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The Effect of Aerobic Training Combined With Martighal Consumption on Vascular Endothelial Growth Factor and Homocysteine in Sedentary Women with Metabolic Syndrome

Elham Sadeghifar[1], Abdolali Banaeifar*[2], Vahid Imanipour[3], Sajad Arshadi[4]

1. PhD Candidate, Department of Physical Education and Sports Sciences, South Tehran Branch, Islamic Azad University, Tehran, Iran.
2. Associate Professor, Department of Physical Education and Sports Sciences, South Tehran Branch, Islamic Azad University, Tehran, Iran.
3. Assistant Professor, Department of Physical Education and Sports Sciences, Parand Branch, Islamic Azad University, Tehran, Iran.
4. Associate Professor, Department of Physical Education and Sports Sciences, South Tehran Branch, Islamic Azad University, Tehran, Iran.

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A B S T R A C T

Introduction: Recently, the role of using medicinal plants during exercise training has been expanded with the aim of improving antioxidant and cardiovascular function in healthy and sick obese populations. The aim of this study was to investigate the effect of aerobic training combined with Martighal extract on the serum levels of vascular endothelial growth factor (VEGF) and homocysteine in females with metabolic syndrome.

Methods: In this clinical trial, 48 obese females (30 ≤ BMI ≤ 36, mean weight: 84.45 ± 5.41 kg) diagnosed with metabolic syndrome aged 30-45 years were randomly allocated into four distinct groups: control (no intervention); Martighal extract (280 mg /daily); aerobic training (alternate days) and combined (aerobic training + Martighal) groups. Baseline concentrations of fasting VEGF and homocysteine, along with anthropometric measurements, were recorded prior to and 48 hours after the final training session for each group. To analyze the data, Analysis of Covariance (ANCOVA) was employed for inter-group comparisons, while the paired-sample t-test was utilized to assess within group changes (P ≤ 0.05).

Results: Compared to the control group, serum VEGF significantly increased in the aerobic, Martighal and combined groups (P=0.001). There was no significant difference in homocysteine levels in response to the interventions (P=0.919).

Conclusion: Despite the mentioned evidence, the effectiveness of Martighal consumption during aerobic exercise cannot be emphasized only by improving VEGF, and it is suggested to measure other markers of vascular endothelial function in order to obtain the mechanisms responsible for Martighal supplementation during exercise in these patients.

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Introduction

Metabolic syndrome is an obesity-related disease that often includes symptoms of chronic diseases such as type 2 diabetes, high blood pressure, and cardiovascular diseases. In other words, people with metabolic syndrome also suffer from diabetes and cardiovascular disorders (1). In another definition, abdominal obesity, insulin resistance, hyperglycemia, high systolic and diastolic blood pressure, low HDL levels, and increased triglycerides, cholesterol, and LDL are indicators of this syndrome (2). People with metabolic syndrome also suffer from cardiovascular disorders and oxidative stress or vascular endothelial disorder, like other abnormalities related to obesity (3). Thus, obesity and metabolic syndrome, due to the direct or indirect damage to the vascular dilatation characteristics of the endothelium, lead to endothelial dysfunction, which has been introduced as the first step in the spread or progression of cardiovascular diseases (4). Obesity is also related to endothelial dysfunction and blood pressure due to other factors such as

* *Corresponding authors:* Abdolali Banaeifar, Associate Professor, Department of Physical Education and Sports Sciences, South Thran Branch, Islamic Azad University, Tehran, Iran. Tel: +98 9056636426, Email: banaeia2006@yahoo.com.

narrowing of blood vessels, increased sympathetic activity and hyperactivity of the renin-angiotensin system and increased insulin resistance (5).

It is well known that the endothelium is one of the important areas in the control and regulation of vascular function and some hormonal and enzymatic components play a key role in this process. Among the hormonal components, clinical studies have reported homocysteine as one of the cardiovascular risk factors and supported it as an indicator of heart attack. higher serum homocysteine, especially in the presence of obesity, is associated with increased risk of heart diseases such as atherosclerosis and coronary artery disease (6, 7). Homocysteine is produced from the demethylation of methionine, which is introduced as a homologue of cysteine. Its high level is associated with the risk of heart attack, arteriosclerosis. Homocysteine has been introduced as a risk factor for coronary and peripheral vascular disease, and can lead to atherosclerosis due to damage to the inner wall of the arteries, interference in blood coagulation pathways, and the oxidation of lipoproteins (8). As a vascular repair factor, the protective effect of VEGF on blood vessels in cardiovascular disease has been reported in a large number of studies (9, 10). Homocysteine can downregulate the expression of VEGF in endothelial cells. Furthermore, the inhibitory effect of homocysteine on the migration of endothelial cells was achieved by downregulating the expression of VEGF using small interfering RNA transfection (11).

In summary, disruption in the systemic levels of components such as homocysteine and VEGF is associated with damage to vascular endothelial function in obese people or those with diseases related to obesity, which include metabolic syndrome. These components may provide suitable solutions with the aim of prevention, control, and improvement of metabolic syndrome in health and wellness science studies. Based on the mentioned evidence, the improvement of vascular endothelial function by pharmaceutical or non-pharmacological treatments is in the focus of health science researchers. In this context, the effective role of exercise training as one of the non-pharmacological treatments on the metabolic, hormonal and genetic components of obesity-related chronic diseases has been frequently proposed, although the findings are more or less contradictory. Farahti et al (2012) reported that 8 weeks of aerobic exercise increased nitric oxide and decreased weight and fat percentage in postmenopausal women (12). In addition, although Vale et al, (2023) reported that 8 weeks of aerobic training leads to a significant decrease in nitric oxide and a decrease in myeloperoxidase in women with metabolic syndrome (13), but Shekarchizadeh et al (2012) reported no change in nitric oxide and VEGF in response to 4 weeks of resistance training (14). In a study by Soori et al, (2016), 10 weeks of aerobic training was associated with a decrease in homocysteine, but no change in cardiovascular risk factors such as LDL and TG in obese women (15).

Apart from the contradictory effects of exercise training on the aforementioned components, which often depend on the difference in the type, duration, intensity, and population studied (12, 13, 14, 15), some recent studies have investigated the effect of exercise training with nutritional supplements, especially antioxidant supplements on cardiovascular function markers. Among these supplements, Martighal plant products in the form of plant extracts or medicines made from it such as silymarin, which is made of elements called flavonolingan with antioxidant properties play an important role in inhibiting free radicals and lipid peroxidation along with increasing antioxidants (16). Reducing the levels of malondialdehyde is one of the most important indicators of oxidative stress (16, 17) and increasing antioxidant capacity (18) and other enzyme antioxidants such as Superoxide dismutase (SOD) are among its other confirmed effects (19). As Shirali et al, (2017) have pointed out a significant increase in SOD in response to 6 weeks of aerobic exercise and consumption of silymarin as one of the products of Martighal (19). In the study by Roghani et al, (2012), Martighal extract consumption (100 mg/kg) for 4 weeks decreased hepatic MDA in diabetic rats (20). Despite its effect on the components of oxidative and antioxidant stress that affect cardiovascular function, the direct role of Martighal supplementation on the markers of vascular endothelial function that were mentioned earlier are less reported. Therefore, based on the contradiction in the findings regarding the effect of exercise training on the indicators of vascular endothelial function on the one hand and the lack of direct evidence on the effect of these components to Martighal, especially in patients with metabolic syndrome, the present study was done with the aim of evaluating the effect of interval aerobic training combined with Martighal consumption on vascular endothelial growth factor and homocysteine in sedentary women with metabolic syndrome.

Material and Methods

Subjects

The study employed a clinical trial (Ethic code: IR.IAU.CTB.REC.1401.139), utilizing an experimental framework that incorporated both pretest and posttest assessments. The study sample frame included voluntarily participating women aged 30-45 years who were obese (30 ≤ BMI ≤ 36, height: 163 ± 5.35 cm) and have been diagnosed with metabolic syndrome, selected through a convenience sampling method. Based on similar articles (13, 19, 20), sample size was calculated with a confidence level of 95% and a test power of 80% and according to previous studies (S = 0.6). To reach a significant difference of at least 5%, 12 people were considered in each group. The study sample was 48 adult obese women with metabolic syndrome who were randomly divided into 4 groups: 1) Aerobic exercise group "8 weeks of interval aerobic training every other day", 2) Martighal group "8 weeks of taking Martighal supplement, 280 mg daily", 3) combined group "8 weeks of interval aerobic exercises with Martighal supplement" and 4) control group "no intervention".

Inclusion or Exclusion Criteria

Obesity (BMI ≥ 36 ≥ 30) and the presence of at least 4 criteria of metabolic syndrome (waist circumference greater than 88, fasting glucose greater than 100 mg/dL, systolic blood pressure greater than 120 and diastole greater than 90, HDL lower than 50 mg/dL and triglycerides above 150 mg) were the inclusion criteria for the study. The study participants were non-smokers, non-pregnant, non-alcoholic and non-athletes. They also abstained from any consistent exercise training over the past six months. Furthermore, these participants did not adhere to a specific diet, and their weight has remained relatively stable, with variations of less than one kilogram. The non-inclusion criteria were the absence of any previous renal disorders, cancer, or seizure episodes. The exclusion criteria were lack of routine involvement in exercise programs, as well as the non-use of dietary supplements or the presence of any medical conditions that could influence the outcome variables under investigation

Anthropometric Measurements

The anthropometric indices were assessed before and after the intervention. For the determination of height, a rigid measuring tape was employed, with participant standing in barefoot to the nearest 0.1 cm. Measurements of the hip and waist circumferences were taken after a standard exhale using a non-stretchable measuring tape to the nearest 0.1 cm. The participants' weight was measured using a Secca scale to the nearest 0.5 kg. Body mass index (BMI) was calculated by dividing the individual's weight in kilograms by their squared height in meters. The percentage of body fat was determined using a body composition monitor (OMRON-BF 508, Finland).

Exercise protocol and Martighal consumption

Participants in the Martighal group were administered a daily 280 mg Martighal extract (21) after breakfast (8-9 am) for eight weeks, during which they were instructed to abstain from all exercise training. The aerobic group underwent an interval aerobic training program on alternate days between 9-11 am over an eight-week period with explicit guidance to refrain from any additional exercise programs beyond the specified aerobic exercise. The combined group engaged in an eight-week protocol that incorporated both aerobic exercise (9-11 am) and the daily intake of 280 mg Martighal extract (8-9 am). Meanwhile, the control group continued with their regular daily activities without any involvement in structured physical activity programs for the same eight-week timeframe.

During the aerobic intervention, participants engaged in interval aerobic exercise at intensities between 55% and 75% of their maximum heart rate (HRmax). Each workout commenced with a 10-minute warm-up, followed by 15 to 40 minutes of aerobic exercise, and ended with a 5 to 10-minute cooldown period. The aerobic training involved level-surface running. For the initial week, the exercise regimen was maintained at a lower intensity, which was incrementally escalated to reach 75% of HRmax during the concluding weeks (22, Modified). The Polar heart rate monitor (manufactured in the

USA) was utilized to precisely regulate the intensity of exercise throughout each session.

Laboratory and Clinical Measurements

Blood specimens were obtained from the participants after an overnight fasting for 12 hours at 8 to 9AM in the morning prior to the initiation of training. Participants were instructed to refrain from engaging in strenuous physical activities for a period of two days preceding the collection of blood samples. After the end of the final exercise session, participants underwent a 48-hour recovery period before their fasting blood samples were drawn similar to the initial pre-training procedure. Serum was promptly extracted from each collected blood sample and preserved at a temperature of -80 degrees Celsius until analysis could be conducted. VEGF was measured using a commercial kit (Cusabio Company, China) with a measurement accuracy of 0.8 pg/ml by ELISA method. Serum homocysteine was also measured calorimetrically using a specialized kit (Zelbio Company, Germany).

Statistical Methods

Comparative statistical analyses were conducted using IBM SPSS Software version 22, with a significance level of less than 5 percent. The Kolmogorov-Smirnov test verified the normal distribution. To compare the data between the groups, ANCOVA test was used along with Bonferroni's post hoc test. Additionally, the paired t-test was employed to assess changes within the groups.

Results

Table 2 shows the change of anthropometric indicators in response to aerobic exercises, martighal supplementation, as well as aerobic exercises combined with martighal supplementation.

Table 1. Distribution of exercise intensity while running during the interval aerobic training (22 modified)

weeks	Exercise intensity (%HRmax)	Time of running
First and second	%55 ≤ intensity ≤ %60	3 × 5 minute
Third and fourth	%60 ≤ intensity ≤ %65	2 × 10 minute
Fifth and Sixth	%65 ≤ intensity ≤ %70	2 × 15 minute
Seventh and eighth	%70 ≤ intensity ≤ %75	2 × 20 minute

Table2. Intra-group variations of anthropometric indices in the pre-test and post-test conditions in the studied groups

Group	Time	Control	Exercise	Martighal	Combine
Height (cm)	*Pre-post test*	160 ± 3.28	162 ± 3.18	163 ± 4.64	162 ± 3.06
	Pre-test	*84.18 ± 3.26*	84.44 ± 3.26	84.92 ± 5.41	84.25 ± 4.14
Weight (kg)	*Post-test*	*84.22 ± 3.39*	79.17 ± 2.20	83.21 ± 5.35	79.62 ± 4.40
	Sig	*0.713*	0.001*	0.001*	0.001*
	Pre-test	*113 ± 9.19*	109 ± 5.96	108 ± 8.21	106 ± 5.48
AC (cm)	*Post-test*	*113 ± 8.80*	103 ± 5.11	106 ± 9.91	100 ± 5.38
	Sig	*0.417*	0.001*	0.338	0.001*
	Pre-test	*114 ± 8.73*	108 ± 6.51	108 ± 8.46	105 ± 6.03
HC (cm0	*Post-test*	*114 ± 9.06*	104 ± 5.03	108 ± 8.96	101 ± 5.55
	Sig	*0.615*	0.001*	0.731	0.001*
	Pre-test	*32.77 ± 1.48*	32.35 ± 1.24	32.13 ± 0.86	32.23 ± 1.23
BMI (kg/m2)	*Post-test*	*32.79 ± 1.53*	30.33 ± 1.20	31.49 ± 1.01	30.47 ± 1.64
	Sig	*0.703*	0.001*	0.001*	0.001*
	Pre-test	*41.69 ± 1.43*	40.59 ± 1.43	40.49 ± 1.02	40.33 ± 1.20
Body fat (%)	*Post-test*	*41.61 ± 1.40*	34.50 ± 0.79	38.63 ± 1.03	34.30 ± 1.67
	Sig	*0.470*	0.001	0.001	0.001

*- **AC**; abdominal circumference, **HC**; hip circumference, **BMI**; body mass index*
- Data compared by paired t-test (p < 0.05)
** represent significant difference between groups*

Based on the results of the ANCOVA test, a significant difference was observed in the change of serum VEGF between the studied groups (P=0.001, F = 72.202, df = 3). On the other hand, based on the results of the Benferroni test (Table 3), a significant difference was observed between the control group and the aerobic, martighal and combination groups. In other words, compared to the control group, serum VEGF increased significantly in the aerobic, martighal and combined groups. No significant difference was observed between the exercise and martighal groups. Nevertheless, a significant difference was observed between the combined group and the aerobic and martighal groups. In other words, the aerobic exercises combined with the consumption of martighal led to a significant increase in serum VEGF compared to the application of each of them alone.

Table 3. Bonferroni post hoc test results for VEGF between the studied groups

Group	Group	Average difference	Standard error	sig
Control	**Aerobic**	*- 16.656*	*1.993*	*0.001*
	Martighal	*- 16.579*	*2.071*	*0.001*
	Combined	*- 29.781*	*2.029*	*0.001*
Aerobic	**Martighal**	*0.077*	*2.032*	*0.999*
	Combined	*- 13.126*	*2.003*	*0.001*
Martighal	**Combined**	*- 13.202*	*1.994*	*0.001*

The intra-group changes in serum VEGF were compared using paired t-test. The findings revealed that in all three groups, the intervention led to a significant increase in serum VEGF compared to the pre-test (Table 4, Fig 1).

Table 4. Data of intra group changes of VEGF in the studied groups

Group	Control	Aerobic	Martighal	Combine
Pre test	*160 ± 5.70*	*161 ± 6.62*	*164 ± 3.73*	*163 ± 4.93*
Post test	*159 ± 4.96*	*176 ± 6.23*	*176 ± 3.60*	*189 ± 5.11*
Sig (paired t test)	*0.497*	*0.001*	*0.001*	*0.001*

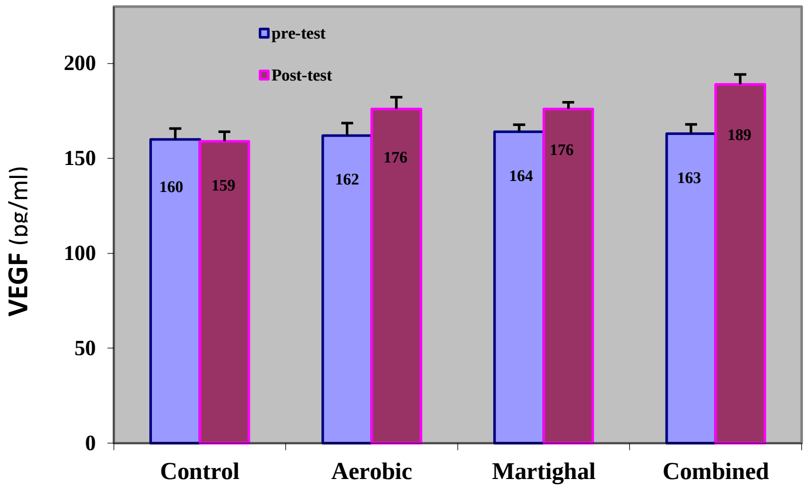

Figure 1. The pattern changes of serum VEGF in the studied groups. Serum VEGF increased significantly in the aerobic, martighal and combined groups compared to the control group.

Based on the results of the ANCOVA test, no significant difference was observed in the changes of serum homocysteine between the studied groups (P=0.919, F = 0.165, df = 3). On the other hand, intra-group changes by the paired t-test revealed no significant difference in serum homocysteine between pre- and post-test in any of the control, exercise and martighal groups, but in the combined group, there was a significant decrease compared to the pre-test (Table 5).

Table 5. Data of intra group changes of *homocysteine* in the studied groups

Group	Control	Aerobic	Martighal	Combine
Pre test	*46.23 ± 10.60*	*42.63 ± 6.29*	*44.62 ± 7.*	*43.11 ± 5.35*
Post test	*45.31 ± 13.85*	*40.96 ± 7.97*	*43.15 ± 8.95*	*40.86 ± 4.90*
Sig (paired t test)	*0.800*	*0.505*	*0.164*	*0.001*

Discussion

The findings of the study showed a significant increase in VEGF in response to aerobic training and Martighal supplementation in obese women with metabolic syndrome compared to the control group. On the other hand, the increase in VEGF in the combined group or in other words in the group that consumed Martighal extract during aerobic training was much higher than each of them alone. Nevertheless, aerobic training and Martighal consumption alone or in combination with each other did not lead to changes in serum homocysteine compared to the control group. Regarding the effect of exercise training or nutritional supplements on the components affecting cardiovascular function, there are consistent and inconsistent findings. In this context, although no study that tested the effect of Martighal was available, but Sahafian et al, (2016) pointed out that exercise activity combined with the consumption of Caffeine and Ginseng led to an increase in VEGF in heart tissue in laboratory rats (23). Mehri Elwar et al, (2016) have pointed out the increase in serum levels of vascular endothelial growth factor in young men in response to 5-week resistance training (24). Toloui Azar et al, (2019) also reported an increase in vascular endothelial growth factor following aerobic and resistance training in inactive women (25). Farzanegi et al, (2014) also reported an increase in VEGF and a decrease in systolic and diastolic blood pressure following aerobic training in postmenopausal women with hypertension (26). On the other hand, despite the fact that so far, no study has been reported on the effect of Martighal consumption during sports training, but Jahangiri et al, (2017) found an increase in VEGF along with a decrease in TNF-α in the heart of diabetic rats after 6 weeks of aerobic swimming training with the use of arbutin (27).

On the other hand, Etemad et al, (2016) mentioned a significant decrease in serum homocysteine in response to 8 weeks of resistance training (28). Bizheh et al, (2011) also cited that short-term exercise training in the form of 3 weeks of aerobic training was associated with a significant decrease in serum homocysteine in sedentary overweight men (29). In addition, a significant decrease has been reported by Soori et al (2016) in serum homocysteine in response to 10 weeks of aerobic training (5 sessions/weekly) in obese or overweight women (15).

Nevertheless, Bahram et al, (2013), Antunes et al, (2015) and Rousseau et al, (2005) reported the lack of effect of exercise training on homocysteine (30, 31, 32). In the study by Subasi et al, (2012), although 3 months of aerobic and resistance training were associated with improvement in body composition, homocysteine levels and lipid profile did not change significantly (33). The lack of change in homocysteine after exercise has also been reported by Nikbakht et al, (2007) (34). Some studies have also pointed to the effectiveness of pharmaceutical or antioxidant supplements on serum homocysteine levels. In this context, although no study evaluated the effect of martighal on homocysteine; however, in the study by Habibian et al, (2016), although 8 weeks of aerobic exercise and vitamin C consumption and their combination led to a decrease in homocysteine and insulin resistance in obese girls, the improvement in the combined group was far greater than the application of each of them alone (35). Despite the aforementioned contradictory evidence, the consumption of Martighal during aerobic exercise in the present study did not lead to a change in homocysteine levels compared to the control group, but the findings of the independent t-test indicated a significant decrease compared to the baseline levels.

In summary, the findings of the present study indicated the cardiovascular effects of consuming Martighal extract during aerobic training in women with metabolic syndrome. Because its consumption during exercises leads to improvement of VEGF compared to the application of each of them alone. On the other hand, unlike other groups that only experienced aerobic training or Martighal supplementation, their combination led to a decrease in homocysteine compared to baseline levels. In this context, although the direct response of homocysteine and VEGF to martighal has not been studied yet, its antioxidant effects have been reported many times. In such a way that it has been introduced as a regenerator of free radicals and maintaining the cell membrane by increasing the levels of cellular glutathione (36, 37). Martighal compounds inhibit or slow down the lipoperoxidation process that causes cell membrane damage (38, 39). Some other studies have also supported the anti-oxidative stress effects of martighal, which have been shown by reducing MDA and H2O2 (40).

The present study points out that the consumption of martighal extract during aerobic training was associated with an increase in VEGF compared to the application of any of the supplement or exercise alone, in patients with metabolic syndrome and this improvement was one of the strengths of the present study. However, based only on this improvement, it is not possible to refer to their cardiovascular effects and vascular endothelial function. So that the lack of measurement of other vascular endothelial indicators such as nitric oxide or endothelial microparticle (EMPs) is one of the limitations of the present study and the need to measure them in order to better understand the mechanisms responsible for the effect of aerobic exercise and martighal extract on vascular endothelial function.

Conclusion

Based on the findings, consumption of martighal and aerobic exercise was associated with an increase in serum VEGF in females with metabolic syndrome but the use of martighal during aerobic exercise led to a significant increase compared to the application of each of them alone. However, homocysteine levels were not affected in response to any of the interventions. However, based only on these findings, it is not possible to interpret the cardiovascular effects of martighal during aerobic exercise, and understanding the mechanisms responsible for it requires more studies in this field.

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Conflict of Interest

No conflict of interest has been declared by the authors.

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