, and measurement methods. In this way, some studies show the ineffectiveness of the or nonincrease of interleukin 15 after exercise. Louise et al. (28). In a research study, tissue samples were taken from the broad muscle of six subjects with an average age of 25. These people performed weight training twice a week, with three sets and ten repetitions in each set, with 70% (1RM), using the Cybex machine. There was no significant difference in interleukin 15 mRNA of these people. Also, in this study, the plasma levels of this cytokine did not increase after exercise, which probably means that the exercise activity was ineffective. In earlier studies, this cytokine's plasma levels probably changed in response to high-intensity resistance training. the intensity and duration of the training program of this research were enough for the skeletal muscles in the secretion of interleukin 15. Several mechanisms have been proposed to produce the double effect of low-pressure resistance training with blood flow restriction, increased calling of the Fast-twitch muscle fibers in hypoxia conditions (2, 3), creating Reactive oxygen species (ROS) Including Nitric Oxide (4), Increase in protein synthesis and hypertrophy (3), Increase heat shock protein (7), and muscle cell swelling and cell signaling (8, 9). The effect of nitric oxide in the production and stimulation of cytokines is one of the essential reasons for the release of cytokines from skeletal muscle. Environmental hypoxia probably expands the effect of exercise on muscle and leads to the production and stimulation of influential factors in muscle growth. With the release of nitric oxide, a cascade of cytokines, such as interleukin 15, is released to modulate macrophage functions and, stimulate another effect of this cytokine in the immune system, as follows: Production and survival of T and B lymphocytes, natural killer cell growth, development and proliferation, Inhibition of T lymphocytes apoptosis , Proliferation and activation of interferon gamma, Synthesis of antibodies, interaction between Monocyte– macrophage and granulocytes system, stimulation of M, G1, A immunoglobulins production and also Blocking the function of tumor necrosis factor alpha (TNF-α) (15). It has been shown that an eccentric resistance training session causes myokines' release and stimulates cell proliferation (29, 30). After all, considering the few studies on this new scientific topic, more studies are suggested. This research showed that the blood variables studied, including interleukin 15 and tumor necrosis factor-alpha, increased and decreased in non-athletes responding to low-intensity resistance activities with blood flow restriction. All the results of this research indicate that this type o exercise is more effective and better than similar resistance exercises without blood flow restriction. In general, it can be concluded that Sports activities, especially low-intensity resistance exercises , if performed along with blood flow restriction, can be effective in stimulating the known factor in muscle growth and reducing the known factor of inflammation and muscle damage caused by physical activity. This study had some limitations ; which included failure to control possible stress and anxiety caused by blood sampling in subjects out of control of the nutritional status of the subjects before the test and lack of control of the plasma volume in the subjects.

Conclusion

The results of this research can be a way for coaches to design short-term exercises to increase.

Muscle hypertrophy reduces muscle damage, accelerates rehabilitation, protects athletes, and increases their performance level.

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