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Effect of 8 Weeks of Aerobic Training Combined with Vitamin D Supplementation on Nitric Oxide and Endothelin-1 in Patients with Hypertension

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ABSTRACT

Background: This study aimed to investigate the effect of 8 weeks of aerobic exercise combined with vitamin D supplementation on nitric oxide (NO) and endothelin-1 (ET-1) in patients with hypertension.

Materials and Methods: In this quasi-experimental study, 40 eligible men and women with hypertension were randomly divided into four groups: supplement, placebo + exercise, supplement + exercise, and control. The training program included eight weeks of aerobic exercise running on a treadmill for 8 weeks, 3 sessions per week. The supplementation program included the intake of vitamin D supplements (2000 IU) daily in a double-blind manner. The placebo program was the intake of a capsule containing maltodextrin. Blood sampling was taken to evaluate biochemical variables 48 hours before and after the intervention in a fasting state.

Results: After 8 weeks of aerobic exercise plus vitamin D supplementation, there was no significant effect on body mass index, NO, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, vitamin D level, and weight ($P>0.05$). However, the ET-1 level and systolic blood pressure were changed significantly in the supplement, supplement + exercise, and exercise + placebo groups compared to the control group ($P<0.05$).

Conclusion: Eight weeks of vitamin D supplementation combined with aerobic exercise can reduce ET-1 level and improves systolic blood pressure in people with hypertension.

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Introduction

Blood pressure is the pressure exerted by blood circulation on the wall of blood vessels [1]. Pre-hypertension is defined as systolic blood pressure of 120-139 mm Hg or diastolic blood pressure of 80-89 mm Hg, based on two or more blood pressure measurements in sitting position [1]. Hypertension, sometimes called arterial blood pressure, is a chronic disease in which the blood pressure in the arteries rises and is summarized by two systolic and diastolic measurements. About 90-95% of hypertension cases are classified as primary hypertension, which is defined as high blood pressure without a known underlying cause. The remaining 5-10% is classified as secondary hypertension [2]. Recently, attention has been paid to the inflammatory pathways and mediators by which immune cells may contribute to hypertension. When immune cells are activated or bind to a target organ, they produce cytokines that determine a local inflammatory response that contributes to systemic arterial hypertension (AH), atherosclerosis, and adverse cardiovascular outcomes [3]. In the systemic AH, proinflammatory cytokines and chemokines including TNF-α, C-reactive protein (CRP), and monocyte chemoattractant protein-1 (MCP-1) are released, which are related to with the decrease in expression and activity of endothelial nitric oxide (NO) synthase, oxidative stress, and decrease in the NO bioavailability [4, 5]. This leads to chronic low-grade inflammation, platelet aggregation, fibroproliferation and endothelial dysfunction, which is a key event in the development of atherosclerosis [4, 5]. Endothelial dysfunction is also associated with increased endothelin-1 (ET-1), a vasoconstrictor, reducing the capacity of the endothelium to dilate in response to hemodynamic stimuli [1].

Vitamin D deficiency has previously been shown that increase the risk of several diseases including common cancers (colon, breast and prostate cancers), diabetes mellitus, coronary artery disease, hypertension, ischemic stroke, and autoimmune diseases [6]. It is now known that, in addition to the musculoskeletal system, most tissues and cell types express specific receptors for vitamin D. This includes the immune and cardiovascular systems [7]. In recent years, the function of vitamin D in other organs has increasingly been reported. Many pathophysiology studies have shown the cardiovascular protective effects of vitamin D. This vitamin reduces the production of renin and weakens the activity of the renin-angiotensin-aldosterone system and leads to a delay in the onset of hypertension, arteriosclerosis and heart failure [8].

An important contributing factor to the reduction in the risk of cardiovascular diseases is thought to be improved endothelial function. It has been shown that regular aerobic exercise (daily walking), independent of weight loss and changes in diet, improves endothelium-dependent vasodilation in overweight and obese adults [9]. The mechanisms responsible for exercise-induced increases in endothelial vasodilator function in overweight and obese adults are not well understood. Although regular aerobic exercise has been shown to have a favorable effect on the NO bioavailability, the impairment of endothelium-dependent vasodilators in overweight and obesity has been shown to be independent of NO deficiency [10]. Mohammadi et al., by examining 16 weeks of aerobic exercises with different intensities of low (30-40% maximum oxygen consumption) and moderate (55-65% maximum oxygen consumption) at 3 sessions per week, each for 30 minutes, on 25 obese men with a mean age of 52 years, concluded that moderate-intensity aerobic exercise leads to an increase in NO [11].

According to the existing literature, aerobic exercises can be useful in improving the condition of vasodilators. Therefore, the present study aims to examine the effect of 8 weeks of aerobic exercise along with vitamin D supplementation on NO and ET-1 in patients with hypertension. It is hypothesized that aerobic exercises along with vitamin D supplementation can affect ET-1 and NO.

Materials and Methods

This is a quasi-experimental study with a pre-test/post-test design. The study population consists of male and female patients aged 30-50 years suffering from hypertension and vitamin D deficiency in Urmia, Iran. The criteria for entering the study were no regular diet and exercise program in the past year, age 30-50 years, having vitamin D deficiency, having a blood pressure of 120-139 mm Hg, no specific and metabolic diseases, no liver diseases, and not smoking tobacco and consuming alcohol (>20 g per day). Exclusion criteria were the existence of other disorders such as autoimmune hepatitis, joint diseases, celiac disease, Wilson's disease, coronary artery diseases and surgery, kidney failure, hypothyroidism, as well as open surgery and angiography, muscular-skeletal injuries affecting the exercise, taking special drugs (nutritional and sports supplements), using anabolic steroids, and any drugs or supplements during the research, any acute illness or discomfort during the research, taking antihypertensive drugs, acute injury caused by exercise during the research, unwillingness to continue cooperation, or medical prohibition.

The participants were randomly divided into four groups of 10 (five women and five men in each group) including supplement, placebo + exercise, supplement + exercise and control. One week before the start of the intervention, the subjects were given the necessary explanations about the research and how to implement the protocol, the advantages and disadvantages of participating in the research, possible inconveniences related to blood sampling, and all the points that must be observed. Then, the verbal and written informed consents were obtained from them.

The exercise program for the exercise groups included 8 weeks of aerobic exercise running on a treadmill (three sessions per week, each for 45 minutes) with low intensity (40-60% maximum heart rate). The exercise in the first week was started with an intensity of 40% maximum heart rate; in the second week with an intensity of 45%; in the third and fourth weeks with an intensity of 55%; in the fifth and sixth weeks with an intensity of 55%, and finally in the seventh and eighth weeks with an intensity of 60% maximum heart rate. The subjects' heart rate was measured using a Polar heart rate monitor. In all the sessions, the subjects performed stretching and soft movements for 10 minutes to warm up and 5 minutes to cool down at the end of the main exercise. The control and supplement groups did not perform any regular sports activities during this period [12].

Fasting blood samples (48 hours before and 48 hours after the end of the last training session) were taken by a laboratory specialist to determine the levels of study variables. Blood samples (5 cc) were collected in tubes containing EDTA anticoagulant. After centrifugation (for nine minutes at 4500 rpm) and plasma isolation, the assessment was done by the enzymatic method using ELAN 2000 autoanalyzer.

An ELISA kit (Padtan Gostar Isar Co., Iran) was used to measure the biochemical factors of lipid profile, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), as well as the serum level of vitamin D. Also, an ELISA kit (Navand Salamat Co., Iran) was used to measure the NO level. Moreover, an ELISA kit (ZellBio, Germany) was applied for the quantitative measurement of ET-1 using the ELISA processor (EUROIMMUN Analyzer I-2P, Germany).

All collected data were analyzed in SPSS software, version 26, considering a significance level of $P<0.05$. Kolmogorov-Smirnov test was used to check the normal distribution of data and Levene's test was used to check the homogeneity of variances. Repeated-measures ANOVA was used to perform within-group (time effect) and between-group (group effect) comparisons.

Results

The descriptive characteristics of the participants are presented in Table 1. There were no significant differences between the groups in any study variables in the pre-test phase ($P>0.05$). Based on the ANOVA results, after 8 weeks of aerobic exercises with vitamin D supplementation, there was no significant difference between the groups regarding BMI, weight, NO, TG, TC, HDL, LDL, and vitamin D levels (Table 2); however, it caused a significant difference in ET-1 ($F=13.45$, $P=0.001$) and systolic blood pressure ($F=6.83$, $P=0.001$). After performing the one-way ANOVA test, the results also showed a significant difference between the pre-test and post-test values of ET-1 level ($F=245.53$, $P=0.01$) and systolic blood pressure ($F=6.83$, $P=0.01$).

Discussion

The purpose of this study was to examine the effect of 8 weeks of aerobic exercise along with vitamin D supplementation on NO and ET-1 in patients with hypertension. The results showed that this combined treatment caused a significant difference in ET-1 and systolic blood pressure, but it had no effect on BMI, weight, NO, TG,

Table 1. Characteristics of the participants in each group

Group	Mean±SD				
	Age (y)	Height (cm)	Weight (kg)	BMI (Kg/m²)	Vitamin D (nm/mL)
Control	41.2±5.4	159.3±7.4	66.16±12.79	26.13±0.37	28.33±4.66
Supplement	39.1±2.9	159.3±7.4	73.6±6.83	26.07±0.64	30.17±3.81
Supplement +exercise	38.3±3.8	161.2±71.3	69.9±4.43	25.99±0.84	30.17±3.68
Placebo + exercise	45.6±2.9	163.5±6.4	71.3±6.81	25.85±0.74	28.42±8.85

Table 2. Results of repeated measures ANOVA

Variables	Time	Mean±SD				Time Effect	Time×Group Effect	Group Effect
		Control Group	Supplement Group	Supplement + Exercise Group	Placebo + Exercise Group			
BMI (Kg/m^2)	Pre-test	26.13±0.37	26.07±0.64	25.99±0.84	25.75±0.74	F=35.12	F=11.39	F=2.65
	Post-test	26.17±0.36	25.98±0.63	25.24±0.75	25.23±0.75	P=0.03	P=0.11	P=0.54
NO (µmol/L)	Pre-test	8.09±41.38	10.31±42.32	9.56±40.58	13.18±37.77	F=69.16	F=13.61	F=2.06
	Post-test	10.14±43.08	13.18±37.77	12.94±62.39	12.31±43.78	P=0.001	P=0.01	P=0.12
ET-1 (pg/mL)	Pre-test	2.72±0.019	2.71±0.013	2.72±0.018	2.72±0.018	F=363.2	F=123.75	F=13.45
	Post-test	2.72±0.021	2.55±0.018	1.91±0.017	2±0.019	P=0.001	P=0.001	P=0.001
TG (mg/dL)	Pre-test	138.1±55.06	157.9±98.49	174.5±104.1	108.1±40.04	F=12.01	F=1.27	F=1.43
	Post-test	132.07±47.85	133.1±68.03	160.8±84.51	34.33±10.85	P=0.001	P=0.29	P=0.25
TC (mg/dL)	Pre-test	165.3±40.84	148.3±48.89	163.2±50.81	143.3±18.14	F=16.97	F=4.32	F=0.77
	Post-test	166.1±38.7	141.7±48.81	147.4±44.5	137.8±19.89	P=0.001	P=0.01	P=0.51
HDL (mg/dL)	Pre-test	45.1±12.32	38.1±9.08	40.6±9.99	40.1±10.28	F=15.78	F=5.85	F=1.13
	Post-test	45.5±12.6	39.9±9.14	51.3±8.13	42.5±10.87	P=0.001	P=0.002	P=0.34
LDL (mg/dL)	Pre-test	86.8±27.72	74±33.62	84.7±26.99	68.6±14.56	F=9.87	F=3.15	F=1.15
	Post-test	87.4±27.72	71.2±31.35	87.6±22.87	67±14.35	P=0.003	P=0.037	P=0.34
Systolic blood pressure (mmHg)	Pre-test	137.25±2.76	130.82±2.81	140.5±2.49	129.75±2.49	F=171.09	F=25	F=6.83
	Post-test	135.12±2.99	137.37±2.84	124.75±1.49	130.25±2.24	P=0.001	P=0.001	P=0.001
Diastolic blood pressure (mm Hg)	Pre-test	89.12±2.22	83.2±2.44	90.37±2.6	79.17±2.5	F=3.12	F=2.63	F=1.57
	Post-test	75.1±2.99	69.40±2.24	78.1±2.82	83.97±2.65	P=0.001	P=0.03	P=0.06
Vitamin D (nm/mL)	Pre-test	28.33±4.66	30.17±3.81	30.17±3.68	28.42±8.85	F=45.63	F=4.09	F=1.85
	Post-test	28.92±4.62	36.92±5.34	37.21±4.13	34.14±7.95	P=0.001	P=0.001	P=0.15
Weight (kg)	Pre-test	66.16±12.79	73.6±6.83	69.9±4.43	71.3±6.81	F=36	F=36	F=2.44
	Post-test	66.9±11.89	78.1±6.55	73.6±5.44	76.6±8.36	P=0.001	P=0.001	P=0.08

TC, HDL, LDL, and vitamin D levels. Thus, it had no significant effect on lipid profile. Many factors can lead to different results regarding the effect of aerobic exercise on lipoprotein levels, such as different durations or intensities. Some authors believe that, to maintain this effect longer, the aerobic exercises also need to be longer and have higher intensities. Dunn et al. [13] suggested that, as long as there is sufficient training intensity, short-term training can also improve plasma lipids. Kraus et al. [14] reported that total energy intake and exercise intensity were the main factors influencing lipoproteins. O'Donovan et al. [15] in a study on the effect of exercise intensity on changes in blood lipids, found that in the same amount of exercise, a higher intensity can lead to more obvious changes in blood lipids. Thus, it can be said that possible reason for the lack of change in blood lipid levels in this study can be the short duration or low intensity of aerobic exercises.

Recent studies have shown that exercise is an effective non-pharmacological method for treating endothelium disorders, especially due to its chronic effects in

increasing eNOS and subsequent NO production [16, 17]. However, the findings of this study showed that NO levels did not change significantly after 8 weeks of aerobic exercise plus vitamin D supplementation. Previous studies have shown that the type, duration and protocol of the exercise, individual differences of the participants, and genetic factors may have a role in the discrepancy between the results of different studies. The results of this research are consistent with the results of Pál et al. [18], Bilici et al. [19], Skrzypczyk et al. [20], and Sülü et al. [21] while are against the results of some studies [22, 23]. For example, Hojatoleslami et al. [24] reported that 8 weeks of aerobic exercise significantly improved the NO level in menopausal women with pre-hypertension.

It has been reported that patients with primary hypertension have increased vascular ET-1 activity, which may be pathophysiologically related to their increased vascular tone [25]. Increased vascular response to ET-1 has also been reported in an animal model of hypertension [26]. In addition, ET-1 has a strong proliferative activity in vascular smooth muscle cells and, therefore, plays a role in the development of atherosclerosis [27]. It has also been reported that the expression of ET-1 increases in human atherosclerotic lesions [28]. On the other hand, it is well known that regular exercise has beneficial effects on the cardiovascular system [29]. Chronic exercise reduces blood pressure in patients with moderate blood pressure [30, 31]. The decrease in arterial compliance due to aging causes an increase in systolic blood pressure, but exercise can prevent the decrease in arterial compliance [32]. The results of these studies are consistent with our results. In the study by Meada et al. [33] the levels of ET-1 in middle-aged people decreased significantly after 3 months of aerobic exercise which is consistent with the findings of the present study. In addition, Nyberg et al. [34] showed that skeletal muscle ET-1 levels increase with the increase of age in healthy individuals, while exercise reduce skeletal muscle ET-1 levels in middle-aged and elderly healthy individuals [34, 35]. In addition, plasma ET-1 concentration was higher in hypertensive subjects which was normalized by aerobic exercise. Similarly, aging increased plasma ET-1 concentrations in healthy men. They concluded that lifelong physical activity opposes this age effect.

According to the results of this study, vitamin D supplementation alone can reduce ET-1 and systolic blood pressure. Therefore, it is recommended to use this supplement for people who are probably facing vitamin D deficiency and hypertension. Since the use of vitamin D supplement along with aerobic exercise improved the beneficial effects of exercise on reducing ET-1, it is better to take have exercise activity in addition to taking vitamin D supplement to reduce high blood pressure.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committe of Kurdistan University of Medical Sciences, Sanandaj, Iran (Code: IR.MUK.REC.1401.006).

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Authors contribution's

All authors contributed equally in all part of this research.

Conflict of interest

Study design and supervision: Mohammad Rahman Rahimi, Roghaiyeh afsargharehbagh, and Nasser Rostamzadeh; conceptualization, methodology, software, validation, formal analysis, research, resources, data management, writing, visualization, supervision and project management: Mozaffar Jan Faza; Final approval: All authors.

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References

[1] Boeno FP, Ramis TR, Munhoz SV, Farinha JB, Moritz CEJ, Leal-Menezes R, et al. Effect of aerobic and resistance exercise training on inflammation, endothelial function and ambulatory blood pressure in middle-aged hypertensive patients. J Hypertens. 2020; 38(12):2501-9. [DOI:10.1097/HJH.0000000000002581] [PMID]

[2] Sehgal S, Daniel J, Sharma M. A comparative study to find the effect of aerobic exercise training versus resistance exercise training in adults with pre-hypertension. Indian J Public Health Res Dev. 2023; 14(1):347-52. [Link]

[3] De Miguel C, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: New understandings and potential therapeutic targets. Curr Hypertens Rep. 2015; 17(1):507. [DOI:10.1007/s11906-014-0507-z] [PMID] [PMCID]

[4] You T, Arsenis NC, Disanzo BL, Lamonte MJ. Effects of exercise training on chronic inflammation in obesity: Current evidence and potential mechanisms. Sports Med. 2013; 43(4):243-56. [DOI:10.1007/s40279-013-0023-3] [PMID]

[5] Vaziri ND, Rodríguez-Iturbe B. Mechanisms of disease: Oxidative stress and inflammation in the pathogenesis of hypertension. Nat Clin Pract Nephrol. 2006; 2(10):582-93. [DOI:10.1038/ncpneph0283] [PMID]

[6] Sheehy S, Palmer JR, Cozier Y, Bertrand KA, Rosenberg L. Vitamin D and risk of hypertension among Black women. J Clin Hypertens (Greenwich). 2023; 25(2):168-74. [DOI:10.1111/jch.14615] [PMID] [PMCID]

[7] Pál É, Ungvári Z, Benyó Z, Várbíró S. Role of vitamin D deficiency in the pathogenesis of cardiovascular and cerebrovascular diseases. Nutrients. 2023; 15(2):334. [DOI:10.3390/nu15020334] [PMID] [PMCID]

[8] Cui A, Xiao P, Ma Y, Fan Z, Zhou F, Zheng J, et al. Prevalence, trend, and predictor analyses of vitamin D deficiency in the US population, 2001-2018. Front Nutr. 2022; 9:965376. [DOI:10.3389/fnut.2022.965376] [PMID] [PMCID]

[9] Mestek ML, Westby CM, Van Guilder GP, Greiner JJ, Stauffer BL, DeSouza CA. Regular aerobic exercise, without weight loss, improves endothelium-dependent vasodilation in overweight and obese adults. Obesity (Silver Spring). 2010; 18(8):1667-9. [DOI:10.1038/oby.2009.467] [PMID]

[10] Van Guilder GP, Hoetzer GL, Smith DT, Irmiger HM, Greiner JJ, Stauffer BL, et al. Endothelial t-PA release is impaired in overweight and obese adults but can be improved with regular aerobic exercise. Am J Physiol Endocrinol Metab. 2005; 289(5):E807-13. [DOI:10.1152/ajpendo.00072.2005] [PMID]

[11] Mohammadi R, Fathei M, Hejazi K. [Effect of eight-weeks aerobic training on serum levels of nitric oxide and endothelin-1 in overweight elderly men (Persian)]. Iran J Ageing. 2018; 13(1):74-85. [DOI:10.21859/sija.13.1.74]

[12] Sadeh MR, Sharifatpour R. The effect of eight weeks of aerobic exercise on balance function and physiological cost Index in Multiple Sclerosis Patients. J Community Health Res. 2020; 9(4):273-81. [Link]

[13] Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW 3rd, Blair SN. Reduction in cardiovascular disease risk factors: 6-month results from Project Active. Prev Med. 1997; 26(6):883-92. [DOI:10.1006/pmed.1997.0218] [PMID]

[14] Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002; 347(19):1483-92. [DOI:10.1056/NEJMoa020194] [PMID]

[15] O'Donovan G, Owen A, Bird SR, Kearney EM, Nevill AM, Jones DW, et al. Changes in cardiorespiratory fitness and coronary heart disease risk factors following 24 wk of moderate-or high-intensity exercise of equal energy cost. J Appl Physiol (1985). 2005; 98(5):1619-25. [DOI:10.1152/japplphysiol.01310.2004] [PMID]

[16] Poveda JJ, Riestra A, Salas E, Cagigas ML, López-Somoza C, Amado JA, et al. Contribution of nitric oxide to exercise-induced changes in healthy volunteers: Effects of acute exercise and long-term physical training. Eur J Clin Invest. 1997; 27(11):967-71. [DOI:10.1046/j.1365-2362.1997.2220763.x] [PMID]

[17] Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. Lipids Health Dis. 2017; 16(1):132. [DOI:10.1186/s12944-017-0515-5] [PMID] [PMCID]

[18] Pál É, Ungvári Z, Benyó Z, Várbíró S. Role of vitamin D deficiency in the pathogenesis of cardiovascular and cerebrovascular diseases. Nutrients. 2023; 15(2):334. [PMID]

[19] Bilici ME, Erdeve ŞS, Çetinkaya S, Aycan Z. "The effect of 2000 ıu/day vitamin D supplementation on insulin resistance and cardiovascular risk parameters in vitamin D deficient obese adolescents." urk J Pediatr. 2019; 61(5):723-32. [PMID]

[20] Skrzypczyk P, Ofiara A, Szyszka M, Dziedzic-Jankowska K, Sołtyski J, Pańczyk-Tomaszewska M. Vitamin D in children with primary hypertension. Arterial Hypertens. 2018; 22(3):127-34. [Link]

[21] Sülü A, Altay E, Köşger P, Kıztanır H, Uçar B. The relationship between Vitamin D level and ambulatory blood pressure parameters and cardiovascular risk factors. Eur Arch Med Res. 2023; 39(1):6-12. [DOI:10.4274/eamr.galenos.2022.61224]

[22] Fujie S, Sanada K, Hamaoka T, Iemitsu M. Time-dependent relationships between exercise training-induced changes in nitric oxide production and hormone regulation. Exp Gerontol. 2022; 166:111888. [DOI:10.1016/j.exger.2022.111888] [PMID]

[23] Jain A, Bozovicar K, Mehrotra V, Bratkovic T, Johnson MH, Jha I. Investigating the specificity of endothelin-traps as a potential therapeutic tool for endothelin-1 related disorders. World J Diabetes. 2022; 13(6):434-41. [DOI:10.4239/wjd.v13.i6.434] [PMID] [PMCID]

[24] Hojatoleslami L, Tadibi V, Behpoor N. [Effect of eight weeks aerobic training on nitric oxide and apelin levels in women with pre-hypertension (Persian)]. J Sport Exerc Physiol. 2019; 12(2):107-18. [DOI:10.52547/joeppa.12.2.107]

[25] Cardillo C, Kilcoyne CM, Waclawiw M, Cannon RO 3rd, Panza JA. Role of endothelin in the increased vascular tone of patients with essential hypertension. Hypertension. 1999; 33(2):753-8. [DOI:10.1161/01.HYP.33.2.753] [PMID]

[26] Suzuki N, Miyauchi T, Tomobe Y, Matsumoto H, Goto K, Masaki T, et al. Plasma concentrations of endothelin-1 in spontaneously hypertensive rats and DOCA-salt hypertensive rats. Biochem Biophys Res Commun. 1990; 167(3):941-7. [DOI:10.1016/0006-291X(90)90614-S] [PMID]

[27] Rubanyi GM, Polokoff MA. Endothelins: Molecular biology, biochemistry, pharmacology, physiology, and pathophysiology. Pharmacol Rev. 1994; 46(3):325-415. [PMID]

[28] Winkles JA, Alberts GF, Brogi E, Libby P. Endothelin-1 and endothelin receptor mRNA expression in normal and atherosclerotic human arteries. Biochem Biophys Res Commun. 1993; 191(3):1081-8. [DOI:10.1006/bbrc.1993.1327] [PMID]

[29] Golbidi S, Laher I. Exercise and the cardiovascular system. Cardiol Res Pract. 2012; 2012:210852. [DOI:10.1155/2012/210852] [PMID] [PMCID]

[30] Saco-Ledo G, Valenzuela PL, Ruiz-Hurtado G, Ruilope LM, Lucia A. Exercise reduces ambulatory blood pressure in patients with hypertension: A systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2020; 9(24):e018487. [DOI:10.1161/JAHA.120.018487] [PMID] [PMCID]

[31] Ciolac EG, Guimarães GV, D'Avila VM, Bortolotto LA, Doria EL, Bocchi EA. Acute aerobic exercise reduces 24-h ambulatory blood pressure levels in long-term-treated hypertensive patients. 2008; 63(6):753-8. [DOI:10.1590/S1807-59322008000600008] [PMID] [PMCID]

[32] Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. Circulation. 2000; 102(11):1270-5. [DOI:10.1161/01.CIR.102.11.1270] [PMID]

[33] Maeda S, Tanabe T, Miyauchi T, Otsuki T, Sugawara J, Iemitsu M, et al. Aerobic exercise training reduces plasma endothelin-1 concentration in older women. J Appl Physiol (1985). 2003; 95(1):336-41. [DOI:10.1152/japplphysiol.01016.2002] [PMID]

[34] Nyberg M, Mortensen SP, Hellsten Y. Physical activity opposes the age-related increase in skeletal muscle and plasma endothelin-1 levels and normalizes plasma endothelin-1 levels in individuals with essential hypertension. Acta Physiol (Oxf). 2013; 207(3):524-35. [DOI:10.1111/apha.12048] [PMID]

[35] Kuczmarski AV, Welti LM, Moreau KL, Wenner MM. ET-1 as a sex-specific mechanism impacting age-related changes in vascular function. Front Aging. 2021; 2:727416. [DOI:10.3389/fragi.2021.727416] [PMID] [PMCID]

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