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Effect of Concurrent Training on inflammatory markers of Beta Thalassemia Major Patients

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Original Article

Abstract

Introduction: Chronic vascular inflammatory state plays an important role in the pathophysiology of thalassemia. Cross-sectional studies suggest that exercise has anti-inflammatory effects, leading to lower levels of several proatherogenic inflammatory markers. However, this has yet to be confirmed by randomized prospective trials. The present pilot study examined the effect of Concurrent) Training on inflammatory markers of Beta Thalassemia Major Patients.

Methods: In this semi-experimental study, 18 patients with Beta Thalassemia major were selected as convenient samples and voluntarily divided in two groups: experimental (n=9) and control group (n=9). The subjects of the experimental group attended the concurrent (Resistance-Endurance) Training for eight weeks (3 Sessions per week and each sessions 90 min). Subjects' blood samples were taken before and after training protocol in order to measurement hs-CRP, IL-6, IL-1_β andIL-12 Serum levels. The levels of these markers were measured by using an enzyme-linked Electro immune assay (ELISA) kits. For data analysis the Repeated measures ANOVA, was used. All statistical analysis was performed by SPSS software (V.19). The level of significance was considered $P<0.05$.

Results: The results indicated reduction of HS-CRP and IL-6 after eight weeks of concurrent training compared to the control group ($P<0.05$), but IL-1_β and IL-12 was increased in training group ($P<0.05$).

Conclusion: The reduction of HS-CRP and IL-6serum level and its natural range in the exercise protocol, can be a regulating response to inflammatory condition in patients under certain exercise conditions without any pathological importance and maybe improved chronic vascular inflammation. We demonstrated that concurrent (resistance-endurance) training is inversely correlated with levels of pro-inflammatory markers in Beta Thalassemia major patients, possibly retarding the process of atherosclerosis andresults showed that immune modulation.

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Introduction:

Beta-Thalassemia is a congenital hemolytic disorder caused by a partial or complete deficiency of β-globin chain synthesis. Patients with beta-thalassemia major suffer from severe anemia and other serious complications from early childhood. The disease is treated by chronic blood transfusion. However, this can cause severe iron overload resulting in progressive organ failure (1,2). Patients with SCD (sickle cell disease) tolerate a systemic pro-inflammatory vascular milieu created by chronic ischemia/reperfusion injury and profound erythrocyte hemolysis. In addition to this chronic low level inflammation, exposure to relatively innocuous, sub-clinical inflammatory stimuli appears to ignite an exaggerated, potentiallyfatal inflammatory response inpatients. The etiology of this inflammatory hyper-reactivity is not well understood. There is ample evidence that, in steady state, a cadre of inflammatory cells, especially monocytes, exhibit a primed phenotype. Such priming, or propensity to activate, likely contributes to baseline inflammation, and is requisite for the inflated inflammatory response (3). Infectious complications and immune abnormalities have always been considered as causes of morbidity and mortality in β-thalassemia. A wide range of functional and quantitative immune alterations have been described in β-thalassemia patients with multiple transfusions. These abnormalities seem to be acquired and secondary to allogenic stimulation of the antibody-producing cells by continuous blood transfusions, together with iron overload (4,5).

However chronic systemic inflammation is associated with the development of various diseases, such as atherosclerosis and diabetes. Age and physical inactivity related to these diseases could lead to development and progression of cardiovascular disease (CVD) (6,7). Cytokines are secreted proteins that influence the survival, proliferation, differentiation and function of immune cells andother organ systems (8). Cytokines can be secreted by a varietyof cells including neutrophils, activated macrophages, fibroblasts, endothelial cells and damaged muscle cells (9).

Inflammatory markers (cytokines) and Training

Themuscle itself can also release cytokines as a result of motor unitcontractions. For example, it has been a consistent finding that interleukin 6 (IL-6) increases by several folds in response to endurance exercise (10). These increases in IL-6 could be in partrelated to the decrease in glycogen levels that occur duringendurance exercise. There is also a lower magnitude of IL-6 response to RT than to endurance exercise. For further details, Hirose *et al*. (11) gave a clear explanation about the differencesin RE and endurance regarding cytokine responses the physiological responseto tissue injury is inflammation, which involves the productionof cytokines (10). In addition, cytokine response may vary by the type of exercise, intensity, duration, recovery between exercise bouts and training status (12,13). The most studied cytokines regarding exercise are: IL-6, IL-1 β, IL-8, IL-1 ra, IL-10, IL-15 amd tumor necrosis factoralpha (TNF-α). In addition IL-2 IL-4, IL-5, IL-13 and IL-12 have received some attentionin relation to RT. Some of the cytokines functions have beenbetter characterized than others. For instance, IL-1β, IL-8 and TNF-α are considered pro-inflammatory. The IL-1 family is part of the innate immune system thatregulates functions of the adaptive immune system (14). IL-1β is the secreted isoform of IL-1. IL-1β does not generally increaseafter endurance exercise (15) and might remain unchanged (16) or slightly increased (17) after RT. In addition to CRP, a well establishes marker of inflammationand CVD risk (18), Although CRP does not seem to change after anacute bout of RT (19), long term RT can affect its basal levels (16,20). Regular moderate exercise promotes anti-inflammatory effects in skeletal muscle and adipose tissue (12) and canbe used as a therapeutic and preventive modality to mitigate degenerative processes associated with age and reduce systemic inflammation markers (21,22). However, existing literature presents conflicting and inconsistent findings regarding the effects of the exercise training on the inflammatory markers. Some studies demonstrate a decrease in TNF-> (21), IL-6 (22,23), and CRP (16); on the other hand, other studies have not found reductions in some of these inflammatory markers (24,25).

Recently, Donges et al. (26), comparing the effect of 10 wk of resistance training (RT) and endurance training (ET) in sedentaryhealthy

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subjects on inflammatory markers related to CV Drisk, verified reductions only in CRP in RT, with no alteration in IL-6 in both groups. The performance of ET and RT has been recommended to prevent chronic diseases (27).

Various studies have addressed the interaction between changes in indicators of inflammatory markers and exercise. Besides, few studies have analyzed the interaction between physical activity and inflammatory function of the above mentioned patients. In addition, no study demonstrated the effects of the association of ET and RT in inflammatory markers, known as concurrent training (CT), with these two types of exercises performed in isolation. Therefore, because of the inconsistent findings on the effects of exercise training on systemic inflammatory markers, the purpose of the present study was to determine the respective effects of 8 Wk of Concurrent Exercise on HS-CRP, IL-6, IL-1$_\beta$ and IL-12 of Beta Thalassemia Major (BTM) Patients. This implies that a broad array of cytokines maybe increased after an exercise bout, thus evaluating the magnitude of the pro to anti-inflammatory ratio should be considered in future studies.

Methods:

Subjects.

This semi-experimental study was performed in Aprill 2015. Research subjects included 18 beta Thalassemia major patients in Abureyhan specific diseases center of Bandar Abbas) were selected as convenient samples that voluntarily participated in the study. Finally, after obtaining informed consent they were voluntarily grouped into experimental (n=9) and control (n=9) groups. Obtaining the history, physical cardiology examination, and echocardiography were performed on all patients. Due to the potential impact of hematocrit changes on the results, blood sampling and echo of all patients were taken at least 72 hours after blood transfusion. One week before the concurrent exercise program, the subjects were familiarized with research steps and training program. Anthropometric characteristics of subjects, including height, weight, body mass index and body surface area and the maximum aerobic capacity and hemoglobin leveles were measured one week before the exercise program (Table 1). It should be mentioned that the subjects' diet, medication and blood transfusions were considered.

Training protocols

Before the beginning of the study, the subjects performed a familiarization trial with two sets of training of moderate intensity, with 48 h of rest between them. The purpose of the familiarization trials was to reduce learning effects and establish the reproducibility on two training tests. After the familiarization stage and teaching the implementation techniques, the workout program including 8 weeks of concurrent resistance-endurance training was performed as three sessions a week for a total of 24 sessions. The subjects performed both concurrent resistance-endurance training at the same session. Resistance training was always performed before endurance training to prevent premature fatigue caused by endurance training. For the implementation of this resistance protocol the one-repetition maximum (1RM) of the subjects was determined by using the formula Max Power=Load/1-0.02 (reap) on Leg extension, lat, Dumbbell Cur Dead Lift and leg press exercises. In order to control the intensity of the exercise to perform endurance protocol, the maximum heart frequency of subjects (based on maximum heart rate equation (220- age) ±10) was calculated. Also, to keep the heart rate during the endurance exercise, PM45 heart rate monitor was used. The subjects had a 10 minute warm up before each session and had a 5 minute recovery after the session. Exercise protocole have been shown in figure 1 (28).

All training were performed in Azad University of Bandar Abbas gym. The subjects' diet was based on their regular diet and they were asked not to use drugs other than their usual drugs.

Cytokines assay

Blood samples (10 mL) were obtained from the antecubital vein in the morning (08:00–09:00 a.m.) after a 12 h over night fast before and 1 d after the training period to avoid acute fluctuations in the levels ofhs-CRP, IL-6, IL-1$_\beta$ and IL-12 concentration. All samples were collected, processed, divided in to aliquots, and stored locally at j70-C until later analysis. Serum samples were used forhs-CRP, IL-6, IL-1$_\beta$ and IL-12, and

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inflammatory markers analyzed. IL-1$_\beta$ and IL-12 was measured by ELISA using kits specified to human samples (Boster Kit, USA), IL-6 were determined by an enzyme-linked electro immune Lessons assay according to the specifications of the (Cobas e 411, Germany manufacturer. HS-CRP were determined by an enzyme-linked Electroimmune lessans assay according to the specifications of the (integra 400 plus, Roche, Germany manufacturer. Cytokines are presented in values of picograms per milliliter (pgImLj1), and CRP is presented in milligram per liter (mgILj1).

Satistical analysis

A repeated measurement analysis (ANOVA) was performed to find the significance of change in: HS-CRP, IL-6, IL-1$_\beta$ and IL-12 during pre-training, post-training protocols. Kolmogorov-Smirnov test was used to check the normality of the data. Statistical significance was considered as $P<0.05$. All data were presented as mean values±standard error of the mean (SEM). The SPSS version 19.0 was used for analyzing the data and Excel was used to generate graphs.

Results:

According to the characteristics of subjects, no significant difference was determined between the groups (age: 24.6±3.5 years; body surface area: 1.46±06 kg; height: 150.5±1.3 cm; weight: 47.43±1.2 Kg; BMI: 19.95±2.4kg.m^{-2}; HG: 10.08±0.05 and VO2max: 48.3±4.2 mL/kg/min) and results showed that prior to intervention, all variables were homogeneous (Table 1).

Amongst the inflammatory biomarkers analyzed by repeated measurement analysis in the two group, significant changes were observed after 8 weeks protocol in experimental group. The Repeated measures ANOVA showed that the 8 weeks of Concurrent training have effect on the serum level of HS-CRP, IL-6, IL-1$_\beta$ and IL-12 ($P<0.05$) Table 2.

The serum levels of HS-CRP though significantly decreased after 8 weeks of Concurrent training in comparison with the control group ($P=0.0003$). Table 2. The serum levels of IL-6 though significantly decreased after 8 weeks of Concurrent training in comparison with the control group ($P=0.001$).

Also in training group the levels of IL-12 in post-test were significantly increased from pre-test ($P=0.002$). Comparison of the findings shows significantly higher level of IL-1$_\beta$ in all patients in exprimental group (Figure 2). Depictshs-CRP changes among various groups. IL-6 changes have been shown in (Figure 3). IL-1$_\beta$ changes have been shown in (Figure 4). IL-12 changes have been shown in (Figure 5).

Table 1. Anthropometric and Biochemical characteristics of subjects at Baseline

Group/characteristics	Control	Exercise	P-value
Age (years)	26.67±3.6	22.62±3.5	0.655*
Weight (kg)	46.27±1.47	48.59±1.05	0.842*
Height (cm)	149±1.26	152±1.42	0.543*
BMI (kg.m^{-2})	20.31±2.66	19.6±2.14	0.667*
VO$_{2max}$ (ml.kg^{-1}.min^{-1})	47.3±3.34	49.1±4.86	0.506*
BSA	1.48±0.07	1.44±0.06	0.617*
HGb (g.dl-1)	10.9±0.01	10.8±0.9	0.558*
Hs-crp (mg.1^{-1})	3.25±1.75	1.5±0.5	0.974*
IL-12 (pg.ml^{-1})	1.134±0.14	1.130±0.21	0.655*
IL-6 (pg.ml^{-1})	4.07±1.85	3.16±0.95	0.517*
IL-1β (pg.ml^{-1})	0.11±0.04	0.10±0.02	0.742*

Data are mean ± SD. *No significant differences were observed between groups ($P> 0.05$).

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Table 2. Compares difference between groups after 8 weeks of Concurrent Exercise protocol

Group/characteristics	F	Post test	P-value between groups	
	Control	Exercise	Control	Exercise
HS-CRP (mg.l^{-1})	3.27±1.1	1.05±0.58	0.63	0.01*
IL-12 (pg.ml^{-1})	1.31±0.12	2.77±0.44	0.88	0.02*
IL-6 (pg.ml^{-1})	3.98±1.9	1.85±0.45	0.62	0.001*
IL-1β (pg.ml^{-1})	0.11±0.02	0.30±0.05	0.51	0.004*

Data are mean ± SD. * P< 0.05 significant difference between groups after 8 weeks of Concurrent Exercise protocol.

	Time	First(4 weeks)	Second(4 weeks)
Resistane Exercise	Leg press	$\frac{60-65\%}{12}$	$\frac{65-70\%}{8}\times 2$
	Lat	$\frac{60-65\%}{12}$	$\frac{65-70\%}{8}\times 2$
	Leg extension	$\frac{60-65\%}{12}$	$\frac{65-70\%}{8}\times 2$
	Dumbbell Curl	$\frac{60-65\%}{12}$	$\frac{65-70\%}{8}\times 2$
	Dead Lift	$\frac{60-65\%}{12}$	$\frac{65-70\%}{8}\times 2$
Endurance Exercise	Treadmil	$\frac{60-65\%}{10min}\times 2$	$\frac{65-70}{13min}\%$

Figure 1. Concurrent Exercise protocol

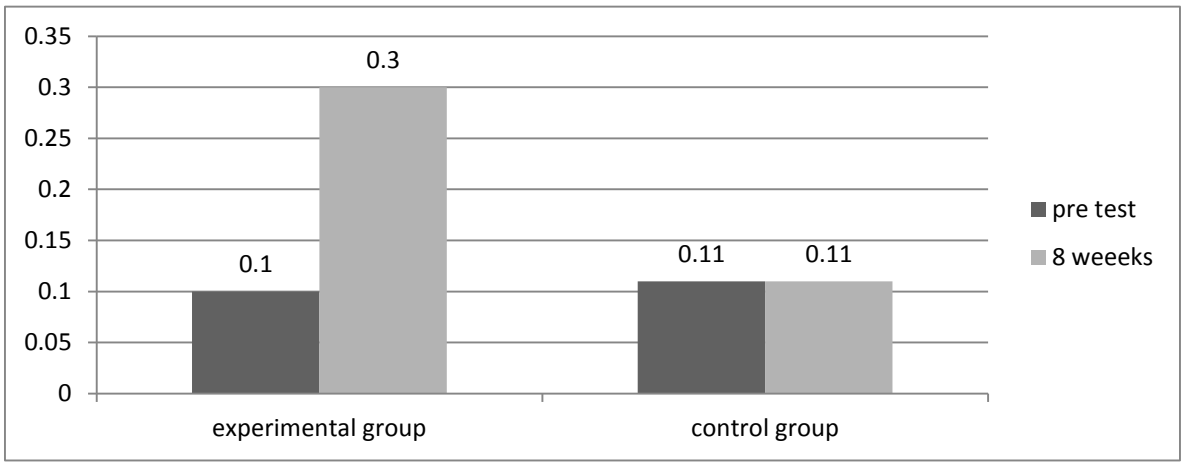

Figure 2. Variation of IL-1$_\beta$ (pg. ml^{-1}) concentration among different groups

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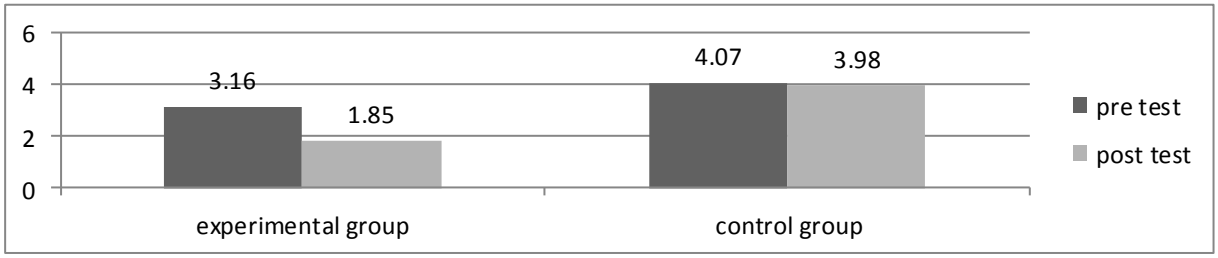

Figure 3. Variation of IL-6 (pg. ml^{-1}) concentration among different groups

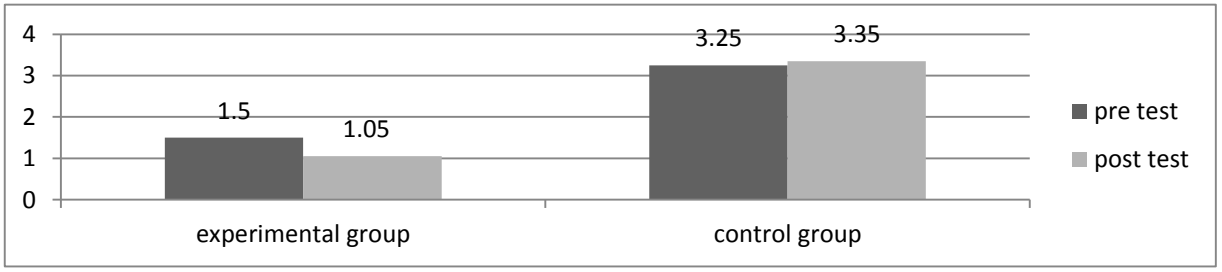

Figure 4.Variation of HS-CRP (mg. l^{-1}) concentration among different groups

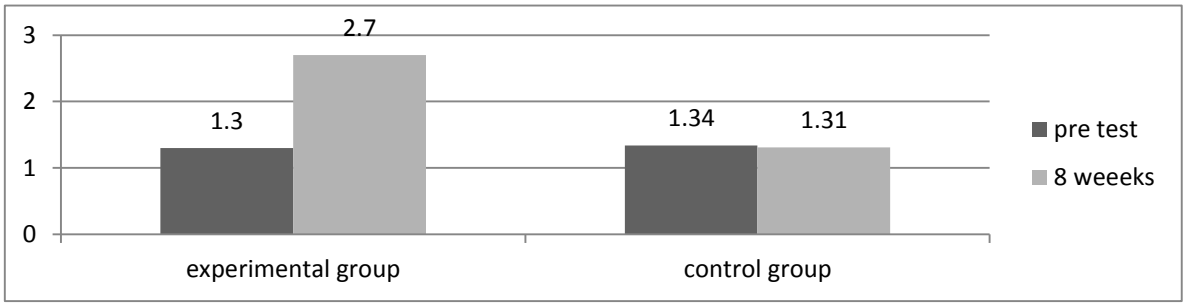

Figure 5. Variation ofI L-12 (pg. ml^{-1}) concentration among different groups

Conclusion:

In this research we investigated changes in certain inflammatory marker s including IL-1β, CRP (HS-CRP), IL-6, and IL-12. Observed decreased serum CRP (hs-CRP), IL-6, and increased serum IL-12 and IL-1β after8 weeks of Concurrent training. These inflammatory biomarkers' concentration was measured prior to training, as well as 14 hours after the exercise. It can be concluded that Concurrent exercise effect on inflammatory markers. While the recommendation to exercise for people with age-related chronic disorders is one of the treatment protocols, these training prescriptions might differ in terms of intensity. In other words, recommending Concurrent exercise will be the best option for prevention and treatment of these diseases in Beta Thalassemia Major. Sickle cell disease is well recognised as a chronic inflammatory disease (Belcher *et al*, 2000, 2003; Klings & Farber, 2001; Jison*et al*, 2004). Patients with SCD in crisis show elevated tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) compared with steady state SCD.

In addition, IL-1, IL-6 and interferon-γ (IFN-γ) are elevated in steady state SCD compared with controls. It is unknown from these studies how iron overload will affect the levels of chronic inflammation in SCD. Elevations of the pro-inflammatory cytokines TNF-α and IL-2 have also been demonstrated in iron overloaded patients with thalassaemia (Del Vecchio*etal*, 2002). These cytokines returned to normal after treatment with the iron chelator deferiprone (L1) (Del Vecchio *et al*, 2002).

Although it is unknown whether Thalassemia major diseases develop similar inflammatory

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responses. Inflammation has a significant role in the pathogenesis of several chronic diseases including cardiovascular disease CVD, type 2 diabetes mellitus, Alzheimer's disease, osteoporosis, and certain cancers (29).

Although it is believed that a single bout of exercise induces immune activation, different studies have shown different results (29,30). These differences may be due to factors, including differences in subject features, the type and intensity of the exercise, period of intervention, the time of taking blood samples and inherentvariability in methods for quantifying the circulating level of cytokines. Nevertheless, extensive evidence suggests that both acute and chronic exercises can improve markers of systemic low-grade inflammation (31-33).

A Concurrent training induces a transient increase in immune markers such as leukocyte numbers, and the release of chemical mediators such as cytokines and chemokines. These changes depend on the intensity and duration of the training period. The leukocyte and cytokine concentrations return to their resting level a few hours after the end of the exercise bout (31). Accordingly, it is expected for each training session (even during a low-intensity resistance or endurance exercise) to slightly induce immune system activation. Although our results, in case of some markers, showed immune modulation. It is important to note that in this study, participants were Beta Thalassemia Major (BTM) Patientswho do not exercised regularly and regular resistance or endurance training, because of its anti-inflammatory effects, limits immune activation during workout (32).

Our findings about IL-6 after 8wk Concurrent protocol support those of previously published studies, which reported that muscle IL-6 release is very low during moderate exercise. For example, a study performed on female subjects, during a 30-minute brisk walk on a treadmill, showed that plasma IL-6 concentration increased from 1.3 to 2 pg/m (33). During training, IL-6 cytokine is released by muscle fibers and induces an increase in the level of other anti-inflammatory cytokines such as IL-10. Furthermore, IL-6 also acts as a suppressor in the production of TNF-α, as a pro-inflammatory cytokine (12). Gharagozloo et al. Also demonstrated a significant decreasing in IL-2, IFN-γ, and IL-4 production by activated lymphocytes from patients with β-thalassemia compared to the normal group (34). However, Salasa and colleagues showed that stimulated blood mononuclear cells from thalassemia patients produce more IFN-γ than control group. This might be due to infections in β-thalassemia patients (35). For example in someprotocols IL-6 increased at 3 (19), 6 (36), 12 (37) or even 24 h, while in another study (38) IL-6 returned to baseline levels at 6 h. The increases in IL-6 with RT seem to be of a lesser magnitud than those seen in endurance exercise (39). Only one study (37) showed a decrease in IL-1β, where the rest showed no changes in this cytokine (40). The studies presented employed a broad variation of muscles groups, had different intensities and training protocols and in general they failed to demonstrate a consistency in the increase or a significant change in most of the circulating cytokines measured after a single RT bout in untrained men and women (18,19,40).

A possible explanation could be related to the intervals for sampling which were too separate from the exercise bout leading to clearance of cytokines from circulation before being measured. The CRP is synthesized by the liver in response to inflammatory factors, primarily IL-6, and, to a lesser extent, IL-1 and TNF-α. Furthermore, CRP is used mainly as a marker of subclinical chronic vascular inflammation, and has a predictive value of future cardiovascular events. We found that 8 weeks of Concurrent training decreases the level of HS-CRP in experimental group. The IL-12, as an anti-inflammatory cytokine, can be increased by exercise training, and in turn decrease vascular wall inflammation (41). Our data showed that that 8 weeks of Concurrent training could increase IL-12. Some exercise interventions have shown that regular exercise decreases the level of IL-1β (42,43); Uchida *et al*. evaluated IL-1β, IL-6 and IL-10 responses to different intensities of a bench press exercise maintaining the same total work load in RT untrained men. Authors reported no changes in circulating cytokines after 24 h compared with Pre-exercise. Thus, this research group (44) accounted for the differences in work load in their study but the timing of the samples and the type of exercise protocol differs from the studies mentioned previously (19,40). MacIntyre *et al*. (45) Results

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from another study suggest that RT can induce mRNA expression of IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10 and TNF-αin muscle tissue without its increment on plasma (40). As an explanation of their findings, the authors suggest that higher intensity could increase stress hormones and IL-6 leading to higher anti-inflammatory cytokine responses (46). However like IL-12 we found that even after 8 weeks of Concurrent training, IL-1β could be increased in participants who training. Accordingly, iron overload may suppress Th1 immunity in thalassemia patients with increased serum ferritin levels (1,47,48). Therefore, increased production of IL-1β and IL-12 might be contributed to abnormalities in iron metabolism and it is probably due to over stimulation of Th17. In fact iron deposition in 9 reticule endothelial system such as macrophages and epithelial cells may influence the regulation of Th17 responses in thalassemia patients and results in higher levels of its cytokines in the circulation. On the other hand, multiple blood transfusions may cause that immune system in β-thalassemia patients become under constant alloantigen stimulation, despite the suppressed immune responses due to iron overload (49).

The present study was a semi-experimental study with a small population. Our subjects were Beta Thalassemia Major (BTM) Patients therefore our data could not be generalized to other populations. Although in this study, diet was controlled, but factors such as stress and environmental conditions as well as the specific conditions of patients and limited samples size could have affected the results. More studies are needed to confirm our results.

In summary, we found that HS-CRP, and IL-6 significantly decreased while IL-1$_\beta$ and IL-12 significantly increased at rest (14 hours after 8 weeks of Concurrent training. On the other hand, this paper showed that immune modulation and inflammatory status 14 hours after) 8 weeks of Concurrent training in Beta Thalassemia Major (BTM) Patients. In simpler terms, Concurrent training is more effective in reducing vascular inflammation than resistance or endurance training. This observation may help Beta Thalassemia Major Patients with diseases-related chronic vascular inflammation and we can predict a pattern of cardiovascular events in these patients. Finally, this cytokine profile clinically can be used as related markers for assessing disease severity, indicators in following of vascular inflammation disease and consequently therapeutic intervention.

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تأثیر تمرین هم‌زمان بر شاخص‌های التهابی بیماران بتا تالاسمی ماژور

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چکیده

مقدمه: *التهاب - عروقی مزمن نقش مهمی در پاتوفیزیولوژی بیماری تالاسمی دارد. مطالعات مقطعی نشان می‌دهد که فعالیت ورزشی دارای اثرات ضد التهابی است، که منجر به کاهش برخی از شاخص‌های التهابی می‌گردد. با این وجود، این موضوع هنوز نیاز به مطالعه بیشتری دارد.*

روش کار: *در تحقیق حاضر، تأثیر تمرین هم‌زمان مقاومتی - استقامتی بر روی شاخص‌های التهابی بیماران مبتلا به بتا تالاسمی ماژور مورد بررسی قرار گرفت. این مطالعه به صورت نیمه تجربی انجام شده است. بدین منظور ۱۸ بیمار مبتلا به بتا تالاسمی ماژور (میانگین سنی ۳/۵۴±۲۴/۴) به عنوان نمونه در دسترس انتخاب و داوطلبانه به دو گروه تقسیم شدند: گروه تمرینی (n=۹) و گروه کنترل (n=۹) آزمودنی های گروه تمرینی به مدت هشت هفته (۳ جلسه در هفته و هر جلسه ۹۰ دقیقه) در تمرین مقاومتی - استقامتی هم‌زمان شرکت کردند. نمونه خون افراد قبل و بعد از انجام پروتکل تمرینی به منظور اندازه‌گیری سطوح سرمی hs-CRP، IL-6، IL-1β و IL-12 گرفته شد. سطوح این شاخص ها با استفاده از کیت (ELISA) اندازه‌گیری شد. برای تجزیه و تحلیل داده‌ها از آزمون ANOVA استفاده شد. تمام تجزیه و تحلیل آماری با استفاده از نرم‌افزار (SPSS V.19) انجام شد. سطح معنی‌داری P< ۰/۰۵ در نظر گرفته شد.*

نتایج: *نتایج نشان داد سطوح مقادیر HS-CRP و IL-6 در گروه تمرینی پس از هشت هفته تمرین هم‌زمان مقاومتی - استقامتی نسبت به گروه کنترل کاهش یافته است (P< ۰/۰۵) و همچنین سطوح مقادیر IL-1 و IL-12 در گروه تمرینی در مقایسه با گروه کنترل افزایش یافته است (P> ۰/۰۵).*

نتیجه‌گیری: *کاهش سطوح سرمی HS-CRP و IL-6 و دامنه طبیعی آن در پروتکل تمرین می‌تواند پاسخ تنظیم کننده‌ای به وضعیت التهابی بیماران تالاسمی ماژور، تحت شرایط خاص فعالیت ورزشی و بدون نشانه‌ی پاتولوژیک باشد و احتمال می‌رود منجر به بهبود التهاب مزمن عروقی گردد. یافته‌ها نشان می‌دهد تمرین هم‌زمان (مقاومتی - استقامتی) با تغییر قابل قبول مقادیر شاخص های التهابی بیماران بتا تالاسمی ماژور، می‌تواند در روند تأخیر آترواسکلروز نیز نقش مؤثری ایفاء کند.*

کلیدواژه‌ها: *تمرین هم‌زمان مقاومتی - استقامتی، بتا تالاسمی ماژور، شاخص‌های التهابی*

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