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Original Article

The Effect of 12 Weeks of Compound Set Training on Cardiotrophin-1 and Platelet Levels and Their Relationship in Young Male Bodybuilders

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Abstract

Background: Cardiotrophin-1 (CT-1) and platelets (PLA) have an important role in heart disorders of athletes, and training is believed to affect these two parameters. Accordingly, this study investigated the effect of 12 weeks of compound set training on CT-1 and PLA and their relationship in active young males.

Methods: In this semi-experimental study, subjects included 30 active male bodybuilders in Ardabil who were randomly assigned to exercise (n = 15) and control (n = 15) groups after matching height, weight, body mass index (BMI), maximal oxygen uptake, and one-repetition maximum (1-RM). They performed 12 weeks of compound training (three 60-minute weekly sessions), 15 seconds at each station with 40%–60% 1-RM, and a 45-second interval rest. Before and after 12 weeks, 5 mL of blood was taken from the brachial vein. In addition, serum CT-1 was measured using an enzyme-linked immunosorbent assay (ELISA) kit and a Hyperion ELISA device. Further, serum PLA was estimated using a platelet kit. Independent and dependent t-tests were utilized to examine the difference between the means of intergroup and intragroup data. Finally, the Pearson correlation coefficient was used to investigate the relationship between variables.

Results: Serum CT-1 and PLA significantly increased after 12 weeks of compound set training compared to before 12 weeks of compound set training versus the control group ($P < 0.05$). There was no significant relationship between CT-1 and PLA before and after 12 weeks of compound set training in two groups ($P > 0.05$).

Conclusion: Overall, 12 weeks of compound training affected CT-1 and PLA levels. Thus, coaches and athletes can consider these results to maintain health and prevent syncope and thrombosis in athletes. Moreover, they should perform compound set training with caution.

Keywords: Bodybuilding men, Compound set training, Cardiotrophin-1, Platelets, Relationship

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Background

Performing resistance exercises is part of a training program that applies various types of external resistance to increase or prevent the decrease of muscle volume, maintaining muscle strength, power, and endurance in people (1, 2). These exercises improve muscular strength and endurance, the capability of function and self-determination, and well-being while diminishing complaints in people suffering from cardiovascular disease (CVD) (3, 4). Resistance training (RT) is one of the most powerful tools for improving physical fitness (5) and results in hemodynamic alterations in skeletal and cardiac muscles (6). Compound set (agonist-agonist muscle groups) training is a type of RT that causes strengths in short periods (7).

RT has a positive effect on health and physical fitness (8), but it may cause sudden cardiac death (SCD) and myocardial infarction (MI) during exercise due to homeostasis disorders (9, 10). Although young athletes are healthier than other people, they may experience SCD in sports (9, 11). An increase in the risk of sports-related SCD and MI during strenuous exercise in young athletes has been reported in some studies (5, 9). The SCD of a young athlete is a really rare event and is a tragedy (9, 10). The researchers indicated that 2%–10% of young athletes who die suddenly have no evidence of structural heart disease (2, 10, 12). At least 30% of the SCD occurs in athletes under 30 years old during athletic exercises (2, 10, 13). Myocardial fibrosis due to high-intensity and high-volume exercise can lead to malignant arrhythmias and SCD in sports (14-16). The risk of SCD approximately doubles during sports until about 1 hour after its cessation (10, 12, 17). Cardiotrophin-1 (CT-1) is a 2.5 kDa protein (203 amino acids in length)

(2) and a new member of the interleukin (IL)-6 family of cytokines (18-20). Cardio-myocytes and noncardiac cells in the heart synthesize CT. Once CT-1 is produced by the heart, it is secreted through the coronary sinus into the peripheral systemic circulation (9, 21-23). CT-1 has various functions, such as myocardial conservation, estimating the heart for unhealthy situations, exerting hemodynamic influences on endocrine (24). It is an active inveigler of cardiac hypertrophy and atherosclerosis (18), stimulates cardiac fibroblasts, and protects myocytes from cell death (8). According to reports, CT-1 increased in ischemic disease after an acute coronary syndrome (6) and an acute protocol exercise on a treadmill in patients with hypertrophic cardiomyopathy (25). CT-1 may be a predictor of sudden death in exercise (25) for the initial screening and diagnosis of acute MI in young athletes (8, 10, 12). Therefore, CT-1 is an encouraging biomarker for approximating the existence, intensity, and anticipation of atherosclerotic CVD (24). There is an association between CT-1 and the formation of atherosclerosis (24). Intense physical exercise in humans is attributed to the concentration of CT-1 in plasma. Some exercises in healthy subjects transiently increase plasma CT-1 concentration (26, 27). In addition, CT-1 is a diagnostic indicator of mortality in cardiac hypertrophic conditions. Strength training in athletes leads to left ventricular hypertrophy (18), which has been shown to increase plasma CT-1 in humans (1). Mortality and the risk of sudden death in exercise are associated with severe ventricular hypertrophy. CT-1 is related to cardiac arrhythmias, arterial fibrillation, sympathetic heart failure, and sudden death in exercise (22).

Coronary thrombosis is the most critical homeostasis disturbance causing SCD during athletic exercises (9). Prothrombotic factors might play an essential role in SCD (8). Likewise, platelets (PLA) are coagulation factors that have a crucial role in CVDs (4, 28). The risk of abnormal blood clot formation increases due to increased PLA in coronary arteries (10, 12, 29). Acute exercises lead to the transient activation of the coagulation system, increasing SCD (10, 12, 17, 30). Both acute and regular exercises affect PLA function. It has been shown that there are patterns for hemostasis, thrombosis, and plaque rupture during sports-related SCD exercise (9). Thrombosis and plaque rupture as the urgent mechanisms of SCD in athletes, occur with coronary stenosis (31). In addition to the role of PLA in thrombosis, its function is essential for inflammatory reactions and immune responses (4, 28). RT temporarily increases plasma PLA levels in healthy individuals (13, 25), and PLA also affects IL-6 and CT-1 release (25). Further, CT-1 extends the quantity of PLA and red blood cells (24). High-intensity training, such as reduced exertion, causes rapid, transient changes in the number of PLAs (thrombocytes) in the circulation (32). When this increase is massive, it may have thrombogenic side effects in young and older people (32). Nonetheless, Hulmi et al demonstrated that 21 weeks of RT did not change the acute reduced-exertion-induced platelet response (32).

Objectives

Recently, compound set training has been performed by many young athletes to improve strength and hypertrophy muscles (32). Considering the importance of the issue and the fact that no study has so far been conducted in this regard, this study seeks to evaluate the effect of 12 weeks of compound set training on CT-1 and PLA and their relationship in young male bodybuilders.

Materials and Methods

The subjects, including 30 active men aged 20–30 years residing in Ardabil, voluntarily participated in this clinical trial study. They completed the consent form and a questionnaire, including medical and sports information, and were randomly divided into control and experimental groups. The number of samples was determined to be 15 people in each group, using the formula for determining the sample size in experimental studies (S = 14 [standard deviation] and D = 7 [possible precision]) and taking into account the error of the first type of estimation of 0.05. In addition, z was stimated from z score table. (33).

$$n = \frac{S_x^2 \times Z_{\alpha/2}^2}{D^2}$$

Additionally, the number of samples was 10 people in previous studies and Morgan's table (33, 34). The inclusion criteria included 4 years of RT and a lack of consuming caffeine, alcohol, cigarettes, tobacco, and anti-oxidant supplements (e.g., excessive consumption of vitamins C and E, iron, magnesium, copper, and zinc). The other inclusion criteria were no history of any CVDs and diseases affecting hematological factors (e.g., muscle damage) and no use of anti-inflammatory drugs (e.g., aspirin, ibuprofen, antibiotics, naproxen, and betamethasone). On the other hand, the exclusion criteria included smoking and alcohol consumption, a history of certain diseases, and injuries during training, which were obtained based on self-report and medical tests.

Compound Set Training

All subjects were present in the Ardabil gym at 8 AM, one day before starting training to determine demographic characteristics, including height, weight, body mass index (BMI), maximal oxygen uptake (Vo_{2max}), and one-repetition maximum (1-RM). They were asked to stand barefoot with minimal clothing, with their backs, heads, shoulders, hips, and heels touching the Seca scale (Germany). Then, in this position, the height and weight of the subjects were measured in centimeters and kilograms. The seven-step Bruce's maximal test was used

to estimate Vo_{2max}. In addition, the exhaustion time was recorded, and Vo_{2max} values were calculated by the Pollack formula at mL/kg/min. Further, the Brzycki formula was utilized to determine a 1-RM of the upper and lower limp muscles in chest press and squat movements.

Brzycki formula: ((repetition × 0.02780) -1.02780) / weight (kg) = 1-RM (33, 34, 35).

Next, a maximum repetition of the upper and lower limbs of muscles was calculated and matched.

In the compound set training group, subjects performed 60 minutes of exercise consisting of 10 stations (front leg, barbell curl, leg press, front lat pull down, chest press, parallel, barbell shoulder press, back lat cable pulley row, and back leg) after 10 minutes of warming up. Exercise at each station lasted for 15 seconds, and the rest time between stations was 45 seconds. Moreover, exercise was performed with 40%–60% 1-RM, and the subjects cooled down for 5 minutes at the end of the exercise (2).

Measurements

Overall, 5 mL of the blood was taken from the brachial vein before and after 12 weeks. Blood samples were centrifuged for 10-15 minutes at 3000 pm. The serum was stored at -20 ˚C. Furthermore, serum CT-1 was measured using an enzyme-linked immunosorbent assay kit (ZellBio, Germany) and a Hyperion enzyme-linked immunosorbent assay device (US). Moreover, serum PLAs were measured using a PLA kit (Mahsa Yaran Iran Company). The data were presented as means and standard deviations. The Shapiro-Wilk test was used to evaluate data normality. Additionally, one-way analysis of variance and post-hoc Bonferroni tests were employed to determine the difference between CT-1 and PLA intra- and inter-groups before and after 12 weeks of compound set training. Further, the Pearson correlation coefficient was utilized to examine the relationship between CT-1 and PLA. SPSS software (version 25) was used for data analysis, and the significant level was $P < 0.05$. The ethical principles for the implementation process were observed under the Helsinki Declaration.

Results

The results of the Shapiro-Wilk test confirmed that the data had a normal distribution (Table 1). Table 2 summarizes the demographic characteristics of the subjects. Moreover, the variance of the groups at the beginning of the research was homogeneous in terms of age (F = 1.311, $P = 0.362$), weight (F = 1.907, $P = 0.304$), height (F = 1.821, $P = 0.188$), BMI (F = 0.910, $P = 0.348$), Vo_{2max} (F = 0.196, $P = 0.661$), upper 1-RM (F = 2.358, $P = 0.136$), lower 1-RM (F = 1.591, $P = 0.217$), CT-1 (F = 3.343, $P = 0.078$), and PLA (F = 3.0590, $P = 0.68$).

Based on the results (Table 2), no significant difference was found between the demographic characteristics of the subjects at the beginning of the study and before 12 weeks of compound set training ($P > 0.05$).

The results (Table 3) demonstrated that there was a significant difference between CT-1 and PLA in the two exercise and control groups before and after 12 weeks of compound set training.

No significant difference was observed between CT-1 and PLA in the two exercise and control groups at the beginning of the study (Table 4). Based on the findings, 12 weeks of compound set training significantly increased CT-1 ($P = 0.0001$) and PLA ($P = 0.0001$). In addition, CT-1 ($P = 0.0001$) and PLA ($P = 0.001$) significantly increased in the exercise group compared to the control group. However, there was no significant difference between CT-1 and PLA in the control group before and after 12 weeks ($P > 0.05$).

Moreover, the results represented no significant relationship between CT-1 and PLA in young male bodybuilders before and after 12 weeks of compound set training.

Discussion

Table 2. Demographic Characteristics of the Subjects in Exercise and Control Groups

Variables	Control (n = 15)	Exercise (n = 15)	*P* value
Age (year), Mean ± SD	25.13 ± 1.36	24.67 ± 1.72	0.416
Weight (kg), Mean ± SD	67.20 ± 3.12	67.60 ± 2.29	0.692
Height (cm), Mean ± SD	174.73 ± 2.76	175.33 ± 2.74	0.555
BMI (kg/m²), Mean ± SD	22.01 ± 0.91	21.99 ± 0.74	0.958
1-RM upper limbs (kg), Mean ± SD	32.80 ± 0.77	32.67 ± 0.72	0.630
1-RM lower limbs (kg), Mean ± SD	73.53 ± 1.73	73.13 ± 0.83	0.426
Vo_{2max} (mL/kg/min), Mean ± SD	105.07 ± 0.96	104.53 ± s1.36	0.224

Note. SD: standard deviation; BMI: Body mass index; 1-RM: One-repetition maximum; Vo_{2max}: Maximal oxygen uptake.

Table 1. Shapiro-Wilk Test Results Related to the Normality of Data Distribution

Group	Age	Weight	Height	BMI	Vo_{2max}	Upper 1-RM	Lower 1-RM	CT-1 Pre	CT-1 Post	PLA Pre	PlA Post
Control	*P* = 0.261	*P* = 0.157	*P* = 0.231	*P* = 0.017	*P* = 0.004	*P* = 0.183	*P* = 0.032	*P* = 0.020	*P* = 0.000	*P* = 0.714	*P* = 0.855
	Z = 0.929	Z = 0.914	Z = 0.925	Z = 0.850	Z = 0.806	Z = 0.919	Z = 0.868	Z = 0.854	Z = 0.616	Z = 0.961	Z = 0.970
Exercise	*P* = 0.505	*P* = 0.109	*P* = 0.604	*P* = 0.101	*P* = 0.002	*P* = 0.004	*P* = 0.606	*P* = 0.088	*P* = 0.067	*P* = 0.930	*P* = 0.586
	Z = 0.949	Z = 0.904	Z = 0.955	Z = 0.902	Z = 0.783	Z = 0.799	Z = 0.955	Z = 0.898	Z = 0.890	Z = 0.976	Z = 0.954

Note. CT-1: Carditrophin-1; PLA: Platelets; Vo_{2max}: Maximal oxygen uptake; 1-RM: One-repetition maximum.

Table 3. Results of One-Way ANOVA Test of Cardiotrophin-1 and Platelets in Exercise and Control Groups Before and After 12 Weeks of Compound Set Training

Parameters		Sum of Squares	df	Mean Square	F	*P* Value
CT-1 (Pg/mL)	Between groups	65.116	3	21.705	9.889	0.0001*
	Within groups	122.921	56	2.195		
	Total	188.037	59			
PLA (10^3/μL)	Between groups	2598.317	3	866.106	27.271	0.0001*
	Within groups	1778.533	56	31.708		
	Total	4376.850	59			

Note. ANOVA: Analysis of variance; CT-1: Carditrophin-1; PLA: Platelets;
*Significant difference at $P<0.05$.

Table 4. Results of Post Hoc Bonferroni Test of Cardiotrophin-1 and Platelets in Exercise and Control Groups Before and After 12 Weeks of Compound Set Training

Variables	Groups	Mean ± SD Before 12 Weeks of Training	Mean ± SD After 12 Weeks of Training	Mean Difference	Df	*P* Value
CT-1 (Pg/mL)	Exercise	13.69 ± 0.96	16.16 ± 2.07	-5.421	14	0.0001*
	Control	13.63 ± 1.43	13.52 ± 1.28	-0.265	14	0.795
PLA (10^3/μL)	Exercise	284.47 ± 3.44	299.87 ± 6.09	-27.40	14	0.0001*
	Control	284.67 ± 7.65	284.93 ± 7.43	-8.239	14	0.546

Note. CT-1: Carditrophin-1; PLA: Platelets; SD: Standard deviation.
* Significant difference at the level of $P<0.05$.

The findings of this study confirmed that CT-1 significantly increased after 12 weeks of compound set training. In other words, CT-1 concentration increased with exercise in healthy subjects. Exercise and exercise-induced hypoxia cause the release of noradrenaline and increase CT-1 concentrations (26, 27). Hypoxia-induced factor 1 increases CT-1 expression, leading to the maintenance of cardiomyocytes in response to ischemia. Myocardial ischemia is probably due to the stretching of the myocardial ventricular wall, resulting in local pressure of myocardial contraction in exercise. This mechanical stretch activates the protein kinase B/signal transducer and activator of the transcription (AKT/STAT) pathway and IL-6 and CT-1 messenger RNA expression (25, 36, 37). Myocardial ischemia, a dynamic process that occurs during exercise, could probably increase CT-1 (35) after 12 weeks of compound set training in this study. Twelve weeks of compound set training in the present study could probably lead to temporary hypoxia (27). Exercise and physical activity lead to a temporary decrease in oxygen consumption in organs, especially muscle organs, because of increasing the demand for oxygen consumption in the heart and muscles. Further, exercise increases the speed of hemoglobin passing through alveolar capillaries and decreases their saturation percentage (18, 27). Endocrine (e.g., fibroblast growth factor-2, aldosterone, and norepinephrine) and autocrine factors may augment the expression of CT-1 (27). CT-1 activates the Janus kinase (JAK)-STAT, mitogen-activated protein (MAPK) signal transduction pathways, and adenosine monophosphate-activated protein kinase in cardiomyocytes (18). The mechanism of STAT activation is a signaling cascade that induces nuclear factor-kappa B (18). It should be noted that the nuclear factor-kappa B is stimulated/activated by CT-1 and related cardiomyocyte conservation using selective inhibitors (e.g., p38 MAPK, ERKs, or AKT) in rat cardiomyocytes. CT-1 activates intracellular kinases in cultured cardiomyocytes (25, 27). Exercise-induced mechanical traction activates JAK/STAT pathways and possibly stimulates IL-6 RNA and CT-1 expression (25, 27). The JAK/STAT pathway defends cardiomyocytes against ischemia/reperfusion injury by reducing reactive oxygen species production (23), and this reduction promotes the effects of CT-1 through the aforementioned pathways (10). This issue needs further investigation. Another probable reason for the increase of CT-1 after training is the increase of IL-6. IL-6 and its secreted CT-1 are a part of the immune system (29). IL-6 is one of the most essential predominant pro-inflammatory cytokines in atherosclerosis (22). It has a vital role in the development and progression of inflammatory atherosclerosis and is known as a risk factor for coronary heart disease (27).

The results related to the increase of CT-1 after 12 weeks of the compound set training in this study are consistent with the findings of Kilim and Lakshmi et al (38), Calabrò et al (26), González et al (1), and Daryanoosh et al (39). However, our findings contradict those of Gholaman et al (40), Marti et al (41), Amooali et al (42), and Rendo-Urteaga et al (43). Gholaman et al found that high-intensity interval training and moderate-intensity continuous training decreased the levels of CT-1 and insulin resistance in women with type 2 diabetes. In addition, high-intensity interval training was not superior to moderate-intensity continuous training in terms of observed changes in CT-1 levels and insulin resistance.

Marti et al reported a significant decrease in CT-1 expression in peripheral blood mononuclear cells after 10 weeks of a lifestyle intervention (calorie restriction and physical activity) in obese children (41). Rendo-Urteaga et al demonstrated that a weight loss program (nutritional intervention and physical activity) resulted in decreased serum CT-1 levels, which was associated with a significant decrease in insulin resistance (43). Conversely, Amooali et al showed that there was no significant difference in the serum levels of CT-1 12 after weeks of aerobic exercise in hypertensive elderly women (42). These differences are due to the gender of subjects, their training history, the type, intensity, and duration of the training, and the health status or illness of the subjects.

The finding of the present study also revealed that blood PLA increased significantly after 12 weeks of compound set training. Inflammatory and coagulation processes are not separate. PLAs are activated when several cytokines are released, mediating inflammation (2, 44). Beyond the critical role of PLAs in thrombosis, they can assist and modulate inflammatory reactions and immune responses (19). Exercise increases PLA counts. This increase is due to physical activity and the release of fresh PLAs from the spleen, bone marrow, and other body reserves. Some studies reported that epinephrine secretion causes muscular contraction of the spleen (where one-third of the PLA is stored). Epinephrine levels increase during physical activity, especially high-intensity training. This mechanism can explain PLA proliferation after exercise in this study (13, 45). Other mechanisms include levels of troponin, adenosine triphosphate, blood, lactic acid pH, and blood catecholamines, which increase PLA count after exercise. The increase of PLA in this study is probably due to the release of these substances from the arteries of the spleen, lungs, and red bone marrow. Another possible reason is the increases in body temperature, sweating rate, or plasma catecholamine concentrations (26, 45).

Our results regarding the increase in serum CT-1 levels and PLA after 12 weeks of compound set training conform to the findings of Monserrat et al (25), Daryanoosh et al (39), Amooali et al (42), and Tayebi et al (13). However, our findings contradict those of Hulmi et al (32), demonstrating that blood PLA did not change after RT. These contradictory results are due to differences in the intensity, duration and protocol of the exercise, the gender, the level of physical fitness of the subjects, and subjects' health or sickness status in different studies.

Our results revealed that CT-1 levels and PLA increased after 12 weeks of compound set training (30). There was no significant relationship between CT-1 and PLA before and after 12 weeks of compound set training in young male bodybuilders.

In this study, young bodybuilders and athletes were screened before starting compound set training for coagulation and inflammatory factors to prevent blood coagulation and inflammation. In addition, coaches and athletes performed compound set training with proper intensity to maintain health and prevent thrombosis in athletes. The limitation of the present study was the impossibility of controlling factors such as mental state, sleep, and rest at night before blood sampling.

Considering the relationship between inflammatory factors and ILs with CT-1 and PLA, it is suggested that future researchers measure these indicators. Further, it is recommended that researchers perform similar studies on girls, women, and adolescents.

Conclusion

It can be concluded from the results of the present study that 12 weeks compound set training improves the level of cardiotrophin-1 and platelets in active young males.

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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

The present study was approved by the Ethics Committee of Ardabil University of Medical Sciences (IR.ARUMS.REC.1398.187) and registered in the Iranian Clinical Trial Center (IRCT20181114041655N3).

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