Research in Molecular Medicine

8-week Aerobic Exercise and Vitamin D Supplementation: Impact on Hypertension With Vitamin D Deficiency

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Citation Janfaza M, Bahnamon M, Afsargharehbagh R. 8-week Aerobic Exercise and Vitamin D Supplementation: Impact on Hypertension With Vitamin D Deficiency. Research in Molecular Medicine. 2023; 11(3):187-194. https://doi.org/10.32598/rmm.11.3.1301.2

Article Type:
Research Paper

Article info:
Received: 12 May 2024
Revised: 25 May 2024
Accepted: 03 Jul 2024

ABSTRACT

Background: This research aims to investigate the performance of 8 weeks of aerobic exercise and vitamin D supplementation on nitric oxide (NO) and endothelin 1 (ET-1) indicators in patients with high blood pressure and vitamin D deficiency.

Materials and Methods: In this quasi-experimental research, 40 qualified men and women were randomly divided into four groups (supplement group, placebo + exercise group, supplement + exercise group, and control group). The training program of the experimental groups included 8 weeks of aerobic exercise running on a treadmill (3 sessions per week). Two groups (exercise + supplement and supplement group) received vitamin D supplement daily in the amount of 2000 international units in a double-blind manner, and the exercise + placebo group received a placebo capsule containing maltodextrin daily. Blood sampling was done to evaluate biochemical variables 48 hours before and after the intervention in a fasting state.

Results: The research results show that after 8 weeks of aerobic training with vitamin D supplementation, there was no significant effect on body mass index, NO, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), vitamin D, and weight ($P<0.05$), but the effects were significant on ET-1 level and systolic blood pressure which changed in the supplement, supplement+exercise, and exercise+placebo groups compared to the control group ($P<0.05$). Also, the vitamin D increase showed a significant change ($P<0.05$).

Conclusion: Based on the results of the present study, taking vitamin D supplements for 8 weeks along with aerobic activity reduces ET-1, increases NO, and improves blood pressure in hypertensive people with vitamin D deficiencies.

Keywords:
Vitamin D deficiency, Nitric oxide (NO), Endothelin 1 (ET-1), Aerobic exercise, High blood pressure, Vitamin D

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Introduction

Hypertension is a common health concern in today's society, which is a significant risk factor for cardiovascular diseases and mortality [1]. Recent research suggests that vitamin D deficiency may exacerbate blood pressure, as it significantly regulates blood pressure and vascular function [2]. In addition, imbalances in serum levels of nitric oxide (NO) and endothelin 1 (ET-1) play a decisive role in the pathophysiology of hypertension and affect vascular tone and endothelial function [3]. Due to the complex interaction between vitamin D deficiency, hypertension, and endothelial dysfunction, many studies have investigated adjunctive interventions such as aerobic exercise and vitamin D supplementation to reduce these risks [4]. Aerobic exercise enhances endothelial function and NO bioavailability through various mechanisms. Endothelial cells release NO in response to shear stress caused by increased blood flow during exercise, leading to vasodilation and improved blood flow regulation. In addition, exercise increases the activity of endothelial NO synthase (eNOS) and increases NO production. These effects help maintain vascular homeostasis and regulate blood pressure [5]. Aerobic exercise improves cardiovascular health by increasing endothelial function and NO production [6]. Also, vitamin D supplementation may have vascular protective effects by balancing serum levels of ET-1 and improving endothelial function [7]. Vitamin D plays a multifaceted role in cardiovascular health, including regulating ET-1, a potent vasoconstrictor peptide. Vitamin D receptors are expressed in endothelial cells, where vitamin D modulates the expression and secretion of ET-1. Vitamin D deficiency has been linked to endothelial dysfunction and increased levels of ET-1, contributing to vasoconstriction and high blood pressure. Vitamin D supplementation may reduce these effects by restoring endothelial function and reducing ET-1-mediated vasoconstriction [8]. Combining aerobic exercise with vitamin D supplementation may synergistically affect NO and ET-1 levels in patients with hypertension with vitamin D deficiency. Aerobic exercise increases NO production and endothelial function, while vitamin D supplementation regulates ET-1 levels and improves endothelial function. The combined intervention may, therefore, provide a holistic approach to managing hypertension and reducing cardiovascular risks in this population [9].

This study aimed to investigate the effects of 8 weeks of aerobic training with vitamin D supplementation on NO and ET-1 indices in patients with hypertension and vitamin D deficiency. By shedding light on the molecular mechanisms underlying these interventions, we provide insight into potential therapeutic strategies for managing high blood pressure and associated cardiovascular risks in people with vitamin D deficiency.

Materials and Methods

This research is quasi-experimental with a pre-test and post-test design. The statistical population comprised male and female patients (30 to 50 years old) with hypertension and vitamin D deficiency living in Urmia City, Iran. The participants were randomly divided into four groups of 5 women and 5 men in each group (supplement group, placebo + exercise group, supplement + exercise group, and a control group, 10 people in each group) [10].

One week before the intervention, the subjects were given the necessary explanations for conducting the research. Before starting the study, the subjects were invited to participate in a briefing session to learn about the training protocol and its steps. After mentioning the necessary points about the protocol implementation, the advantages and disadvantages of participating in the research, the possible discomforts related to blood selection, and all the points that should be observed, the consent form was provided. If the subjects accepted the conditions, they signed the form. This research has observed all the ethical considerations necessary for working on human samples.

The inclusion criteria included lacking diet and regular exercise program in the past year, being 30 to 50 years old, having vitamin D deficiency, having blood pressure of 120-139 mm Hg, lacking specific and metabolic diseases of liver diseases, non-smoking and alcoholic beverages (more than 20 g/day). The exclusion criteria included the presence of other disorders such as autoimmune hepatitis, arthritis, celiac disease, Wilson's disease, coronary artery disease and surgery, kidney failure, hypothyroidism, open surgery and angiography, no musculoskeletal injuries affecting the process of training, not taking certain medications (dietary and sports supplements) during the entire anabolic steroid consumption plan, no medication or supplement during the research, suffering from any acute disease or discomfort during the research, taking antihypertensive drugs, having injury, acute injury-induced training during the study, unwillingness to continue cooperation or performing any regular exercise outside of the research protocol or medical prohibition.

Table 1. The effect of physical activity on patients with vitamin D deficiency

Groups	Mean±SD				
	Age (y)	Height (cm)	Weight (kg)	Body Mass Index (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
Vitamin D	39.1±2.9	159.3±7.4	73.6±6.83	26.07±0.64	30.17±3.81
Exercise + vitamin D	38.3±3.8	71.3±161.2	69.9±4.43	25.99±0.84	30.17±3.68
Exercise + placebo	45.6±2.9	163.5±6.4	71.3±6.81	25.85±0.74	28.42±8.85

The training program of the experimental groups consisted of 8 weeks of aerobic training of running on a treadmill (three sessions per week and each session for 45 minutes) with low intensity, i.e. 40% to 60% of the maximum heart rate. The activity started in the first week with an intensity of 40% of the maximum heart rate, the second week with an intensity of 45%, the third and fourth weeks with an intensity of 50%, the fifth and sixth weeks with an intensity of 55%, and finally in the seventh week and the eighth with a maximum heart rate of 60%. The control and supplement groups performed no regular exercise during this period. The subjects' heart rate was monitored using a polar pacemaker. In all sessions, the subjects performed stretching and relaxation exercises for 10 minutes to warm up and 5 minutes of cooling down at the end of the main activity [11].

In each blood sampling, fasting blood samples (48 hours before the start of the study and 48 hours after the end of the last training session) were taken by the laboratory specialist to determine the levels of the research variables. Blood samples (5 mL) were collected in tubes containing EDTA anticoagulant, and after centrifugation (9 min at 4500 rpm) and plasma isolation, they were examined using ELAN 2000 auto-analyzer [12], to measure the biochemical factors of lipid profile, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Vitamin D serum levels were also measured using the ELISA research kit (Noand Salamat Co., Iran).

For the quantitative measurement of ET-1, we employed the ELISA research kit (ZellBio, Germany), utilizing the ELISA L-2P processor (made by Eroummun, Germany).

The Kolmogorov-Smirnov test was used to investigate the normal distribution of data, and Levene's test to investigate the homogeneity of variances. The repeated measures analysis of variance (ANOVA) was used to determine intra-group (time effect), intergroup (group effect), and time-group interactions. All collected data were analyzed using SPSS software version 26 at a significance level of <0.05.

Results

The descriptive characteristics of the subjects are presented in Table 1. They are reported based on the Mean±SD of body mass index, BMI percentage, and vitamin D levels.

Statistically, none of the research variables in the pre-test had a significant difference between the groups (P>0.05). According to the results of repeated measure ANOVA, after 8 weeks of aerobic training with vitamin D supplementation, there was no significant difference between groups regarding BMI, NO, TG, TC, HDL, LDL, vitamin D, and weight. However, for ET-1 (F=13.45, P=0.001) and systolic blood pressure (F=6.83, P=0.001), 8 weeks of aerobic training plus vitamin D supplementation created a significant difference between groups. After performing the one-way ANOVA, the results showed a significant difference between the pre-test and post-test values of ET-1 and systolic blood pressure levels (P=0.01, F=245.53, P=0.01, F=6.83, respectively) (Table 2).

Discussion

This study shows the effect of 8 weeks of aerobic training combined with vitamin D supplementation on NO and endothelin-1 levels in patients with hypertension and vitamin D deficiency. The available data encompass variables such as BMI, vitamin D levels, NO, endothelin-1, lipid profiles, and pre-test and post-test results from the intervention.

Table 2. Results of variance analysis of repeated serum levels of variables in hypertensive patients

Variables	Time of Intervention	Mean±SD						Group
		Control	Practice+Vitamin D	Vitamin D	Exercise+Placebo	Time	Time×Group	
BMI (kg/m²)	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
S BP(mm Hg)	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
D B P (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	69.4±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

Abbreviations: BMI: Body mass index; NO: Nitric oxide; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ET-1: Endothelin-1; S BP: Systolic blood pressure; D BP: Diastolic blood pressure.

The research results indicate that the mean BMI differed among the studied groups; however, the effect of vitamin D supplementation on reducing BMI was insignificant (P=0.54).

In the exercise+supplement group, systolic and diastolic blood pressure decreased significantly after the intervention compared to pre-test levels (P=0.001). The combined effects of vitamin D supplementation and aerobic exercise on lipid variables varied, but generally, these effects were significant (P<0.05). Based on these findings, aerobic training combined with vitamin D supplementation can significantly improve NO levels, endothelin-1, and blood pressure in patients with hypertension and vitamin D deficiency. These results suggest improved cardiovascular health and a reduced risk of associated diseases.

Scientifically, the effects of aerobic exercise and vitamin D deficiency on lipoprotein levels in hypertensive patients can depend on several factors.

Exercise physiology

The intensity of aerobic exercise can help regulate the metabolism of fats and lipoproteins. This effect is attributed to changes in the activity of enzymes and genes associated with fat metabolism, leading to an increase in HDL and a reduction in LDL levels. [13]. Some researchers argue that longer durations and higher intensities of training are necessary to sustain these effects over time. For instance, Krasniqi et al. [14] suggested that while sufficient exercise intensity is critical, short-term exercise can also improve plasma lipids.

Lipoprotein biochemistry

Aerobic exercise can enhance lipid metabolism by reducing LDL and increasing HDL levels [15]. Additionally, recent studies have shown that exercise serves as an effective non-pharmacological intervention for endothelium disorders, primarily due to its sustained effects on increasing eNOS and subsequent NO production [16].

Effect of vitamin D

Vitamin D is crucial for calcium and bone metabolism but also influences the immune system, inflammation, and vascular function through affecting lipoprotein levels [17]. However, the findings of this study indicate that NO levels had significant changes after 8 weeks of aerobic exercise combined with vitamin D supplementation, which is consistent with the results of Hoseini et al., and Hamid Rad et al. studies [18, 19].

Individual differences

Individual differences such as genetics, nutrition, physical activity levels, and clinical conditions significantly influence an individual's response to exercise and vitamin D [14]. Previous studies have indicated that factors such as the type, duration, exercise design, individual differences of participants, and genetic factors may contribute to variations in study outcomes.

The results of this study are consistent with findings from several researchers [13, 20-25]. However, they contradict some other studies [26-28]. For example, Hojjat Eslami et al. found that 8 weeks of aerobic training combined with vitamin D supplementation significantly improved NO levels in patients with hypertension and menopause [29].

Studies have shown that patients with hypertension and vitamin D deficiency have increased ET-1 vascular activity, which may be pathophysiologically related to increased vascular tone [30].

An increase in the vascular response to ET-1 has also been reported in an animal model of hypertension [31]. In addition, ET-1 has strong proliferative activity in vascular smooth muscle cells and, therefore, is involved in the development of atherosclerosis [32]. ET-1 expression has also been reported to increase in human atherosclerotic lesions that are vitamin D deficient [33]. On the other hand, it is well known that regular exercise benefits the cardiovascular system. Regular exercise lowers blood pressure in patients with hypertension as well as increases vitamin D supplementation [33]. Age-induced decrease in arterial adaptation increases systolic blood pressure, and vitamin D deficiency is directly correlated. At the same time, exercise training prevents this decrease in arterial adaptation and prevents its reduction with concomitant vitamin D supplementation [34], which is consistent with the results of these studies. Also, in the study of Liu et al., [35] ET-1 levels in middle-aged people were significantly reduced after 3 months of aerobic exercise, so the findings of the study of Moreau et al. agree with the findings of the present study [36]. Furthermore, Bordbar Azari et al. (2023) reported that the levels of ET-1 in skeletal muscle increase with age in healthy individuals. However, exercise training was found to decrease ET-1 levels in the skeletal muscles of middle-aged and elderly healthy adults and to enhance the expression of ET-A receptors in skeletal muscles. Additionally, plasma ET-1 concentrations are elevated in individuals with hypertension but can be normalized through aerobic exercise. In relation to high blood pressure, aging increases plasma ET-1 concentrations in healthy men, but lifelong physical activity appears to counteract this age-related effect [37]. Moreover, vitamin D supplementation has a positive impact on skeletal muscle health and bone density in patients with hypertension and vitamin D deficiency [37, 38].

Conclusion

Various factors can change in lipoprotein and vitamin D levels in hypotensive patients. These changes are usually caused by changes in the body's biochemistry and response to exercise and vitamin D intake, which may improve cardiovascular risk factors and physiological functions. Vitamin D, as a steroid hormone, plays a crucial role in regulating lipid metabolism. This vitamin influences the expression of lipid and lipoprotein metabolism genes, including LDL and HDL. Vitamin D contributes to fat transport and cholesterol metabolism by activating vitamin D receptors in various tissues. For instance, research has demonstrated that adequate vitamin D levels can decrease LDL and VLDL levels while increasing HDL levels, reducing the risk of cardiovascular diseases. In addition, regular physical activity significantly contributes to improving lipoprotein profiles and vitamin D levels. Regular exercise enhances insulin sensitivity and improves hormonal balance, which can lead to reduced inflammation and better metabolic status. Moreover, physical activity aids in the increased production of vitamin D in the skin through sun exposure. A study indicated that individuals who exercise regularly exhibit higher vitamin D levels than those with lower activity levels. These two factors can synergistically exert positive effects on cardiovascular health. Also, the effects of vitamin D and exercise on lipoprotein profiles indirectly influence blood pressure and cardiovascular health. Vitamin D may help regulate blood pressure by reducing the production of inflammatory hormones and improving endothelial function.

On the other hand, exercise enhances vascular capacity and improves blood flow. For example, regular physical activity increases NO production, a crucial mediator in vasodilation and blood pressure reduction. These molecular changes not only aid in improving the cardiovascular status of patients with hypotension but may also reduce the risk of obesity and diabetes-related diseases. Vitamin D may improve cardiovascular risk factors and physiological functions. According to the results of this study, vitamin D supplementation combined with aerobic exercise can lower serum levels of ET-1, decrease systolic blood pressure, and increase vitamin D in patients. Therefore, individuals at risk of vitamin D deficiency and high blood pressure are encouraged to consider this supplement. Since combining vitamin D supplementation with aerobic training enhances the positive effects of exercise on reducing ET-1 levels, it is advisable to engage in regular aerobic activity throughout the week to lower blood pressure alongside vitamin D supplementation further.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethis Committe of The Ethics Committee of the University of Kurdistan, Sanandaj, Iran (Code: IR. UOK. REC.1401.006).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contribution's

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the mnuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors thank all the paprticipants who helped them conduct this study.

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