Original Article

Modulation of blood hemostasis by concurrent training in obese women with low-mobility

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Abstract

***Background & Aims*:** Obesity is a risk factor for the development of cardiovascular diseases; it can in part be explained by a disturbance in the blood hemostasis. The balance of the coagulation and fibrinolysis factors has an important role in maintaining hemostasis. Thus, the aim of this study was to modulate blood hemostasis by concurrent training in obese women with low-mobility.

***Materials & Methods*:** 20 women (25-30 years, BMI>30 kg/m^2) with low mobility were randomly divided into control and concurrent training groups. Concurrent training was performed at 23 minutes sub-maximal aerobic training, two sets with 10 repetitions of 10RM resistance exercise for 8 weeks. Coagulation and fibrinolysis factors were measured using the ELISA kits. Analysis of data performed using dependent *t*-test and Analysis of variance.

***Results*:** In concurrent training, fibrinolysis factors like t-PA (p=0.001), plasminogen, and D-dimer (p=0.001) increased significantly. Coagulation factors (fibrinogen and PTT) decreased significantly (p=0.001); however, PAI-1 (p=0.001) and PT (p=0.001) increased significantly.

***Conclusion*:** The results of this study showed that fibrinolysis factors affected by concurrent training because, in this type of training, the combination of the effect of aerobic training on plasma volume and resistance training on blood proteins improves fibrinolysis. Further studies are suggested about the effect of this type of training on coagulation factors.

***Keywords*:** Concurrent training, Blood hemostasis, Coagulation, Fibrinolysis, Obesity, low-mobility

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Introduction

Cardiovascular disease (CVD) is one of the most common causes of mortality in many countries(1). The prevalence of these diseases is due to an increase in risk factors such as sedentary lifestyle, obesity, smoking, alcohol consumption, hypertension, increase in blood glucose levels and cholesterol(2). However, in developing countries, the number of deaths due to CVD increased from 20 - 25% to 35-40%. One of the most important causes of coronary artery disease is atherosclerosis. The main challenge related to the atherosclerosis is the ability to measure thrombosis and

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the process of fibrinolysis disorder. In patients with excess blood hemostatic imbalances that lead to over-coagulation, even a partial rupture in the vein leads to excessive clotting(3). In the past decade, it has been determined that coagulation and fibrinolysis balance, as well as novel biomarkers, play an important role in the pathogenesis of the chronic disease, including CVD(4). Coagulation and fibrinolysis parameters are important predictors of CVD, independent from the common risk factors(5). Fibrin-rich clot formed at the end of the blood coagulation cascade plays a temporary role and must be removed when normal tissue structure and functions are restored. The fibrinolysis system is the main mechanism designed for the clot removal and controls the enzymatic degradation of fibrin. The dominant mechanism for *in vivo* fibrinolysis is the plasminogen-plasmin system, which can be activated by intrinsic and extrinsic pathways(6).Also, Fibrinolysis and coagulation factors such as Tissue plasminogen activator (t-PA), Plasminogen activator inhibitor type1 (PAI-1), Plasminogen, Fibrinogen, D-dimer, Prothrombin time (PT), and Partial thromboplastin time (PTT) can disrupt the blood hemostasis(7). Various studies have examined the role of physical activation t-PA. Tissue plasminogen activator (t-PA) was measured before and after a short maximal bicycle exercise test. Compared to resting levels, t-PA was significantly elevated immediately post-exercise. These results indicate that in conjunction with an activation of pro-coagulant factors, there is also an increased response by the fibrinolytic system during acute exercise. The increased levels of t-PA helps to maintain a stable condition of the blood by activating more plasmin for potential clot breakdown(8). The release of t-PA during fibrinolysis appears to be the most important mechanism counteracting clotting and preventing thrombosis. Therefore, significant increase in t-PA following exercise may be responsible for minimizing the risk of thrombosis during or after exercise(9).Plasminogen activator inhibitor (PAI-1) is the main inhibitor of t-PA and thus acts as the major inhibitor of the fibrinolysis system(10).

Sedentary lifestyle and obesity are the major risk factors of CVD and predictors for chronic diseases and early deaths(11, 12). Studies show a linear inverse relationship between CVD and mortality rate due to the disequilibrium of the clot and its solubility(13). In their investigation, Womack et al. (2003) showed that intensive and maximal exercise decreased some of the coagulation factors such as PAI-1(13).Following a maximal treadmill exercise test, PAI-1 decreased in healthy males and remained lowered for at least 10 minutes following the completion of exercise(14). Results also showed a decrease in PAI-1 levels as a result of moderate intensity exercise in patients with metabolic syndrome and at risk for CVD (15). Similarly, a decrease in PAI-1 activity levels by as much as 40% during submaximal treadmill walking was observed in patients with peripheral artery disease (16).

An increase in fibrinolysis usually does not occur at the intensity below 50% of HR_{max}, because epinephrine increases at levels close to the lactate threshold(17). The exercise duration may affect fibrinolysis responses to exercise, although the importance of exercise intensity is greater(18). The response to the exercise occurs in the moderate intensity for 1 hour. Therefore, the effect of exercise intensity on fibrinolysis is more important than the duration of exercise. Unless much time is spent exercising. In coagulation, the intensity of exercise is more important than duration. Therefore, the intensity of exercise in coagulation and fibrinolysis is important, but its importance is more obvious in coagulation(19). There is very little research with contradictory results about the effect of concurrent training (resistance-aerobic) on coagulation and fibrinolysis(20). They state that after 8-week concurrent training, fibrinogen, and platelet factors decreased significantly, but PT, PTT, and d-dimer factors increased simultaneously. Coughlin et al. (2018) show that I/D polymorphism of the t-PA

gene neither influence the t-PA antigen nor t-PA activity responses to maximal exercise in young and healthy sedentary males(21). Thus, the concurrent training can be useful in counteracting the threatening complications of hemostasis and the aging process and should be used as an appropriate training protocol for maintaining health in these individuals.

Concurrent training reduces coagulation progression and increases fibrinolysis activity in sedentary young women(22). Researchers have reported a reduction in blood fibrinogen factor and the number of platelets after training, because of a decrease in fat percentage, body weight, Body Mass Index (BMI), and suggested that they are directly related to fibrinogen concentration in the blood. Possibly reducing the activity of cytokines in concurrent training reduces the fibrinogen concentration in the blood or reduces fibrinogen synthesis in the liver that is the adaptation of the musculoskeletal system. Interleukin-1 response decreases by increasing physical fitness, which is effective in reducing the synthesis of fibrinogen in the liver cells(22). The main cause of CVD in young women without traditional risk factors is increasing the clot formation and thrombosis. It seems that performing 10 sessions of aerobic-resistance training with moderate intensity can reduce coagulation activity. Concurrent training will improve body composition, lipoprotein profile and cardiovascular health(23).

There is inadequate information on coagulation and fibrinolysis factors in training intensity, duration, type, different age, and sexes, and there is a need for considering these variables. On the other hand, some of studies about the effect of concurrent training on factors such as t-PA, PAI-1, fibrinogen, plasminogen, fibrin d-dimer, PT, and PTT have provided contradictory results. Thus, the aim of this study was considering the modulation of blood hemostasis by concurrent training in obese women with low-mobility.

Materials and Methods

Subjects:

The purpose of this semi-experimental study was to consider the effect of concurrent training on coagulation and fibrinolysis factors in sedentary obese women. The statistical population consisted of low-mobility obese women who registered for weight loss and physical fitness in Nahavand sports clubs. The low-mobility criterion was based on the Beck's Physical Activity Questionnaire. For this purpose, 20 women (25-30 years) with low mobility and BMI> 30 kg / m^2 voluntarily participated in this study. The subjects were randomly divided into control (without training intervention) and concurrent training groups (Table 1). First, the CARE guidelines checklist and the informed consent form were given to all of the subjects in the research project. All subjects completed and signed it.Prior to the beginning of the training, researchers provided the subjects with the necessary information to get acquainted with the protocols and safety issues in the sport. Also, the PAR-Q form was administered to subjects before the training to examine the health status of subjects and to exclude subjects with the specific disease from the research project.

Concurrent training:

The concurrent group completed 3 sessions per week for 8 weeks. In the training group, a combination of both aerobic(moderate-intensity continuous ET,m Ciolac)(24)and resistance methods (Progressive Resistance Exercise. I. J. Macqueen) with a free weight and machine weight (10 minutes warm up, 23 minutes submaximal aerobic training, 2 sets of 10RM with 10 repetitions of maximum resistance exercise and 5 minutes of cool down) were provided. There were 3 minutes of active rest between aerobic and resistance exercises. The combination of two sub-aerobic exercise and resistance programs with the same intensity and approximately half the time of each program was

considered. The capacity of concurrent exercises, duration, and intensity were similar to those of the submaximal aerobic, and resistance exercise (Table 1).

Table 1. Type, intensity, repetition, and duration of concurrent training

			Week 1-2	Week 3-4	Week 5-6	Week 7-8
Concurrent training	Aerobic	Duration	15 min	18 min	20 min	23 min
		Intensity	60٪ HRMAX	70٪ HRMAX	80٪ HRMAX	85٪ HRMAX
	Resistance	2 set, 10 RMMAX, according to overload and progressive resistance				

Measuring Biochemical Variables:

Blood sampling is performed in two stages, one day before the first exercise session (pre-test) and 6 to 48 hours after the last exercise session (post-test) in the eighth week and after 10 hours of fasting. The blood specimens were centrifuged for 20 minutes at 3000 rpm and the serum was kept at -80 °C. Half an hour before the test, referrals were removed from the refrigerator to reach the laboratory temperature (20-25). Coagulation and fibrinolysis factors were measured using the ELISA kits (Abcam, USA, PAI-1: sensitivity, 0.5 IU/ml, t-PA: sensitivity, 0.5 ng/mL, D-dimer: mean recovery percent, 99-105%, fibrinogen: sensitivity, 1 ng/ml, plasminogen: sensitivity, ~0.5 ng/mL, PTT, kit Randoxr = 0.95, kitRandoxr = 0.98).

Statistical analysis:

After verifying the normality of the data by Kolmogorov-Smirnov test, for statistical analysis, the SPSS software version 20 was used for statistical methods of dependent *t*-test and Analysis of variance. All operations are statistically significant at Alpha 5% and confidence intervals 95%.

Results

In this study, the main fibrinolysis and coagulation factors (t-PA, PAI-1, Plasminogen, Fibrinogen, D-dimer, PT, and PTT) in the two groups of concurrent training and control were evaluated. Demographic characteristics of all subjects were calculated and presented in Table 2.

Table 2. Demographic characteristics of concurrent and control groups

Groups	sex	Age (year)	Height (cm)	Weight (kg)		Body Mass Index (kg/m2)	
				pre-test	Post-test	pre-test	post-test
Concurrent training	female	21.44± 1.58	165.11± 3.78	82.05±4.09	79.50± 3.92	30.58± 1.74	29.22± 1.66
Control	female	24.71± 2.98	162.28± 7.18	80.71± 5.40	80.50± 5.38	30.73± 2.38	30.72± 2.37

The results of the study showed that the mean of t-PA and PAI-1 (Table 3) in the concurrent training increased significantly (p = 0.000). But, in the control group, the increase was not significant (p = 0.998). There was a significant difference between control and concurrent training (Table 4) after 8 weeks in t-PA (p = 0.003) and PAI-1 (p = 0.004).

Fibrinogen decreased significantly in concurrent group (p=0.000), but not in control group (p = 0.858; Table 3). Also, there was a significant difference between concurrent and control group (p = 0.000; Table 4).

Plasminogen increased significantly in the concurrent group (p=0.000), but there was no significant difference in the control group (p=1.000) (Table 3). There was a significant difference between control and concurrent groups in Plasminogen (p = 0.000; Table 4).

Level of D-dimer in the concurrent group increased significantly (p = 0.000), but there was no significant difference in the control group (p = 0.535; Table 3). There was a significant difference between control and concurrent group in D-dimer after 8 weeks (p = 0.000; Table 4).

Compared to the control group, mean of PT in concurrent groups increased significantly (p = 0.000; Table 3). There was a significant difference between the control and concurrent groups after 8 weeks in PT (p = 0.000; Table 4).

Mean of PTT in concurrent groups decreased (p = 0.000), but PTT increased non-significantly in the control group (p=1.000; Table 3). There was a significant difference between the control and concurrent groups after 8 weeks in PTT (p = 0.000; Table 4).

Table 3. Mean and SD of intra-group in term of t-PA, PAI-1, Fibrinogen, Plasminogen, and D-dimer in Concurrent and control groups

Variable	Examination	Mean Concurrent	Sig.	Mean control	Sig.
t-PA (ng/ml)	Pre-test	8.066 ±0.255	0.000*	7.898 ±0.464	0.998
	Post-test	8.769 ±0.262		8.032 ±0.538	
PAI-1 (ng/ml)	Pre-test	17.937 ±0.310	0.000*	17.898 ±0.685	0.998
	Post-test	18.715 ± 0.438		17.800 ±0.365	
Fibrinogen (ng/ml)	Pre-test	179.1 ±5.258	0.000*	179.428 ±5.255	0.858
	Post-test	162.800 ±5.884		175.857 ±4.017	
Plasminogen (ng/ml)	Pre-test	97.250 ±2.821	0.000*	97.785 ±1.149	1.000
	Post-test	108.300 ±3.831		97.857 ±1.951	
D-dimer (ng/ml)	Pre-test	236.800 ±3.765	0.000*	235.571 ±7.091	0.535
	Post-test	310.300 ±6.201		241.857 ±6.517	
PT (second)	Pre-test	12.430 ±0.301	0.000*	12.532 ±0.025	0.614
	Post-test	13.078 ±0.090		12.348 ±0.039	
PTT (second)	Pre-test	34.653 ±0.556	0.000*	34.247 ±0.588	1.000
	Post-test	31.712 ±0.552		34.342 ±0.637	

P<0.05*

Table 4. Comparison of mean difference in t-PA, PAI-1, Plasminogen, Fibrinogen, and D-dimer between groups after 8 weeks of training

Variable	Group	Groups	Mean difference	Sig.
t-PA (ng/ml)	Concurrent (post-test)	Control (post-test)	0.736	0.003
PAI-1 (ng/ml)	Concurrent (post-test)	Control (post-test)	0.915	0.004
Fibrinogen (ng/ml)	Concurrent (post-test)	Control (post-test)	-13.057	0.000*
Plasminogen (ng/ml)	Concurrent (post-test)	Control (post-test)	10.442	0.000*
D-dimer (ng/ml)	Concurrent (post-test)	Control (post-test)	68.442	0.000*
PT (second)	Concurrent (post-test)	Control (post-test)	0.729	0.000*
PTT (second)	Concurrent (post-test)	Control (post-test)	-2.630	0.000*

$P<0.05$*

Discussion and Conclusion

Regular physical activity can modulate blood homeostasis(27), thus the aim of this study was to consider the modulation of blood hemostasis by concurrent training in obese women with low-mobility.The results of the study showed that t-PA in the concurrent group significantly increased after 8 weeks. This increase can be attributed to the interactive effects of aerobic-resistance, with respect to the principles of severity, duration, and repetition of training, by considering the overload and progressive resistance. Diehl et al. (2014) indicated that habitual exercise is an effective lifestyle intervention strategy for improving endothelial fibrinolytic capacity (with increase t-PA) in pathological infected adults(28). The Obesity and diabetes also cause dysfunction in endothelial cell that affect t-PA, but this study shows that exercise can modulate and increase the t-PA which can protect endothelial cell dysfunction. In addition, the results of this study are consistent with the research by Sobhani et al. Concurrent training, in contrast to aerobic and strength training alone, lead to further improvement of body composition and cardiovascular health(22). Concurrent training is a combination of the aerobic and resistance training, and have a positive effect on fibrinolysis factors such as t-PA, with effects on enzymes, lipid factors, and hormones(29). Also, concurrent training can be used to reduce and modify lipid profiles. The control group did not participate in any concurrent exercise intervention, so they did not experience the effects of these exercises.

In this study, Plasminogen and PAI-1 levels increased significantly after 8 weeks of concurrent training. Contrary to the results of this study Lira et al.

(2010) show that sedentary subjects have higher PAI-1 and lipoproteins levels than highly trained athletes(30). One of the reasons for the difference between the results of this study and Lira et al. can be related to the type of subjects. Subjects in the study consisted of immobile obese women who underwent 8-week concurrent training. The duration of exercise, also due to the reduction of BMI, can have a good effect on the function of the endothelial cell and also the cause of clot induction (by PAI-1). However, the body weight and BMI of the subjects did not reach to normal in the present study. It should be noted that few studies have been conducted on the effect of concurrent training on PAI-1. However, in this case, we used the generalization and deduction of studies. According to Sobhani (22) research on the effect of combined aerobic-resistance training on some coagulation factors is not consistent with the current research, so further studies are needed., failure to change or increase body weight in the concurrent group can lead to an increase in PAI-1. It is also possible that, increasing the concentration of PAI-1 in the blood in concurrent training can be due to increased activity of cytokines. Usually, obese women have low levels of physical fitness. The response of Cytokines, especially Interleukin-1, will increase by decreasing physical fitness(31).

Fibrinogen significantly decreased in the concurrent group after 8 weeks of concurrent training. Physical activity reduced the incidence of CVD. Fibrinogen and high-sensitivity C-reactive protein (hsCRP) are novel risk factors, which strongly predict the risk of CVD(32).Fibrinogen is a soluble glycoprotein that acts as a precursor of the fibrin monomer, the primary fibrillar protein involved in clot formation. Fibrinogen is also an important mediator of atherosclerosis. It is produced in the liver, binds to GP1b and GP2b/3a receptors of platelets and stimulates adhesion and aggregation of platelets(33, 34). Consequently, according to the results of this study, the use of Concurrent training has been effective in reducing the risk of CVD by reducing fibrinogen. In addition, inflammatory response stimulates the transfer of fibrinogen and fibrin molecules to the intima(35, 36).Concurrent training includes aerobic and resistance exercises. Therefore, the effect of concurrent training can be due to the interactive effect of these two types of exercise. Researchers (22)have reported a decrease in fat percentage, body weight, and BMI after concurrent training that can result in the reduction of blood fibrinogen levels. This may decrease the concentration of fibrinogen in the bloodstream by reducing Cytokines activity.

The results of this study showed that 8 weeks of concurrent training resulted in a significant increase in d-dimer. There is contradictory information about the effect of concurrent training (resistance-aerobic) on coagulation and fibrinolysis factors. Koehler and Bottoni (2016) showed that neither level of conditioning nor short and intense exercise affected D-dimer levels in participants at low risk for thromboembolic disease(37),but the subjects in this study were overweight and had a risk factor for cardiovascular disease. Also, the results of this research, regardless of the research method and the statistical analysis, are consistent with findings of Sobhani et al. (22). This significant increase can be attributed to the positive effects of severity, duration, and type of training. Concurrent training can be effective in levels of fibrinogen, platelet, and D-dimer. Concurrent training is effective in weight loss, fat mass, and BMI, which can affect coagulation and fibrinolysis factors(29). Contradictory results in d-dimer modification after training may be due to age, changes in catecholamines, decrease in fibrinogen factor, and health status of subjects. Changes of fibrinogen factor and d-dimer have inverse correlation. In activities that fibrinogen factor reduces, the d-dimer factor will increase(6). As age rises, fibrinogen chain or fibrinogen molecules

fragmentation will increase by plasmin, resulting in an increase in the D-dimer factor that has an inverse relationship with fibrinogen degradation. The factors that influence the D-dimer factor are the duration, severity, type of activity, the health of the subjects and their mental and psychological conditions(38). The control group did not participate in any intervention, so they did not experience the effects of these exercises. Therefore, there was a difference between the concurrent and the control group at the D-dimer factor.

The results of the study showed that after 8 weeks of concurrent training, PT significantly increased. These changes can be attributed to the type, intensity, and duration of concurrent training. The results of this study are consistent with the findings Sobhani et al. (22).They found that after exercise, the number of platelets and fibrinogen level in the concurrent exercise decreased significantly and prothrombin time (PT) in the high-intensity exercise and the level of d-dimer in both exercises increased significantly. Some researchers showed that concurrent training, in contrast to endurance and strength training, would further improve body composition and cardiovascular health(39). Concurrent training increases the pre-inflammatory cytokine levels (TNF-α) and cortisol hormone. Concurrent training can also be used to modify lipid profiles. It should be noted that according to Table 2, the weight of the subjects decreased in the present study. All of these factors can affect the amount of PT in concurrent training.

Beta-adrenoceptor and nitric oxide blocking are both linked to the discontinuation of the VIII coagulation factor. The activity of the Thrombin-antithrombin complexes (TAT) of prothrombin 1 and 2, fibrinopeptide A, and total coagulation factor VIII remains high, and the increase in prothrombin units of 1 and 2 continued. The amounts of the Thrombin-antithrombin complexes, prothrombin 1 and 2 fragments, fibrinopeptide A, returned to baseline values 21 hours after exercise. In the early stages of recovery after exercise, also during exercise the risk of acute coronary syndrome increases(40). The pattern of change in PT duration (the duration of clot formation) can be determined by the type of exercise and the PT time reduced by increasing the duration of the exercises(39). Losing weight as a result of concurrent training can improve coagulation parameters such as PTT. Weight loss due to concurrent training can control oxidative stress, platelet activity, and chronic coagulation factors. About 10% weight loss during concurrent training can control and correct platelet arrhythmias(41).

The reduction of PTT in this research can be attributed to intensity, duration, and the type of training. This decrease can indicate faster blood clotting time, which is very important in patients with CVD. The results of the present study are consistent with the findings Womack(42). There is controversial information about the effect of concurrent exercises on coagulation and fibrinolysis factors. It seems that performing 10 sessions of moderate-intensity combined aerobic training can reduce coagulation activity. Researches showed that concurrent training, in contrast to endurance and strength training, leads to further improvements in body composition and cardiovascular health(23). The duration and type of training influence coagulation and fibrinolysis factors which can change the levels of hormone, enzyme, and lipids in the blood. So far, there has not been a definitive conclusion in this case.

Due to tissue damage and damage to vascular endothelial cells, collagen tissue under the arteries is exposed to platelets and coagulation factors that cause their activity. At the beginning of this route, factor XI is induced by factor XIIa, factors XI and XII are known as contact factors. Then factor IX is converted to factor IXa by factor XIa in the presence of calcium ion. Following this pathway, the complex of factors VIII and IX associated with Ca^{++} and phospholipids in platelet

ultimately activates the x-factor. The time of thromboplastin (PTT) is a selective test to evaluate this pathway and I, II, V, VIII, IX, X, XI and XII factors. It seems that in healthy adults, concurrent exercise causes a change in the coagulation potential. The findings of studies showed an increase, decrease, or no change in PTT after exercise. However, concurrent exercises play a significant protective role in cardiac patients, while exercise training prolong the time of thromboplastin activation and reduce the activity of VIII coagulation factor and fibrinogen levels. Hemostatic changes after aerobic exercise as part of short-term concurrent exercises lead to dangerous events, especially for heart. Of course, it should be noted that the effect of concurrent training components is a function of the intensity, duration of the training and the type of training. In concurrent training, the interactive effect of two types of aerobic and resistance training is very important, which has a great impact on coagulation and fibrinolysis, especially PTT(26).

Conclusion

Intensity, duration, type and stages (such as warming up) of training, especially intensity, are effective in coagulation and fibrinolysis factors. In addition, the results of this study showed that fibrinolysis factors were affected by concurrent training because, in this type of training, the combination of the effect of aerobic training on plasma volume and resistance training on blood proteins improves fibrinolysis. While further studies are suggested about the effect of this type of exercise on coagulation factors.

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Conflicts of interest

There are no conflicts of interest.

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