Women. Health. Bull. 2022; 9(2)

Published online 2022 April.

Original Article

The Effect of Combined Training and L-arginine Supplement on the Serum Levels of Adropin, VEGFR-2, and Nitric Oxide in Post-menopausal Hypertensive Women

Rozita Nourbakhsh[1]*, PhD Candidate; Aliasghar Ravasi[1], PhD; Rahman Soori[1], PhD

[1]Department of Exercise Physiology, Faculty of Physical Education and Sport Sciences, University of Tehran, Tehran, Iran

Corresponding author:* Rozita Nourbakhsh, PhD; Department of Exercise Physiology, Faculty of Physical Education and Sport Sciences, between 15th and 16th Street, North Kargar Street, Tehran, Iran. **Tel: +98 21 88351730; **Fax:** +98 21 88021527; **Email:** rozita.nourbakhsh@ut.ac.ir

Received December 19, 2021; **Revised** January 22, 2022; **Accepted** February 16, 2022

Abstract

Background: Exercise training and L-arginine are believed to have a major role in managing the hypertension and also their combination may cause further improvement in blood pressure. Therefore, the present study aimed to determine the effect of combined training with or without L-arginine ingestion on the circulation of adropin, VEGFR-2, and nitric oxide (NO) in post-menopausal women with hypertension.

Methods: The present study was a randomized double-blind placebo-L-arginine-controlled trial registered in Iranian Registry of Clinical Trials with the code of IRCT20210627051723N1. This work was conducted in the summer and autumn of 2021. We recruited 48 post-menopausal women with hypertension and assigned them randomly (choosing random numbers by participants) in four equal groups, namely training+Larginine (TL), training (T), L-arginine (L), placebo (P) groups. The study intervention (combined training, L-arginine, or both) continued for eight weeks. Before starting and after completing the intervention period, blood samples were collected and the levels of variables was measured via Elisa method. The SPSS version 24 and analysis of covariance test (ANCOVA), along with bonferroni post-hoc test were utilized for data analysis.

Results: The obtained results represented a significant increase in the serum levels of adropin and VEGFR-2 in T and TL groups compared to those in P and L groups ($P<0.001$). Moreover, Nitric Oxide significantly increased in L ($P=0.003$), T ($P<0.001$), and TL ($P<0.001$) groups compared to P group. In addition, systolic blood pressure decreased significantly in T, L, and TL groups compared to that in P group ($P<0.001$), and in TL group compared to L ($P<0.001$) and T ($P=0.048$) groups. On the other hand, we observed a significant decrease in diastolic blood pressure in L ($P=0.002$), T ($P<0.001$), and TL ($P<0.001$) groups compared to that in P group; the same trend was seen in TL group compared to L group ($P=0.003$).

Conclusion: Combined training with or without L-arginine ingestion has positive effects by decreasing blood pressure, which was partly exerted by upregulation of adropin and VEGFR-2. Moreover, L-arginine supplementation was found to be associated with an increase in combined training effect in decreasing blood pressure.

Keywords: Exercise, Hypertension, Arginine, Vascular endothelial growth factor receptor-2 (VEGFR-2)

How to Cite: Nourbakhsh R, Ravasi AA, Soori R. The Effect of Combined Training and L-arginine Supplement on the Serum Levels of Adropin, VEGFR-2, and Nitric Oxide in Post-menopausal Hypertensive Women. Women. Health. Bull. 2022;9(2):70-79. doi: 10.30476/WHB.2022.94390.1164.

1. Introduction

Menopause is considered as a major risk factor for hypertension; thus, it is suggested that women with a family history of hypertension are at a higher risk of hypertension disease during this period (1). Occurrence of hypertension could be affected by different factors, including changes in the adropin levels. A negative correlation has been reported between adropin levels and blood pressure and its related disorders; therefore, normal or higher levels of adropin may have a protective effect against hypertension (2). It was previously reported that adropin acts as an endocrine factor and affects different pathways, including metabolic regulation, insulin sensitivity, and endothelial function (3), whose downregulation was observed in different pathological conditions, such as obesity, type2 diabetes mellitus, cardiovascular diseases, and hypertension (4).

Adropin increases the Nitric Oxide (NO) secretion in human endothelial cells, which is associated with stimulating the vascular endothelial growth factor receptor 2 (VEGFR-2). Adropin effect on protection and improvement of endothelial function is partially exerted with an increase in the endothelial nitric oxide synthase (eNOS) expression (5). In accordance with the importance of angiogenic factors in lowering blood pressure, acute induction of VEGF was associated with vasodilation and decrease in blood pressure; this vasoactive effect of VEGF is probably exerted by VEGFR-2 (dose dependent manner) and consists of NO induction, vascular vasodilators, and prostanoids, such as prostaglandin (6). Different pharmacological and non-pharmacological interventions have been recommended for the control and treatment of hypertension. Out of the non-pharmacological interventions, exercise training has attracted a great

deal of attention (7). Aerobic and resistance training has been proven to positively affect blood pressure and contribute to lowering it in hypertensive people. The effects of these training types in hypertension management are exerted through various mechanisms (8). Moreover, it was reported that combined training (endurance-resistance) plays an important role in controlling hypertension, including that in post-menopausal women (9).

In addition to exercise training, nutritional intervention, like the L-arginine supplementation, improves endothelial function and lowers blood pressure in patients with hypertension (10). L-arginine is involved in controlling blood pressure, decreasing adipose tissue, and reducing endothelin levels (11). L-arginine ingestion was also reported to help lowering blood pressure (12). In addition to exercise training and L-arginine supplementation, a number of researchers have shown that L-arginine ingestion amplifies the exercise training effect for managing the hypertension compared to exercise training alone; this synergistic effect was attributed to downregulation of MMP-2 and MMP-9 levels (13). A significant increase in serum levels of adropin and simultaneous decrease in arterial stiffness were observed following eight weeks of aerobic training in obese subjects (14). Nyberg and colleagues also reported that eight weeks of high-intensity aerobic training can significantly reduce blood pressure in individuals with hypertension, and that the decrease blood pressure was associated with a significant increase in NO levels and cardiovascular fitness (15). Therefore, it seems as though NO upregulation is the potential mechanism for decreasing blood pressure by exercise training (15). Despite previous findings, the followings still remain unclear: 1) Can combined training with L-arginine supplementation cause further improvement in the blood pressure compared to combined training alone? 2) Are changes in the levels of adropin, VEGFR-2, and NO considered as a potential mechanism for combined training- and L-arginine ingestion-related reduction in blood pressure? Therefore, in the present study, for the first time, we investigated the effect of combined training and L-arginine consumption on the adropin, VEGFR-2, and NO circulation levels in post-menopausal women with hypertension.

2. Methods

This research was a randomized double-blind placebo-L-arginine-controlled trial study. It was conducted in the summer and autumn 2021 in Karaj, Iran. Our sample consisted of hypertensive post-menopausal women aged 50 to 60 years. After inviting the women with hypertension, 48 eligible patients were chosen among the recruited individuals to take part in the considered interventions, all of whom participated voluntarily in the study intervention (training, L-arginine, training+L-arginine).

Among the qualified post-menopausal hypertensive women with at least one year elapsed since the first diagnosis of hypertension, 48 participants were selected by the researcher. To estimate the sample size, we utilized the mean±standard deviation of nitric oxide (before: 24.3±0.9 µg.ml; after: 31.7±0.7 µg.ml training program), adropin (before: 4.2±2.6 ng.ml; after: 4.8±2.4 training program µg.ml), and VEGFR-2 (before: 8.4±1.9 µg.ml; after: 11.8±2.6 µg.ml training program) in the hypertensive patients before and after the exercise training intervention (16, 17). The following previously reported formula was used for sample size calculation (18).

$$n=\left(\frac{Z_{1-\alpha/2}+Z_{1-\beta}}{ES}\right)^2$$

All the hypertensive patients signed the informed consent form. Subsequently, they were divided into four equal groups (12 hypertensive women in each group) randomly, namely placebo (P), combined training (T), L-arginine supplement (L), and combined training+L-arginine supplement (TL) groups. For the random allocation, 48 numbers, from 1 to 48, were considered for each participant. At the baseline (when the subjects did not have any information regarding the considered numbers for different groups), numbers 1-12 were assigned to P group, 13-24 to T group, 25-36 to L group, and 37-48 to TL group. Afterwards, each subject chose a number from between 1-48 randomly from a box containing 48 numbers (one sheet for each subject); accordingly, the participants in each group were determined. The allocation of the participants to placebo or L-arginine supplement ingestion was performed as a double-blind procedure. In fact, the placebo or L-arginine supplements were provided to them by a third person (not a person from the research group); the researchers and participants were blinded about the consumed capsule (the placebo or L-arginine) over eight weeks of intervention. In the next step, the pre-test blood sampling and initial measurements (height, weight, body fat percentage, VO_{2max}) were performed. The study intervention consisted of

combined training, L-arginine consumption, or their combination for eight weeks while the control group was asked to not participate in any regular exercise training during these eight weeks.

2.1. Ethical Considerations

The ethics committee of Tehran University approved the present study with the code of IR.UT.SPORT.REC.1400.005. In addition, our study was documented in the Iranian registry of clinical trials (IRCT) under the code of IRCT20210627051723N1. It should be noted that, all the subjects were allowed to withdraw from the considered intervention at any stage without any kind of compulsion by the researchers.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria: confirmation of menopause and hypertension by a physician, not having type 2 diabetes or cardiovascular diseases (except for hypertension), sedentary lifestyle in the previous year, no physical and medical limitations for completing the exercise sessions, not consuming any nutritional supplements for two months before and during the considered intervention period, and voluntary participation. Exclusion criteria: not participating in the combined training program regularly, unwillingness to continue consumption of placebo or L-arginine supplement and performing the exercise training program, injury during exercise sessions, medical contraindications impairing the research intervention (combined training, L-arginine or both), being forced to take any supplement or medication during the eight weeks of intervention.

2.3. Combined Exercise Training (Resistance-Endurance)

We conducted a combined training program during eight weeks, with three sessions per week. In each exercise session, the resistance part was firstly performed, followed by the endurance one. Resistance training (circuit) consisted of nine exercises (bicep curls, triceps extension, low back extension, leg press, chest press, seated rowing, abdominal crunch, upright row, leg extension) with 15 repetitions for the upper limbs and 20 repetitions for the trunk and lower limbs. In fact, resistance training intensity was approximately 50 to 60% one-repetition maximum (1RM). In weeks 1-4 of the training program, each exercise was performed for one cycle whereas from weeks 5-8, each exercise was performed for two cycles; the participants rested for 1 minute between the exercises. On the other hand, the endurance training consisted of 20 minutes running or walking with 60 to 75% of the maximum heart rate. The exercise intensity was controlled by means of polar heart rate monitor during the exercise sessions. The endurance training intensity was considered 60% of the maximum heart rate for the first two weeks, which increased by 5% every two weeks (16). Throughout this period, the control group did not take part in any regular physical activities and continued their daily routine life.

2.4. L-arginine Supplementation

L-arginine supplementation was done for eight weeks. L-arginine was administered 6 g daily (2 g for each meal after breakfast, lunch, and dinner) for the L-arginine supplement and combined training+L-arginine supplement groups. L-arginine was purchased from Karen Company (Iran). At the same time, the subjects in placebo group consumed a similar amount of placebo (capsule containing wheat flour) provided by Roshd company (Iran) (19).

2.5. Measurement of Blood Pressure, Height, Weight, BMI, and Body Fat Percentage

Following subjects' allocation to different groups, their weight and height were measured. In addition, we calculated body mass index (BMI) by dividing the weight (in kilograms) by the square of the height (in meters). BOCA-X1 body composition analyzer was used in order to determine the body fat percentage. On the other hand, systolic and diastolic blood pressure was measured via a digital system (BC 08; Beurer, Ulm, Germany).

2.6. Blood Sample Collection

For blood sampling before and after the eight weeks of intervention, we asked all the participants to be present in the gym at a certain day and time. They were asked to be in the fasted state for 12 hours and have adequate rest and sleep the night before the blood sampling. Beforehand, the subjects were seated for 30 minutes in the sampling environment. The post-test blood samples were collected two days after completing the combined training or L-arginine ingestion intervention, and all the participants were avoided from strenuous exercise or physical activity for two days before. The blood samples were obtained from the brachial vein and were immediately poured into the Falcon tube. They were centrifuged at 3000 rpm for 10 minutes. Subsequently, the serum samples were removed using sampler and kept in a freezer for future laboratory measurement.

2.7. Data Analysis

The normality of the present data distribution was assessed via Shapiro-Wilk test, and the between-group (P, L, T, TL groups) differences were determined employing ANCOVA test along with Bonferroni post-hoc test. We utilized the SPSS version 24 for analyzing our findings; P<0.05 was considered as the significance level.

3. Results

Our subjects consisted of 48 post-menopausal hypertensive women, all of whom were included in the final analysis of outcomes. Table 1 represents the levels of NO, systolic and diastolic blood pressure, body fat, body weight, as well as the participants' age and height in P, L, T, and TL groups before and after eight weeks of intervention (combined training, L-arginine supplement, or both of them), as the mean±standard deviation.

Figure 1 schematically depicts different stages in the present research.

The findings of the analysis of covariance test indicated that the changes in the NO levels, systolic and diastolic blood pressure, as well as those in the body weight and body fat percentage were statistically significant (P<0.001) after the intervention. The Bonferroni post-hoc test showed that NO levels in the L-arginine supplement (L) (P=0.003), combined training (T) (P<0.001), and combined training+L-arginine supplement (TL) (P<0.001) groups significantly increased compared to those in the placebo (P) group. Moreover, systolic blood pressure significantly decreased in L, T, and TL groups compared to that in P group (P<0.001); we observed the same trend in the TL group compared to T (P=0.048) and L (P<0.001) groups (Table 1). In addition, diastolic blood pressure significantly decreased in L (P=0.002), T (P<0.001), and TL groups (P<0.001) compared to that in P group. A significant decrease was also observed in diastolic blood pressure in the TL group compared to that in L (P=0.003) group. Moreover, the present findings represented a significant decrease in body fat percentage and body weight in T and TL groups in comparison with those in L and P groups (P<0.001) (Table 1).

According to the analysis of covariance test results, there were significant between-group differences concerning the serum levels of adropin and VEGFR-2. Bonferroni post-hoc test revealed that adropin levels, following the eight weeks of intervention, were significantly higher in T and TL groups than those in P and L groups (P<0.001). Meanwhile, the observed difference between T and TL, and P and L groups (P>0.99) in terms of adropin levels was not significant. Figure 2 reports adropin levels before and after the intervention. Regarding the serum levels of VEGFR-2, Bonferroni post-hoc test indicated a significant increase in VEGFR-2 level in T and TL groups compared to that in P and L groups (P<0.001). However, the observed changes concerning VEGFR-2 levels between T and

Table 1: Comparison of age, height, NO, SBP, DBP, body fat percentage, and body weight of the groups

Variables	Stages	Placebo	L-arginine	Training	Training+L-arginine	Between-group P values
Age (years)	Pre-test	56.7±2.43	56.2±2.98	55.8±2.33	57.1±2.85	0.656 §
Height (cm)	Pre-test	157.2±4.16	157.6±4.95	158.4±6.09	156.8±3.91	0.873 §
NO (µmol/L)	Pre-test	23.17±3.53	21.86±3.32	23.53±3.71	22.62±4.18	0.711 §
	Post-test	22.94±3.29	25.46±3.89 #	27.89±5.11 #	28.56±4.45 #	<0.001 §§
SBP (mmHg)	Pre-test	144.2±6.28	142.4±6.65	139.8±5.11	141.9±5.83	0.359 §
	Post-test	144.8±6.54	137.2±5.34 #	132.7±4.45 #	131.6±5.75 #*β	<0.001 §§
DBP (mmHg)	Pre-test	86.4±2.84	84.7±2.63	85.8±3.51	85.2±2.95	0.562 §
	Post-test	86.7±2.56	82.8±2.44 #	81.6±3.08 #	80.4±2.43 #*	<0.001 §§
Body fat percentage	Pre-test	35.14±3.54	37.45±3.16	34.57±2.83	35.69±2.65	0.534 §
	Post-test	35.37±3.42	37.33±2.67	32.68±2.71 #	33.98±2.57 #	<0.001 §§
Body weight (kg)	Pre-test	73.44±5.57	75.81±7.95	73.56±4.92	74.29±4.81	0.751 §
	Post-test	73.39±5.68	75.64±7.86	72.38±4.94 #	73.16±4.66 #	<0.001 §§

Significant difference with the placebo group, * Significant difference with the L-arginine group, β Significant difference with the training group. NO: Nitric Oxide, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure. § ANOVA P value for the pre-test; §§ ANCOVA P-value for the post-test

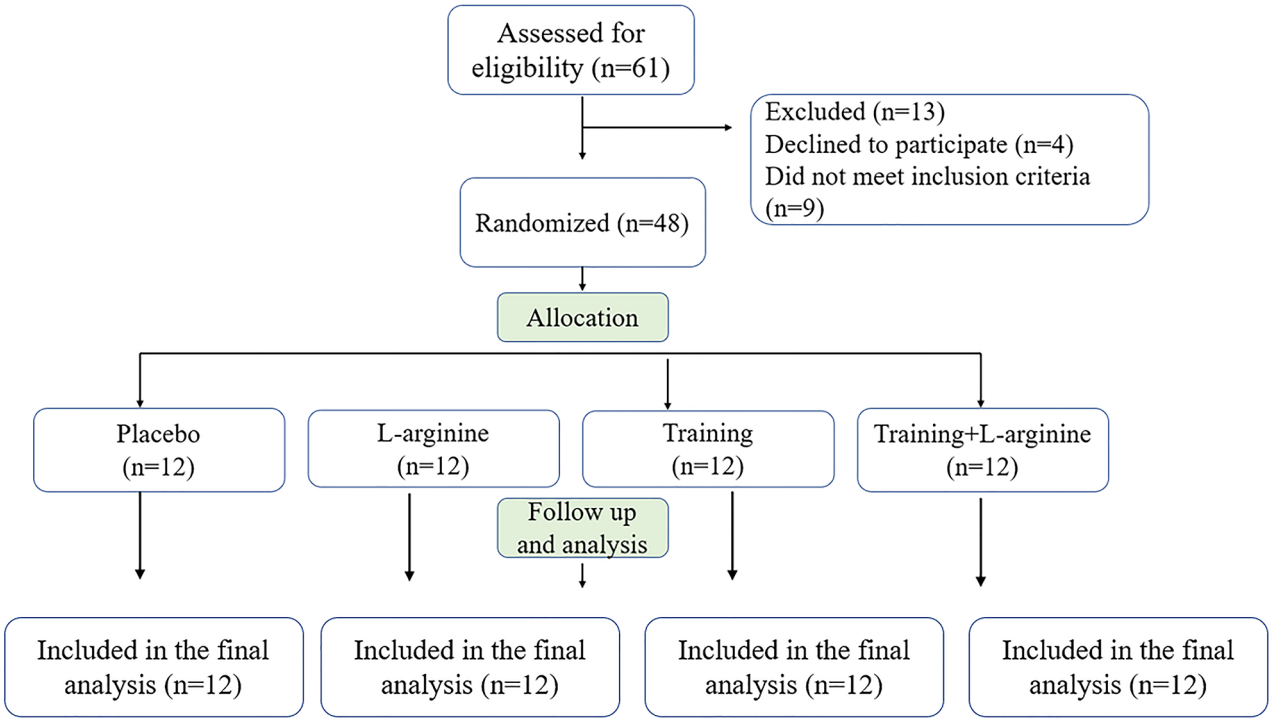

Figure 1: The figure shows the CONSORT diagram.

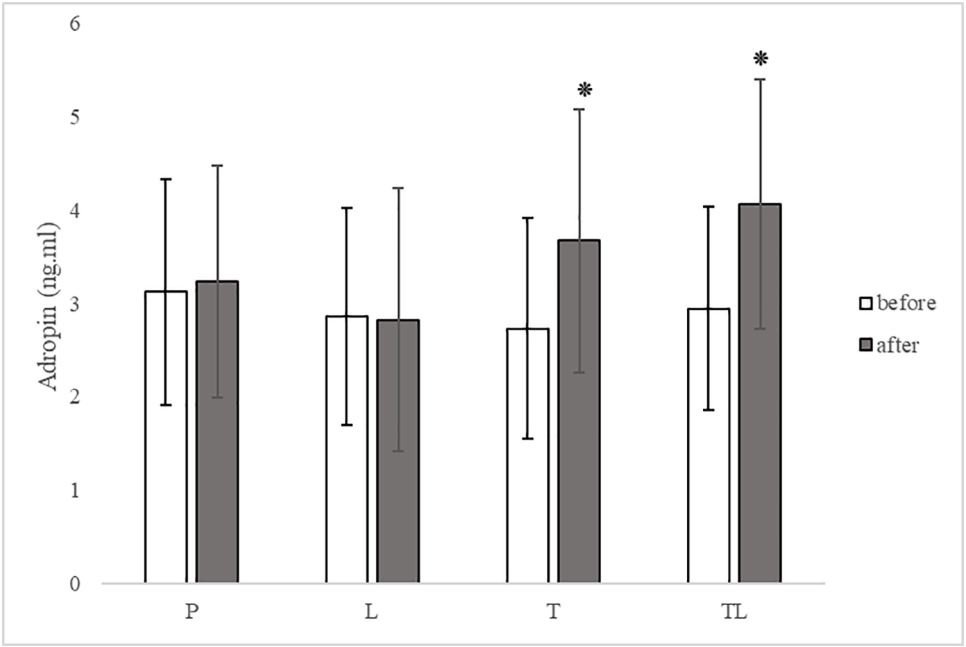

Figure 2: The figure shows the Adropin levels. * Significant increase compared to P and L groups. P: Placebo; L: L-arginine; T: combined training; TL: Combined training+L-arginine

TL group, and between P and L groups were not statistically significant (P>0.99) (Figure 3). Figure 3 illustrates VEGFR-2 levels before and after the eight weeks of intervention.

4. Discussion

The main findings obtained herein included the followings: eight weeks of combined exercise training alone or along with L-arginine ingestion significantly increased the serum levels of adropin and VEGFR-2; additionally, there was a significant increase in NO levels in L, T, and T+LT groups. The reported results regarding the correlation between adropin and hypertension still remain contradictory. Certain researchers have reported that the serum levels of adropin were not correlated with blood pressure variables (5). However, some other have suggested that the levels of adropin

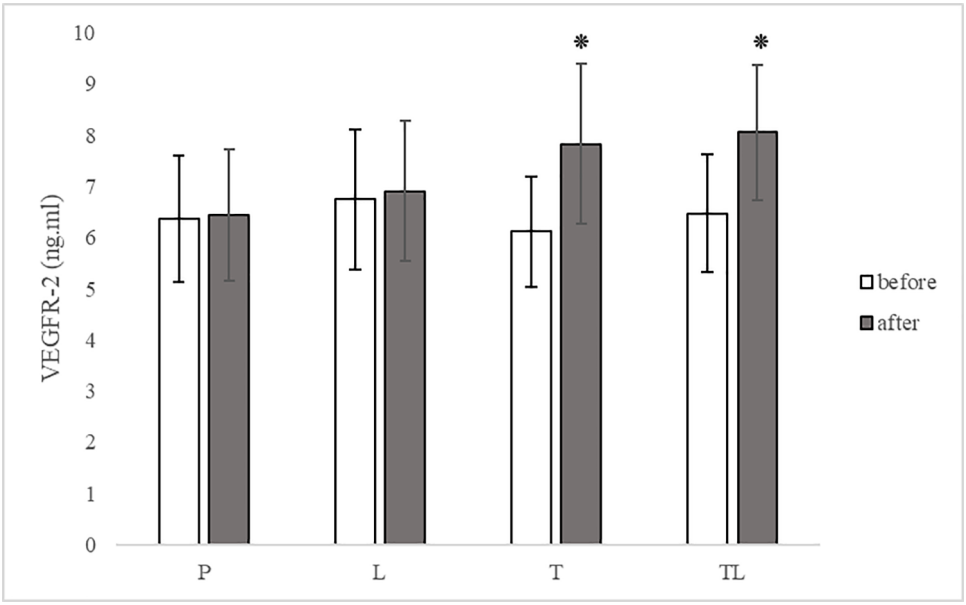

Figure 3: The figure shows the VEGFR-2 levels. * Significant increase compared to P and L groups. P: Placebo; L: L-arginine; T: Combined training; TL: Combined training+L-arginine

circulation are negatively correlated with blood pressure in adults with hypertension (20). On the other hand, a number of papers have observed a higher level of adropin in patients with hypertension compared to healthy control subjects (21). Nonetheless, it has been proven that exercise training can decrease the arterial stiffness in obese adults by increasing NO levels as a result of increasing the serum levels of adropin, thereby lowering blood pressure (14).

In accordance with our findings, the effect of different types of exercise training, including aerobic (22), resistance (23), and combined (16) training, on the upregulation of adropin levels have been reported. Consistent with the above-mentioned studies, some researchers, in a study on human and animal subjects, indicated that 12 weeks of aerobic training (wheel running) in aging mice, resulted in compensating the age-related decline in arterial adropin, and contributed to vasodilation owing to increased adropin dependent NO levels (24). Eight weeks of aerobic training in human participants also attributed to a significant increase in the circulation of adropin, and a simultaneous decrease in body fat percentage and upregulation of NO levels were also observed following aerobic training. These changes eventually resulted in a lower systolic and diastolic blood pressure (24). In another study, our findings were confirmed and a significant increase in adropin levels and simultaneous decrease in BMI were observed after an eight-week aerobic training (25). In line with the present results, it has been suggested that 10 weeks of high-intensity aerobic training in obese adolescent boys significantly increased the adropin levels; yet, body fat percentage and body weight significantly decreased in the trained group. The researchers attributed the adropin upregulation to the improvement in the metabolic markers (22). Moreover, an investigation on the effect of an eight-week resistance training plan in overweight sedentary men indicated a significant increase in the serum levels of adropin. This upregulation was associated with insulin resistance improvement and weight loss. Therefore, the researchers stated that the exerted resistance training duration and intensity were adequate for enhancing the adropin levels (23).

In hypertensive patients, conducting eight weeks of combined training (endurance-resistance) results in a significant increase in the serum levels of adropin and NO in post-menopausal women with hypertension (26) and obese hypertensive men (16). Researchers have ascribed the antihypertensive effect of exercise training to the improved endothelial function and adropin-dependent upregulation of NO levels (16, 24). The present study confirmed the positive correlation between adropin and NO levels; we observed that an increase in adropin levels after eight weeks of combined training resulted in the significant upregulation of NO levels. Although the exact mechanism of exercise training inducing upregulation of adropin levels is unknown, a decrease in body fat percentage may be considered as a possible mechanism. In agreement with our hypothesis, Yosaee and colleagues reported the highest level of adropin in normal weight, healthy overweight, and people with metabolic syndrome, respectively, emphasizing the negative correlation

between adropin levels and body weight and fat mass (27). However, exercise-related increase in serum adropin levels were also reported to be independent from significant changes in body weight and body fat percentage. A study found that aerobic training in obese adolescents for 12 weeks led to a significant increase in the serum levels of adropin, without any significant changes in body weight (28). The protective effects of adropin on endothelium are exerted with an increase in NO synthesis through eNOS activation, and since the Akt and ERK1/2 inhibitors block eNOS activation by adropin, NO production through adropin stimulation is dependent on the Akt and Erk1/2 signaling pathways (29). On the other hand, given the fact that NO is known as the main vasodilator, blood pressure reduction in the present study following adropin upregulation can be considered as an NO-dependent vasodilation. A number of researchers have suggested that VEGFR-2 is of great necessity for adropin signaling in epithelial cells; accordingly, VEGFR-2 could be considered as a third receptor for adropin, which implies that some effects of adropin are exerted by VEGFR-2 (29). In fact, adropin led to an improvement in eNOS bioactivity through VEGFR-2 activation, as an essential receptor resulting in increased eNOS activity and consequently a rise in NO levels (30). VEGF is known as a stimulant for endothelial cells to NO secretion by upregulating eNOS, which leads to vasodilation through downstream signaling pathways, including phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK). Based on the available evidence, the VEGF-induced vasodilation is mediated by binding to VEGFR-2 (31).

The current study corroborates earlier findings, where researchers reported an increase in adropin and VEGFR-2 levels after eight weeks of combined training in obese hypertensive men; it has been reported to significantly decrease systolic blood pressure, and research has concluded that the upregulation of adropin levels could increase NO production, vasodilation, and lowering blood pressure remarkably by VEGFR-2 stimulation (16). Even though there are no similar studies about exercise training effects on the circulating levels of VEGFR-2, a significant increase in VEGFR-2 protein in different brain regions was observed after moderate continuous or high-intensity interval training in rodents (32). Mirdar and co-workers reported that upregulation of lung tissue VEGFR-2 expression after six weeks of high-intensity interval training in Wistar rats was statistically significant (33). However, determining the effects of various types of exercise training modalities on the circulating levels of VEGFR-2 and the involved mechanisms requires further investigation and should be focused on in future studies.

Herein, we observed that eight weeks of L-arginine consumption alone did not have a significant effect on the circulating levels of adropin and VEGFR-2. The observed changes in adropin and VEGFR-2 levels were not different between the combined training and combined training+L-arginine groups. Therefore, L-arginine supplementation with combined training did not have a synergistic effect on adropin and VEGFR-2 levels. Nevertheless, eight weeks of L-arginine ingestion was associated with a significant increase in NO levels and further increase in NO levels (although non-significantly) in the combined training along with L-arginine supplement group. The NO levels in the L-arginine, training, and training+L-arginine groups increased by 16.46, 18.25, and 26.25%, respectively; this emphasizes the greater effectiveness of combined training with L-arginine supplementation. Considering the fact that L-arginine and exercise training can both rise the NO levels, further increase in NO in the training+L-arginine group seems justifiable. In addition, our results indicated that L-arginine and combined training alone or together significantly lowered the systolic and diastolic blood pressure. In addition, there was a significant decrease in systolic blood pressure in the combined TL group compared to that in L and T groups, along with a remarkable improvement in the diastolic blood pressure in TL group compared to that in L group. Thus, L-arginine ingestion simultaneously with combined training synergistically decrease blood pressure in hypertensive individuals.

L-arginine is known as a natural precursor for NO, which is a semi-essential amino acid (34) converted to NO by the NOS enzyme in cells. NO production has been reported to increase arginine uptake (35). There is a great deal of scientific evidence implying that a decrease in NO production in cells is associated with a reduction in metabolism and increase in the body fat mass (36). In contrast, upregulation of NO production by increasing the dietary L-arginine intake declines body fat mass through increased lipolysis (37). Consistent with these statements, enhancement of NO levels after L-arginine supplementation+combined training in our study contributed to a decrease in body fat mass. A previous study also confirmed the L-arginine supplementation or endurance training role alone or together (endurance training+L-arginine) in increasing NO levels in hypertensive patients; increased

NO levels has been reported to occur simultaneously with a reduction in body fat percentage and a decrease in systole and diastolic blood pressure (19). Although L-arginine consumption effects alone or combined with exercise training on VEGFR-2 and adropin levels still remain unknown, previous studies have confirmed the present findings and observed that L-arginine augments the exercise training effect on reducing blood pressure and exerts a synergistic effect (38).

Jahani and colleagues investigated obese men and observed that although four weeks of aerobic training did not significantly affect their blood pressure, aerobic training along with L-arginine ingestion significantly decreased systolic and diastolic blood pressure (39). These results suggested that L-arginine supplementation along with exercise training, even in short term (four weeks), significantly reduces blood pressure. A study indicated that 21 days of aerobic training and L-arginine ingestion could decrease systolic and diastolic blood pressure significantly in type2 diabetic hypertensive patients; the blood pressure improvement was attributed to decreased endothelin-1 and elevated NO levels (40). Overall, our findings showed that upregulation of adropin and VEGFR-2 and the subsequent increase in NO levels as a result of increased eNOS activity helps modulating the blood pressure through vasodilation. However, future studies should investigate different signaling pathways for improving blood pressure through exercise training and L-arginine consumption.

4.1. Limitations

Our research limitations included the small samples size, not measuring the changes in the levels of inflammatory or anti-inflammatory cytokines, antioxidant capacity, and oxidative stress markers, as well as short duration of the intervention, which should be considered in future research. According to our findings, L-arginine ingestion could be recommended for hypertensive patients combined with exercise training in order to enhance its anti-hypertensive effects.

5. Conclusion

It seems as if the antihypertensive effects of combined training with or without L-arginine ingestion are partly exerted owing to the upregulation of adropin levels, thereby increasing the VEGFR-2 levels; this enhances the activity of eNOS, which eventually results in a reduction in systolic and diastolic blood pressure on account of the increase in NO levels and its related vasodilation. In addition, ingestion of L-arginine along with combined training has a synergistic effect on lowering blood pressure.

Acknowledgement

This research was extracted from PhD thesis of Ms. Rozita Nourbakhsh in exercise physiology, faculty of physical education and sport sciences, university of Tehran, Tehran, Iran. The researchers thank all the participants and others who participated in this research.

Ethical Approval

Ethics Review Board of Tehran University approved the present study with the code of IR.UT.SPORT.REC.1400.005. Also, written informed consent was obtained from the participants.

Conflicts of Interest: None declared.

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