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Effect of Home-Based Aerobic Exercise Program on Bleeding Profile and Inflammation in Patients with Behçet's Disease

Ev-Bazlı Aerobik Egzersiz Programının Behçet Hastalarında Kanama Profili ve İnflamasyon Üzerine Etkisi

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ABSTRACT Objective: Sedentary lifestyle is a major risk factor for cardiovascular disease (CVS) and thrombotic complications. The effect of different types of exercise on platelet function has been the subject of a limited number of studies. Behçet's disease is a multisystemic disease characterized by recurrent oral and genital aphthous lesions and uveitis with unknown etiology. There is an unknown cause of the disease and hyperactivation of the procoagulant cascade and associated mortality due to arterial and venous thrombosis. Here, the effect of aerobic exercise on the bleeding profile and acute phase reactants in Behçet's patients was analyzed experimentally. **Material and Methods:** Twenty-four (n=24) patients with Behcet's disease were included in the study. Age, height, weight, sex, smoking, known systemic disease (such as diabetes, hypertension, thyroid) and vascular claudication were investigated. Those who didn't complete the protocole (n=5) were excluded from the study. Before and after moderate intensity aerobic exercise program (4 weeks, 3 times a week, 45 minutes per day) sedimentation (ESR), C-reactive protein (CRP), bleeding profile including prothrombin time (PT), prothrombin time percentage (PT%), activated prothrombin time (aPTT), platelet, collagen epinephrine, collagen adenosine diphosphate (ADP) and international normalized ratio (INR) were recorded. **Results:** Nineteen patients with Behçet's disease were enrolled. The mean age was 37.8±9.8 years. The mean body mass index (BMI) was 28.6±5.5 kg/m^2. Vascular claudication was present in 9 patients (47.4%), smoking in 1 patient (5.3%), and hypertension (10.5%) in 2 patients. While ESR (p=0.028) and collagen ADP (p=0.02) decreased after exercise; platelet count (p=0.005), aPTT (p=0.08), PT (p=0.022) and PT% (p=0.014) were increased. **Conclusion:** Increase in the duration of aggregation and decrease in inflammation after the exercise program supports that thrombosis can be prevented by exercise. We conclude that short term home-based aerobic exercise program has positive effect on homeostasis in patients with Behçet's disease.

Keywords: Aerobic exercise; platelet function; bleeding profile; Behçet's disease; homeostasis

ÖZET Amaç: Sedanter yaşam tarzı kardiyovasküler hastalık (CVS) ve trombotik komplikasyonlar için önemli bir risk faktörüdür. Farklı egzersiz türlerinin trombosit fonksiyonu üzerindeki etkisi sınırlı sayıda çalışmanın konusu olmuştur. Behçet hastalığı, tekrarlayan oral ve genital aftöz lezyonlar ve etiyolojisi bilinmeyen üveit ile karakterize çok sistemli bir hastalıktır. Hastalığın bilinmeyen bir nedeni ve prokoagülan kaskadın hiperaktivasyonu ile arteriyel ve venöz tromboz ilişkili mortalite vardır. Burada Behçet hastalarında aerobik egzersizin kanama profili ve akut faz reaktanları üzerindeki etkisi deneysel olarak analiz edildi. **Gereç ve Yöntemler:** Behçet hastalığı olan 24 (n=24) hasta çalışmaya dahil edildi. Yaş, boy, kilo, cinsiyet, sigara içme, bilinen sistemik hastalık (diyabet, hipertansiyon, tiroid gibi) ve vasküler kladikasyo araştırıldı. Protokolü tamamlamayanlar (n=5) çalışma dışı bırakıldı. Orta yoğunluklu aerobik egzersiz programından önce ve sonra (4 hafta, haftada 3 kez, günde 45 dakika) sedimantasyon (ESR), C-reaktif protein (CRP), protrombin zamanı (PT) dahil kanama profili, protrombin zaman yüzdesi (PT%), aktive edilmiş protrombin zamanı (aPTT), trombosit, kollajen epinefrin, kollajen adenosin difosfat (ADP) ve uluslararası normalleştirilmiş oran (INR) kaydedildi. **Bulgular:** Behçet hastalığı olan 19 hasta çalışmaya dahil edildi. Yaş ortalaması 37.8±9.8 yıl idi. Ortalama vücut kitle indeksi (VKİ) 28.6±5.5 kg/m^2 idi. Dokuz hastada (%47.4) vasküler kladikasyo, 1 hastada (%5.3) sigara içimi ve 2 hastada hipertansiyon (%10.5) mevcuttu. Egzersiz sonrası ESR (p=0.028) ve kollajen ADP (p=0.02) azalırken; trombosit sayısı (p=0.005), Aptt (p=0.08), PT (p=0.022) ve % PT (p=0.014) arttı. **Sonuç:** Egzersiz programından sonra agregasyon süresinin uzaması ve inflamasyondaki azalma trombozun egzersiz ile engellenebileceğini desteklemektedir. Behçet hastalarında kısa dönem ev temelli aerobik egzersiz programının homeostaz üzerinde olumlu etkisi vardır.

Anahtar Kelimeler: Aerobik egzersiz; trombosit fonksiyonu; kanama profili; Behçet hastalığı; homeostaz

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Some of the positive effects of physical activity on CVS are caused by the effect of homeostasis. After the first adhesion of platelets in the damaged area, aggregation involving platelet-platelet adhesion for effective homeostasis is necessary. Following adhesion, platelets are activated with various agonists, such as adenosine diphosphate (ADP) and collagen, at the site of vascular damage. These agonists bind to specific receptors on the platelet surface and activate platelets.[1-5] Numerous lifestyle modifications to reduce the risk of CVS have been of interest to studies. The effects of physical activity on metabolic syndrome, insulin sensitivity, CVS risk and mortality are well defined. Factors including serum lipoproteins, inflammation, markers of thrombosis and coronary artery calcium and carotid intima media have been studied.

Behçet is a chronic inflammatory, systemic disorder characterized by relapses and remissions. It is characterized by oral, genital ulcer, skin lesions, uveitis, vascular and gastrointestinal involvement. The main histopathological finding is widespread vasculitis in the arteries and veins of any size. The cause of the disease is multifactorial and it is thought to be the dysregulation of the immune system with infectious triggers in the genetically predisposed person. The clinic is heterogeneous and its pharmacological treatment depends on the severity of the disease and organ involvement.[7]

Hyperactive autoimmunity induced by environmental triggers causes two types of vascular damage. First vasculitic lesions may be common. Sequela depends on the affected organ systems. Some pathological changes are not vasculitic, but are caused by thrombosis and/or clot formation caused by hypercoagulability. This mechanism is still undefined and it has been shown that excessive thrombin formation and impaired fibrinolytic processes can cause hypercoagulabyl/prothrombotic state.[8] Especially in men with Behçet's disease, lower extremity venous thrombosis and related venous claudication is a serious and frequent symptom. It adversely affects walking capacity.[9] In Behçet's disease, venous involvement is mostly in the lower extremities. In the presence of deep vein thrombosis and rare pulmonary artery embolism and aneurysms, treatment is immunosuppressive and anticoagulant therapy.[10]

There are studies on the effectiveness of different exercise modalities in platelet functions in the literature. It is known that high intensity exercises cause thrombotic complications in the CVS in the acute period.[6-10] In this study, we analyzed the effect of moderate-intensity regular home-based aerobic exercise on homeostasis and inflammation in patients with Behçet's disease with the highlights of current literature.

MATERIAL AND METHODS

The study was planned prospectively and experimentally. Twenty-four (N=24) patients with Behcet's disease were included in the study. Age, height, weight, gender, smoking, known systemic disease (such as diabetes, hypertension, thyroid), history of thrombosis, presence of vascular claudication, and regular exercise were questioned. Those who had contraindicated exercise (orthopedic or cardiac causes) were excluded from the study. Participants prior to and after 4 weeks of moderate aerobic exercise program (3 times a week, 45 minutes per day) sedimentation (ESR), C-reactive protein (CRP) and bleeding profile including platelet count, prothrombin time (PT), prothrombin percentage (PT %), activated prothrombin time (aPTT), collagen epinephrine, collagen adenosine diphosphate (ADP) and international normalized ratio (INR) were recorded. A history of cardiovascular, pulmonary or metabolic diseases, orthopedic problem, stroke, non-Behçet inflammatory diseases, pregnancies were excluded from the study. Five of the participants were excluded from the study because they could not complete the exercise program correctly.

BLOOD SAMPLING AND EVALUATION OF HOMEOSTASIS[11-15]

Blood samples were collected from 3 volunteers with 3.2% buffered trisodium citrate and 1 tube containing K2EDTA as anticoagulant from the volunteers. One of the tubes containing 3.2% buffered trisodium citrate was centrifuged at 4000 rpm and at room temperature for 10 minutes and then worked without waiting. After centrifugation, PT and aPTT tests were performed. Whole blood samples (complete blood count, collagen epinephrine and collagen ADP) were studied without centrifugation.

Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT): PT and aPTT tests were performed with Thromborel S and Actin FS reagents in Sysmex CS 2000i (Sysmex Corporation, Kobe, Japan). PT measurement is based on the measurement of clot formation time after addition of thromboplastin (an activator of the extrinsic pathway) to the citrate plasma sample and the addition of calcium; unit is seconds.

Collagen epinephrine and collagen ADP: Collagen epinephrine and collagen ADP tests were performed in whole blood from tubes taken from volunteers to citrated tubes using PFA-100 (Platelet Function Analyzer) (Semiens Healthcare Diagnostics, Marburg, Germany). PFA-100 is a system that simulates primary homeostasis in vitro and is an alternative method for bleeding time testing. It is used for screening of platelet functions.

Complete blood count and platelet count: The platelet count from K2EDTA-containing tubes was performed using the Sysmex XN-3000 (Sysmex, Kobe, Japan) automated hematology device. Platelet counts are performed according to the principles of impedance (PLT-I) and optical fluorescence (PLT-O and PLT-F) in the otonalizer. The PLT-I method uses the principle of direct-flow hydrodynamic focusing to determine the resistance of the particles passing through the hole.

Erythrocyte Sedimentation Rate (ESR): Sedimentation measurements were performed using EDTA tubes in VISION C (SHENZHEN YHLO BIOTECH CO., Shenzhen, China). The level of erythrocytes with infrared LEDs is also determined by VISION.

EXERCISE PROTOCOL

It was reciped as moderate intensity, 4 weeks lasting at least 3 times a week for 45 minutes per a day home-based aerobic exercise program. Aerobic exercise types such as walking, running, cycling, aerobic dance, swimming were recommended. Any symptom; shortness of breath, severe muscle pain, syncope, palpitations, sudden blood pressure decrease or increase and discomfort were recommended to interrupt the exercise. Patients (n=5) who discontinued or did not complete home-based aerobic exercise program were excluded from the study.

STATISTICS

Analysis was performed by using Statistical Package for the Social Sciences 22 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, USA). Continuous data were presented as mean±standard deviation and categorical variables were summarized as percentages. Shapiro Wilk test was used for the evaluation of normal distrubution. Comparisons were made by using McNemar tests for categorical variables, paired samples t tests for normally distributed continuous variables and Wilcoxon sign test when the distribution was skewed. A p value <0.05 was considered statistically significant. The study is approved by local ethic committe (protokol no: 2018/299) and Helsinky declaration principles were followed.

RESULTS

A total of 10 male and 9 female patients with Behçet's disease (n=19) were included in the study. The mean age was 37.8±9.8 years. The mean BMI was 28.6±5.5 kg/m^2. Vascular claudication was present in 9 patients (47.4%), smoking in 1 patient (5.3%), and hypertension (10.5%) in 2 patients. None of the patients had a history of regular exercise and thrombosis. Laboratory parameters before and after exercise program are summarized in Table 1. While ESR (p=0.028) and collagen ADP (p=0.02) decreased after the exercise; platelet (p=0.005), aPTT (p=0.08), PT (p=0.022) and PT% (p=0.014) were increased. They were all in normal range interval before and after the exercise program.

DISCUSSION

Cardiovascular (CVS) disease is a major world wide health problem, and metabolic syndrome and type 2 DM increase the risk of CVS disease. Regular physical activity reduces the risk of CVS mortality in relation to lipids, blood pressure, insulin resistance, obesity, hemostasis and endothelial function.[16] Life habits like exercise can affect the risk of vascular thrombotic event. With moderate increase in risk of primary cardiac arrest during intensive exercise, regular moderate-intensity exercise is associated with a reduction in CVS disease risk. According to the evi-

TABLE 1: Comparison of the data before and after exercise program.

	First assesment	After exercise program	t	p
ESR*(mm/hour) (0-20)	14.1±11.3	10.9±8.2	2.500	0.028
CRP (mg/dL) (0-5)	5.5±4.6	6.9±8.4	-1.333	0.207
PT* (11-16 seconds)	12.1±1.1	12.6±0.54	2.508	0.022
PT%* (70-130)	98.2±16.1	104.4±11.2	-2.734	0.014
Platelet* (170-388 103 µg/L)	267947.3±47666	301631.5±38684.2	-3.169	0.005
INR (0.8-1.2)	1.0±0.1	0.97±0.05	2.02	0.058
aPTT* (20-35 seconds)	24.3±2.2	26.1±3.2	3.035	0.08
Collagen epinephrin (82-150 seconds)	119.1±27.4	102±37.3	1.922	0.071
Collagen ADP (62-100 seconds)*	123.1±83.3	73.3±7.6	2.566	0.02

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PT: Prothrombine time; INR: International normalized ratio; aPTT: Activated partial thromboblastine time. *Paired samples t test, p<0.05, Statistically significant.

dence obtained, mild acute exercise does not affect platelet reactivity and coagulation, but increases fibrinolytic activity; moderate acute exercise suppresses platelet reactivity and increases fibrinolysis. While traumatic acute exercise increases platelet reactivity and coagulation, it is known to promote fibrinolytic activity. Therefore, moderate exercise is protective against CVS diseases with anti-thrombotic effects. Medium intensity exercise training reduces platelet reactivity and increases fibrinolysis. We know that these effects return to their original state when the exercise is released and deconditioned.[17]

In our study, we observed an increase in aPTT, PT and PT% values after the short term moderate intensity exercise program. This increase indicates a delay in coagulation, which is something we want. After this increase, patient values were within normal limits, which is an expected result. Beyond its traditional role in hemostasis and thrombosis, the platelet's involvement in the interplay between hemostasis, thrombosis, inflammation, is likely complex and essential in each disease process. Platelets release numerous inflammatory mediators that have no known role in haemostasis. On the other hand inflammation increases procoagulant factors, and also inhibits natural anticoagulant pathways and fibrinolytic activity, causing a thrombotic tendency.[18] In our study, decreasing inflammation (decreasing ESR) after exercise program, may also help reduce the risk of thrombosis. An increase in the number of platelets and a decrease in collagen ADP (showing the platelet function) shows the effect of exercise on platelet functions without any side effects.

The association of acute or compulsive exercise with transient hypercoagulability in untrained people is associated with increased thrombin generation, platelet hyperactivity, and increased activity of various coagulation factors. Increased fibrinolytic activity was reported after exercise. Trained people develop various adaptive mechanisms and improve platelet function in both coagulation and fibrinolytic system.[19] In our study, we observed that short term moderate intensity aerobic exercise (4 weeks) led to an increase in platelet count and function. Platelet activation including monocyte platelet aggregation (MPAs), atherosclerosis, contributes to thrombus formation. Regular exercise may reduce the CVS risk, but the effect of exercise on platelet function is little known. Long-term exercise programs may have structural positive effects on the vascular endothelial compared to short-term ones. Haynes et al. have shown that 6 months of walking exercise cause a significant reductionin atherosclerosis cellular mediator.[20]

CVS events are associated with arterial events involving platelets, endothelium and atherosclerosis. It is also known that there is a temporary increase in CVS risk after acute intensive exercise with data on regular exercise CVS events and decreasing mortal-

ity. None of our patients reported adverse side effects during exercise. Although regular exercise is beneficial, few cases of exercise-associated thrombotic events, venous thromboembolism, and myocardial infarction have been reported. These events are characterized by the vascular wall and fibrinolytic system and the prothrombotic state in which coagulation factors play a role. It is known that high intensity exercise increases the risk of thrombotic event, especially in various exercise modalities. However, the mechanism behind this event is unknown.[21]

The acute effect of different exercise modalities on platelet function has not been sufficiently defined. In the study by Haynes et al. resistance exercises temporarily increased the risk of platelet-mediated thrombosis compared to other aerobic modalities and showed that the increase in arterial function after exercise alleviated the acute effect of exercise in platelet activation.[22,23] For the last 2 decades, it has been known that platelets can be activated or activated more by compelling exercises and therefore may cause coronary ischemia due to exercise.[24] Stress increases the deposition of procoagulant microparticles from platelets and induces thrombin formation. In the the study by Chen et al. it was shown that strenuous exercises contribute to thrombin formation by increasing the release of procoagulant microparticles from platelets.[25] De Meirelles et al. show that regular exercise decreases platelet aggregation with antioxidant and anti-inflammatory effect in people with heart failure.[26] Low-grade inflammation is also a risk factor for CVS diseases. Inflammation contributes to the continuation of the balance between coagulation and fibrinolysis. Regular exercise and physical activity suppress proinflammatory cytokine production, anti-inflammatory mediators and antioxidant development and by increasing fibrinolytic activity has a protective effect against mortality.[27] The effect of high intensity interval training on inflammatory markers and endothelial function has been shown in many studies. In the study by Ahmadizad et al. high-intensity interval training was found to be higher in patients who underwent new revascularization than in those with continuous revascularization.[28] In our study, while the CRP value did not differ significantly, we see that the ESR value has decreased. Exercise program has a positive effect to CVS disease by decreasing inflammation.

Mauer et al. showed that 12-week walking exercise program improves ambulatory function without influencing clot formation in patients with klaudicoperipheral peripheral vascular disease.[29] Re-ambulation period after prolonged immobilization may also be a risk for thrombotic events.[30] Obesity is associated with an increase in thromboembolic events. Lamprecht et al. showed that intense aerobic exercise could be protective against thromboembolic events, and one-time very intensive aerobic exercise was associated with fibrinolytic system activation in obese women.[31] In the study by Kupchak et al. it has been shown to be associated with high tissue plasminogen activity and prolonged fibrinolytic duration after acute exhaustive resistance exercise test.[32] In humans, hyperactive platelets contribute to thrombotic response and exercise temporarily increases platelet function.[33]

Behçet's syndrome is a multisystemic vasculitis that is frequently seen in young adults and disrupts the quality of life by causing serious disability. Disease process, severity and organ involvement, age at onset and gender differences cause difficulties in the development of a single treatment strategy.[34] The disease is a multisystem disorder in unknown etiology and in a single geographic distribution. The disease is characterized by recurrent skin-mucosal lesions and panuveitis. Vascular involvement is more serious and common in men, causing veins and recurrent thrombosis. Lower extremity thrombosis is the most common feature, followed by vena cava thrombosis. Pulmonary artery involvement is the most common arterial involvement and occurs with aneurysm and insitu thrombosis. Lower extremity venous thrombosis and cerebral sinus thrombosis are often the first findings. Immunosuppressive therapy is essential to prevent these attacks and survival.[35]

Gökoglu et al. showed that aerobic and respiratory exercises increased the respiratory muscle strength and endurance, aerobic capacity and maximal ventilator capacity in Behçet's patients.[36] In patients with Behçet's disease, CVS involvement is

rare, but may occur in different characteristics and may be mortal. Silent myocardial ischemia is also common in these patients and patients who have been diagnosed for more than 10 years are recommended myocardial perfusion scintigraphy.[37] In the literature, cases with sudden chest pain, cough, fever, palpitations, severe pulmonary, coronary artery thrombosis and intracardiac aneurysm are observed.[38-40]

Behçet's syndrome is often complicated by thrombosis which occurs in vessels of all sizes. Thrombosis is more frequent in male patients with active disease and represents an important cause of morbidity and mortality. In the study by Emmi et al. it is suggested that an alteration in fibrinogen structure and function are associated with enhanced reactive oxygen species (ROS) production via neutrophil NADPH oxidase.[41] Vasculitic lesions are structural in Behçet's patients and acute exercise may not have been effective in this case. The underlying cause of hypercoagulability has not been identified yet in these patients. However, we observed the positive effect of the short term moderate intensity home exercise program in these patients without side effects on coagulability.

LIMITATIONS OF THE STUDY

The limitations of the study were that we did not take into account the medications, serum lipids and cardiovascular examinations taken by the patients included in the study and the home-exercise program was not accompanied by a supervisor. The study protocol was based on patient declaration, not all patients may be in full compliance with the protocol.

To assess the global disease activity in patients, Behçet syndrome disease activity score (BSAS) was not used in the study. Only laboratory parameters of the patients were examined before and after the protocol.

CONCLUSION

Increase in the duration of aggregation and decrease in inflammation after the exercise program supports that thrombosis can be prevented by exercise in patients with Behçet's syndrome. We conclude that short term home-based moderate intensity aerobic exercise program has a positive effect on homeostasis in patients with Behçet's disease with no CVS complications. For long-term effects of exercise, studies involving longer-term exercise programs are required.

Informed Consent

Written informed consent was obtained from the patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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