Research Article

The effect of L-arginine supplementation along with 6 weeks of Aquatic training on changes in blood pressure and fasting blood sugar in older peoples with Hypertension

Yaser Kazemzadeh [1], Pegah Hooshangi [2*], Yasamin Soltani[3]

1. Assistant Professor, Graduated from Kharazmi University, Tehran, Iran

2. Exercise Physiology Department, East Tehran Branch, Islamic Azad University, Tehran, Iran.

3. PhD student in sports physiology, Sports Physiology Department, Islamshahr Branch, Islamic Azad University, Islamshahr, Iran

Received: 15 August 2022
Revised: 9 September 2022
Accepted: 8 November 2022

Abstract

Background: The factors that control blood pressure, the most important of which are inactivity and improper nutrition. The present study was conducted with the aim of investigating the effect of arginine supplementation on blood pressure and glucose metabolism in elderly people with mild Hypertension.

Materials and Methods: 43 elderly men and women in the age range of 55 to 70 years with mild hypertension were selected as participants and were randomly divided into 4 groups, including the aquatic training group (AT), L-arginine supplementation (ARG), aquatic training + L-arginine supplementation (AT+ARG) and control (CON). AT group did sports training in water for 6 weeks. ARG group received 100 mg of L-arginine per body weight and AT+ ARG group received L-arginine supplement during 6 weeks of water sports training. The control group also received only placebo. The values measured in the present study included aerobic power, systolic blood pressure, diastolic blood pressure and fasting blood glucose. The findings were compared using one-way analysis of variance and Tukey's post hoc test at a significance level of ≥0.05.

Results: The findings of the present study showed that the diastolic blood pressure of the subjects did not differ significantly (P=0.239), but the difference between the systolic blood pressure of the group was significant (P=0.031). Also, the change of fasting blood glucose of the samples in the 4 groups shows a significant difference (P=0.011). L-arginine consumption group and sports training + L-arginine consumption group showed a significant difference with the control group (P=0.0001 and P=0.001, respectively).

Conclusion: The results of the present study showed that consuming L-arginine for 6 weeks in the elderly with hypertension can lead to improvement of their systolic blood pressure and fasting blood sugar, but adding training cannot double its effect. slow All sports training have proven effects in modulating blood pressure and lowering blood sugar in people who have used it for some time, but it seems that observing the double effect of activities on these indicators requires long training programs, which future studies show. It will clarify more.

Keywords:
L-arginine, insulin resistance, hypertension, aquatic training.

***Corresponding author:** Pegah Hooshangi
Address: Exercise Physiology Department, East Tehran Branch, Islamic Azad University, Tehran, Iran.
Email: pegahhooshangi61@gmail.com **Tell**: +989123116155
P H: 0000-0003-0845-7315

1. Introduction

The results of the world's largest study on blood pressure, which was conducted in collaboration with the World Health Organization and hundreds of researchers, showed that the number of people suffering from hypertension in the world has reached one billion and 130 million people, and the number of sufferers has more than doubled in the past 40 years; while, the number of Iranians suffering from hypertension has reached 10 million (Khamseh, 2021). Various factors affect blood pressure, the most important of which are inactivity and improper nutrition. With exercise, the incidence and intensity of cardiovascular and hypertension risk factors are reduced and it becomes possible to reduce the use of antihypertensive drugs and reduce premature death. Consuming special foods that can be effective in dilating blood vessels and regulating blood pressure is one of the other solutions that can be provided to control blood pressure. In the meantime, it has been determined that the consumption of some amino acids can be effective in controlling blood pressure (Vasdev, 2010). Human and animal studies have shown that certain amino acids combined with protein can have antihypertensive effects. Branched-chain amino acids (Jennings et al., 2016), cysteine (Vasdev, 2008), glutathione, glutamate (Stamler, 2009), and arginine (Lucotti, 2006) have a reducing and sometimes preventive effect on hypertension and factors related to insulin resistance and diabetes (Kass, 2012). On the other hand, type 2 diabetes as a metabolic disease has strong underlying and environmental factors among Iranians (Khamseh, 2021). This disease has a higher prevalence in people over 45 years old and studies on its possible mechanisms have been strongly focused.

By improving glucose metabolism in diabetics, the consumption of some amino acids leads to a reduction in the glycation of substances in the blood, and hence reduces the negative effects of high blood sugar on the vessel wall and hypertension in these people (Hu, 2017). It has been shown that the amino acid leucine has positive effects on diabetics (Zhang, 2020). Therefore, positive effects can be obtained by using amino acid supplements in people with hypertension and diabetes (Vasdev, 2010). On the other hand, it is known that sports activities, especially aerobic activities that are performed for long periods of time, lead to the adjustment of systolic and diastolic blood pressure. In a review study, researchers analyzed the results of 13 studies conducted on the effect of physical activities on blood pressure, and it was determined that the duration of the activity is the most important exercise variable in the effectiveness of exercise on blood pressure changes (Carpio-Rivera, 2016). The main mechanisms of cardiovascular diseases are dysfunction of vascular endothelium, so its dysfunction can increase its permeability to plasma components, especially low-density lipoproteins and its deposition in the sub endothelial space, and (LDL) can be used as it is one of the most basic events that occurs in the process of developing atherosclerosis. The effect of nutrition and physical activity on hypertension has been almost proven, however, the interaction of these two factors and the simultaneous actions of these two factors have been less discussed. It is not clear whether these two factors can have a synergistic effect.

Also, there is less information about the effectiveness of each of these factors alone in a simultaneous study in elderly people with hypertension, so in the present study, the researcher sought to answer the question that the effect of arginine supplementation on the indicators What is related to hypertension and glucose metabolism in the body? Also, if you combine the use of this supplement with aquatic training, will their effect increase or not?

2. Materials and Methods

Research method and samples: The statistical population of this research was all people with mild blood pressure in the age range of 55 to 70 years who did not take any special medicine to control blood pressure or other metabolic disorders. Among this population, 43 subjects who had the conditions to participate in the research were selected as subjects. In order to conduct the present study, first by referring to the centers that implement the Dignity Plan of Tehran Municipality, located in the 1st, 2nd and 3rd districts of Tehran, the necessary correspondence regarding the use of the elderly in these places was conducted with the officials of these centers, and the number of 43 women and Elderly men in the age range of 55 to 70 years with mild hypertension were selected and randomly divided into 4 groups including three experimental groups and one control group.

The criteria for entering the subjects in this study were systolic blood pressure above 140 and diastolic blood pressure above 90 mmHg, no consumption of alcohol, smoking, and no history of regular exercise, and none of the subjects took any special medication to control blood pressure or other disorders. They did not use metabolic drugs. There were some metabolic disorders such as diabetes, insulin resistance, blood fat and obesity in some subjects. Other demographic characteristics of the subjects are shown in Table 1:

Table 1: General characteristics of subjects (mean ± standard deviation)

Groups / Variables	control group	L-arginine group	Aquatic training group	L-arginine group along with aquatic training
Number	11	12	10	10
	6 men and 5 women	6 men and 6 women	6 men and 4 women	5 men and 5 women
age (years)	66.4±4.72	62.33±6.52	59.73±3.83	60.46±4.41
height (meters)	164.42±4.64	167.61±5.21	165.11±6.89	161.37±4.48
weight (kg)	71.56±6.90	74.27±8.01	69.12±6.23	68.73±7.37
body mass index (kilograms per square meter)	26.39±2.54	26.53±1.98	25.34±2.11	26.23±1.79
fat percentage (%)	28.46±3.17	26.11±5.09	23.55±5.54	25.11±4.09
Waist to hip ratio	1.01±0.17	0.97±0.09	0.89±0.11	0.91±0.19

After selecting the samples and explaining them about how to implement the work, written consent was taken from them to participate in the research. Then, the samples were randomly divided into 4 groups, including water sports training (AT) and L-arginine supplement consumption (ARG), aquatic training and L-arginine supplement consumption (AT+ARG) and control (CON). . Next, after measuring the dependent variables in the pre-test, the independent variables were applied in different groups for 6 weeks. For this purpose, the AT group performed 45 to 60 minutes of water sports three times a week for 6 weeks. The ARG group received 100 mg of L-arginine per kilogram of body weight twice a day in the form of oral capsules, and the AT+ARG group received L-arginine supplement during 6 weeks of aquatic training.

The control group also received only the placebo (dextrose) in the same capsules. 24 hours after the last activity session, the variables measured in the first week were measured and recorded in the fasting state under the same conditions as the pre-test. Evaluation of variables: The variables measured in this study included aerobic capacity, body composition, ratio of waist circumference to hip circumference, systolic blood pressure, diastolic blood pressure and fasting blood glucose. For this purpose, after coming to the laboratory, the subjects rested for 10 minutes on a comfortable chair, and then their systolic and diastolic blood pressure was measured using Citizen brand CH-456 digital sphygmomanometer made by CITIZEN company in Japan. It reports the pressure type along with the heart rate.

To measure fasting blood glucose, 10 cc of blood was taken from the subject's brachial vein and after clotting, it was kept in the refrigerator for FBS measurement. Before starting the training program and under completely identical conditions, the subjects' body composition and aerobic capacity were measured using the Quine staircase test. Their body composition was also done using the Inbody-270 body composition evaluation device made in South Korea, and after a full body scan, the ratio of waist circumference to hip circumference was provided to the researchers in printed form.

Exercise protocol

The exercise protocol implemented in the present study included a six-week aquatic training program, which was performed three sessions a week (18 sessions in total) and each session lasted 45 to 60 minutes. Each aquatic training session had three phases: warm-up, the main part of the aquatic training, and cool-down. The exercises of the experimental group were done in the indoor pool with water temperature between 26-28 degrees Celsius according to the protocol in Table 2.

Table 2: Steps of the aquatic training protocol

The first stage (warming up for 15 minutes)	the second stage (exercising for 30 minutes)	the third stage (cooling down for 15 minutes)
Stretching movements in water	transferring weight from front to back	doing stretching movements
Walking forward	turning around a square	buoyancy exercises, stretching exercises and deep breathing
Walking backwards	standing on one leg	
Walking sideways	transferring weight from one side to another	
Walking on heels and toes	stepping sideways	
Jacking in the water	Scott	
	Hamstring pull back	
	Open the thigh	
	bike leg	
	Pendulum movements of hands and feet	
	The movement of stepping forward	
	Step to the side	
	Military step forward movement	
	Coordinated walking movement	

Ethical Considerations

Before explaining the research, people were asked to participate in the research by completing the consent form if they were willing and gave informed consent. The exercise implementation process was fully and clearly explained and it was explained to the subjects that this research does not have any risk or harm in terms of intervention or assessment methods. Subjects were able to leave the research at any stage of the research for any reason.

Statistical analysis

After ensuring the normality of the data using the Shapiro-Wilks test, the data were analyzed using one-way analysis of variance and Tukey's post hoc test was used to compare the two groups. All calculations were done using SPSS version 26 statistical software at a significance level of 0.05.

3. Results

The findings of the present study are summarized in Table 3. The result of data analysis using one-way analysis of variance shows that the subjects' diastolic blood pressure did not differ significantly after 6 weeks of applying independent variables (P=0.239), but the difference between the systolic blood pressure of the samples in The post-test was statistically different (P=0.031). Also, the fasting blood glucose changes of the samples in the 4 groups showed a significant difference (P=0.011).

Table 3: Summary of research findings in groups of research groups

Variables / Groups	Fasting blood glucose mg/dl		diastolic blood pressure mmHg		systolic blood pressure mmHg		maximum oxygen consumption ml/kg.min	
	Post Test	Pre Test	Post Test	Pre Test	Post Test	Pre Test	Post Test	Pre Test
CON	122	126	86	85.8	133.8	134.3	22.7	22.1
ARG	113	135	84.2	88.9	131.2	135.7	25.2	24.3
AT	131	143	89.3	91.1	132.9	134.8	24.7	19.8
AT+ARG	100	126	86.5	90.3	132.1	135.1	26.3	23.2

Fasting blood glucose mg/dl diastolic blood pressure mmHg systolic blood pressure mmHg maximum oxygen consumption variable ml/kg.min

The systolic blood pressure values of the samples are shown in chart 1. Based on this, the results of Tukey's post hoc test show a significant difference with the control group (P=0.0001 and P=0.001 respectively). Other groups are not significantly different.

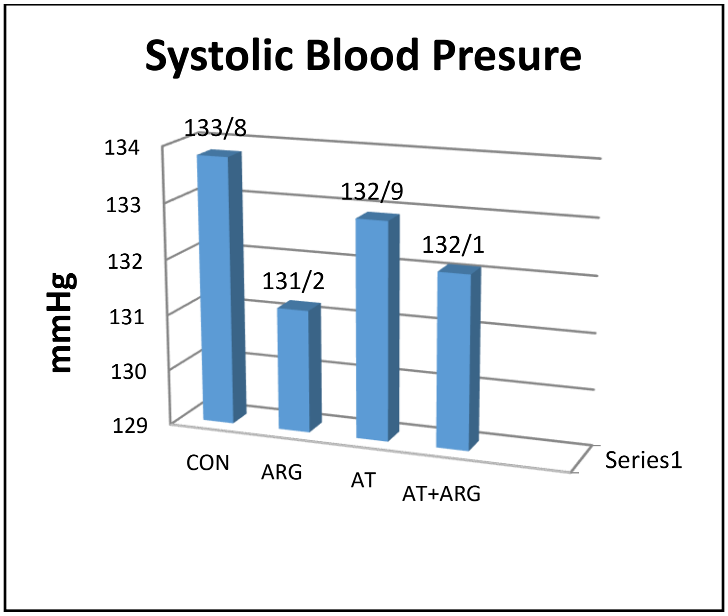

Chart 1: Comparison of systolic blood pressure after a 6-week intervention in research groups

Chart 2 also shows the changes in fasting blood sugar before and after the intervention program in different groups. These results indicate that there is a significant difference between the aquatic training group + L-arginine consumption and the control group (P=0.0001). Also, the aquatic training group is also different from the control group (P=0.001), but there is no significant difference between the other groups.

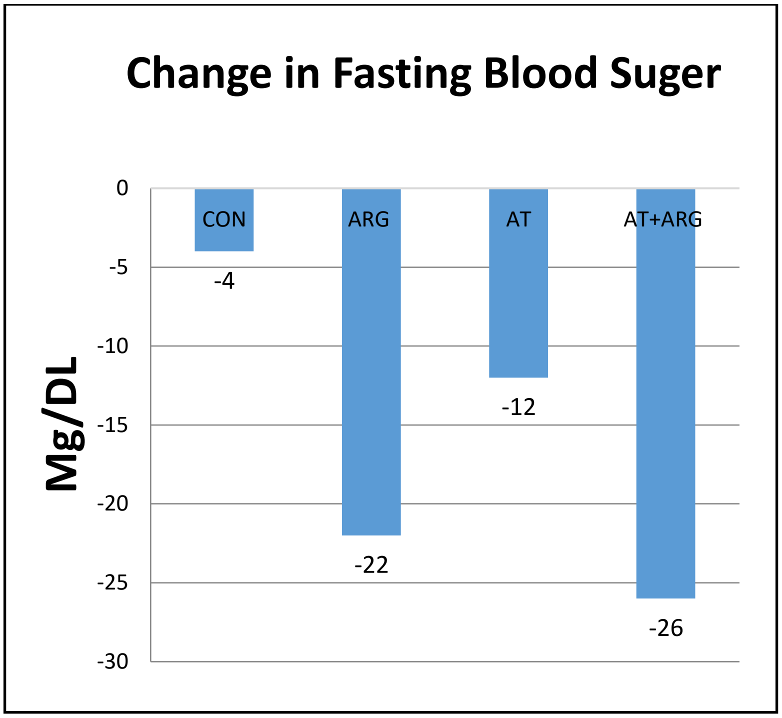

Chart 2: Comparison of changes in fasting blood sugar after 6-week intervention in research groups

4. Discussion

The results of the current research showed that consuming about 6 grams of L-arginine per day and doing sports exercises for 6 weeks lead to a decrease in systolic and blood pressure in the elderly with hypertension, but aquatic exercise alone do not have such an effect. This issue is consistent with the results reported by Mir Fatahi et al. (2018) and Bahrami et al. It is clear that the dosage of L-arginine and the subjects participating in the mentioned studies are the most important reasons for the difference in the results. In the study by Pahlavani et al. (2014), 2 grams of L-arginine per day were used for 45 days in the intervention group, while in the present study, the amount of about 6 grams of L-arginine was used. This was while the studies of Mirftahi (2018) and Bahrami (2018) used 3 and 5 grams of L-arginine, respectively.

More important than that was the study conducted by Asadi and his colleagues (2013) in order to investigate the supplemental effect of L-arginine in a double-blind randomized clinical trial of 57 patients with type 2 diabetes. The results showed that consuming 6 grams of L-arginine per day led to a decrease in total cholesterol, but there was no change in HDL and TG. This issue shows the role of dosage in creating effects of L-arginine on lipid profile. Other differences in different studies are related to the type of subjects. Considering the proven effects of exercise and L-arginine supplementation on blood pressure regulation, it seems that the greatest effect of this factor is in people who have hypertension.

On the other hand, in some researches that used healthy subjects with normal blood pressure, the use of L-arginine supplement and performing sports activities could not cause significant changes in blood pressure. Regarding the effect of the aquatic training program, the results showed that 6 weeks of aquatic training did not change much in adjusting and reducing the blood pressure of the subjects. 6 weeks of aquatic training does not seem to be sufficient for significant changes in blood pressure regulation in elderly subjects, while the American College of Sports Medicine in its latest opinion recommends 3-month exercise programs with an exercise volume of 150 to 250 minutes per week. has proposed for this purpose (). However, in the current study, the researcher was looking for the synergistic effect of two factors, sports activity and L-arginine consumption, and the results showed that this synergistic effect does not occur within 6 weeks. Regarding the reasons for the effect of l-arginine on blood pressure regulation, various mechanisms have been stated, and it seems that a set of these factors are effective in creating such results. Among them, we can mention the effect of L-arginine in stimulating the release of nitric oxide (NO) from vascular endothelium. Nitric oxide is the cause of vasodilation in many arterioles of the body. Nitric oxide synthase (NOs) catalyzes its production by endothelial cells. Since L-arginine is one of the factors that stimulate and activate the above enzyme, its increase in the blood flow can lead to an increase in the production of NO and by increasing the diameter of the vessels, it can reduce vascular resistance.

Arginase enzyme as L-arginine decomposer competes with nitric oxide synthase enzyme in getting L-arginine (Vasdev, 2010). Studies have shown that probably during old age, L-arginine goes more towards catabolic pathways, and for this reason, blood vessels lose their ability to produce nitric oxide, and one of the mechanisms of hypertension in old age is the lack of this amino acid. It is essential in the body of elderly people. For this reason, taking L-arginine can lead to the improvement of this condition in elderly people. Another mechanism by which L-arginine affects vasodilation is via insulin. L-arginine causes the release of insulin from the beta cells of the pancreas, and in turn, insulin causes a decrease in the concentration of asymmetric dimethyl arginine (ADMA) in the plasma. Asymmetric dimethyl arginine is an L-arginine analog that competes with L-arginine for uptake into vascular endothelial cells. Its increase leads to a decrease in cellular uptake of L-arginine (Ide 2007, Mann 2003). Therefore, by reducing the concentration of insulin in the blood, you help increase the absorption of L-arginine by the vascular endothelial cells. Also, the binding of insulin to insulin receptors causes the production of NO through the activation of an insulin-related signaling pathway, resulting in insulin-mediated vasodilation. L-arginine also modulates the function of the renin-angiotensin system (RAS). It inhibits angiotensin-converting enzyme (ACE) activity, thus reducing angiotensin II and its downstream effects (Campese, 1997). The effect of L-arginine on the RAS may be mediated by insulin. Low and moderate concentrations of insulin have been shown to decrease angiotensinogen expression in endothelial cells, while high concentrations upregulate the ACE receptor. L-arginine has been shown to have antioxidant activities that may help regulate redox-sensitive proteins and lower blood pressure.

Effect of L-arginine supplementation on blood pressure Arginine is involved in several important physiological processes and affects many vascular functions. L-arginine deficiency or lack of availability and changes in L-arginine metabolism can contribute to hypertension and endothelial cell dysfunction (Mann, 2003).

The results of the present study showed that consumption of about 6 grams of L-arginine reduces fasting blood glucose concentration. These results are consistent with what was reported by Lucotti et al. (2006), Pahlavani et al. (2014) and Boon et al. (2018). In the research of Bon et al. (2018), the effect of consuming 9 grams of L-arginine per day was investigated in 10 middle-aged Asian and European prediabetes men, and the results of this research showed that 6 weeks of consuming L-arginine had an effect on the basal metabolism and the activity of coffee fat cells. It does not exist in both races. However, glucose tolerance test results, circulating insulin, and peak insulin concentration were improved in European men, but not in South Asian men.

Conclusion

The researcher has concluded that L-arginine supplementation does not change the basic metabolism and activity of fat cells, but it improves some indicators of glucose metabolism in the blood of the European race. This research clearly shows that L-arginine can improve the blood sugar profile of pre-diabetic and diabetic people. However, some animal studies have reported that long-term L-arginine intake may increase insulin resistance. Since L-arginine acts as a stimulator of pancreatic beta-cells to produce insulin (Vassef 2008), it is possible that long-term stimulation of L-arginine leads to fatigue and laziness of pancreatic beta-cells. Also, studies have shown that sports activities and exercises can reduce the effects of long-term abuse of L-arginine. In the same context, Barrera et al showed in 2017 that adding exercise to the L-arginine supplement use program in the long term can reduce the effects of abuse of this supplement in reducing insulin sensitivity in mice. Considering the role of exercise and L-arginine consumption in increasing the secretion of growth hormone from the pituitary gland, the results of this study confirmed the role of L-arginine in attenuated insulin resistance.

In general, the results of the present study showed that consuming L-arginine for 6 weeks in the elderly with hypertension can lead to improvement of their systolic blood pressure and blood sugar profile, but adding aquatic exercise could not double its effect. Although exercise training has proven effects in modulating blood pressure and reducing blood sugar in diabetic and pre-diabetic people, it seems that observing the double effect of activity on these indicators requires longer training programs, which future studies will investigate. It will clarify more.

Acknowledgements

The authors would like to thanks all the participants who participated in this research.

Funding

This study did not have any funds.

Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: Y.K., P.H., Y.S.; Methodology: Y.K., P.H., Y.S.; Software: Y.K., P.H., Y.S.; Validation: Y.K., P.H., Y.S.; Formal analysis: P.H., Y.S.; Investigation: Y.K., P.H.; Resources: Y.K., P.H., Y.S.; Data curation: P.H., Y.S.; Writing - original draft: Y.K., P.H., Y.S.; Writing - review & editing: Y.K., P.H.; Visualization: Y.K., P.H., Y.S.; Supervision: P.H., Y.S.; Project administration: Y.K., P.H., Y.S.; Funding acquisition: Y.K., P.H.

References

1. Mirftahi Maryam, Saedi Soumae Olya Ahmed, Sotoudeh Giti, Mohajeri Tehrani Mohammad Reza, Keshavarz Seyed Ali, Hosseini Mostafa, Seifi Rad Soroush. Investigating the effect of L-arginine supplementation on blood pressure in overweight people with pre-diabetes. Iranian Journal of Diabetes and Lipid, Bimonthly, April-May 2013, Volume 11 (Number 4) 393-399. 2. Asadi Sara, Mozafari Khosravi Hassan, Rahimi

2. Mahnaz, Naghizadeh Mohammad Mehdi. The effect of L-arginine supplementation on the lipid profile of patients with type 2 diabetes. Journal of Fasa University of Medical Sciences, fourth year, number 1, spring 2013.

3. Jennings A, MacGregor A, Pallister T, Spector T, Cassidy A. Associations between branched chain amino acid intake and biomarkers of adiposity and cardiometabolic health independent of genetic factors: A twin study. Int J Cardiol. 2016 Nov 15;223:992-998. doi: 10.1016/j.ijcard.2016.08.307. Epub 2016 Aug 23. PMID: 27591698; PMCID: PMC5074005.

4. Pahlavani N, Salehi Abarghouei A, Karimian J, Rouhani MH, Entezari MH. The Effect of Supplementation of L -Arginine on the Lipid Profile, Fasting Blood Sugar and Blood Pressure in Healthy Subjects with thepreventive Approach of Cardiovascular Diseases. *J RafsanjanUniv Med Sci* 2015; 14(6): 493-506.

5. Bahrami Davood, Mozaffari-Khosravi H. The Effect of Oral L-arginine Supplementation on Blood Pressure in Patients with Metabolic Syndrome: A Randomized Clinical Trial. IRANIAN JOURNAL OF DIABETES AND OBESITY, VOLUME 10, NUMBER 1, SPRING 2018.

6. Vianna LC, Fernandes IA, Barbosa TC, Amaral TG, Rocha NG, Secher NH, Nóbrega AC. Absent increase in vertebral artery blood flow during l-arginine infusion in hypertensive men. Am J Physiol Regul Integr Comp Physiol. 2018 Oct 1;315(4):R820-R824. doi: 10.1152/ajpregu.00088.2018. Epub 2018 Jun 27. PMID: 29949408.

7. Stamler J, Caggiula A, Grandits GA, Kjelsberg M, Cutler JA. Relationship to blood pressure of combinations of dietary macronutrients. Findings of the Multiple Risk Factor Intervention Trial (MRFIT). Circulation. 1996 Nov 15;94(10):2417-23. doi: 10.1161/01.cir.94.10.2417. PMID: 8921782.

8. Vasdev S, Gill V. Effect of soybean in diet on blood pressure. Hypertens Canada 2006; 88:3-5.

9. Campese VM, Amar M, Anjali C, Medhat T, Wurgaft A. Effect of L-arginine on systemic and renal haemodynamics in salt-sensitive patients with essential hypertension. J Hum Hypertens. 1997 Aug;11(8):527-32. doi: 10.1038/sj.jhh.1000485. PMID: 9322835..

10. Mann GE, Yudilevich DL, Sobrevia L. Regulation of amino acid and glucose transporters in endothelial and smooth muscle cells. Physiol Rev. 2003 Jan;83(1):183-252. doi: 10.1152/physrev.00022.2002. PMID: 12506130..

11. Eid HM, Reims H, Arnesen H, Kjeldsen SE, Lyberg T, Seljeflot I. Decreased levels of asymmetric dimethylarginine during acute hyperinsulinemia. Metabolism. 2007 Apr;56(4):464-9. doi: 10.1016/j.metabol.2006.11.003. PMID: 17379002..

12. Salgueiro RB, Gerlinger-Romero F, Guimarães-Ferreira L, de Castro Barbosa T, Nunes MT. Exercise training reverses the negative effects of chronic L-arginine supplementation on insulin sensitivity. Life Sci. 2017 Dec 15;191:17-23. doi: 10.1016/j.lfs.2017.10.001. Epub 2017 Oct 7. PMID: 28993146..

13. Boon MR, Hanssen MJW, Brans B, Hülsman CJM, Hoeks J, Nahon KJ, Bakker C, van Klinken JB, Havekes B, Schaart G, Jazet IM, Rensen PCN, van Marken Lichtenbelt WD. Effect of L-arginine on energy metabolism, skeletal muscle and brown adipose tissue in South Asian and Europid prediabetic men: a randomised double-blinded crossover study. Diabetologia. 2019 Jan;62(1):112-122. doi: 10.1007/s00125-018-4752-6. Epub 2018 Oct 30. PMID: 30377712; PMCID: PMC6290676.

14. Lucotti P, Setola E, Monti LD, Galluccio E, Costa S, Sandoli EP, Fermo I, Rabaiotti G, Gatti R, Piatti P. Beneficial effects of a long-term oral L-arginine treatment added to a hypocaloric diet and exercise training program in obese, insulin-resistant type 2 diabetic patients. Am J Physiol Endocrinol Metab. 2006 Nov;291(5):E906-12. doi: 10.1152/ajpendo.00002.2006. Epub 2006 Jun 13. PMID: 16772327.

15. Hu S, Han M, Rezaei A, Li D, Wu G, Ma X. L-Arginine Modulates Glucose and Lipid Metabolism in Obesity and Diabetes. Curr Protein Pept Sci. 2017;18(6):599-608. doi: 10.2174/1389203717666160627074017. PMID: 27356939.

16. Poggiogalle E, Fontana M, Giusti AM, Pinto A, Iannucci G, Lenzi A, Donini LM. Amino Acids and Hypertension in Adults. Nutrients. 2019 Jun 27;11(7):1459. doi: 10.3390/nu11071459. PMID: 31252583; PMCID: PMC6683075.

17. Vasdev S, Gill V. The antihypertensive effect of arginine. Int J Angiol. 2008 Spring;17(1):7-22. doi: 10.1055/s-0031-1278274. PMID: 22477366; PMCID: PMC2728371.

18. Kass, L., Weekes, J. & Carpenter, L. Effect of magnesium supplementation on blood pressure: a meta-analysis. *Eur J Clin Nutr* **66,** 411–418 (2012). https://doi.org/10.1038/ejcn.2012.4.

19. Khamseh ME, Sepanlou SG, Hashemi-Madani N, Joukar F, Mehrparvar AH, Faramarzi E, Okati-Aliabad H, Rahimi Z, Rezaianzadeh A, Homayounfar R, Moradpour F, Valizadeh N, Kheirandish M, Zaboli E, Moslem A, Ahmadi A, Hamzeh B, Harooni J, Pourfarzi F, Abolghasemi MR, Safarpour AR, Aminisani N, Mohammadi Z, Eghtesad S, Poustchi H, Malekzadeh R. Nationwide Prevalence of Diabetes and Prediabetes and Associated Risk Factors Among Iranian Adults: Analysis of Data from PERSIAN Cohort Study. Diabetes Ther. 2021 Nov;12(11):2921-2938. doi: 10.1007/s13300-021-01152-5. Epub 2021 Sep 30. PMID: 34595726; PMCID: PMC8521563.

20. Stamler J, Brown IJ, Daviglus ML, Chan Q, Kesteloot H, Ueshima H, Zhao L, Elliott P; INTERMAP Research Group. Glutamic acid, the main dietary amino acid, and blood pressure: the INTERMAP Study (International Collaborative Study of Macronutrients, Micronutrients and Blood Pressure). Circulation. 2009 Jul 21;120(3):221-8. doi: 10.1161/CIRCULATIONAHA.108.839241. Epub 2009 Jul 6. PMID: 19581495; PMCID: PMC4048930.

21. Zhang L, Li F, Guo Q, Duan Y, Wang W, Zhong Y, Yang Y, Yin Y. Leucine Supplementation: A Novel Strategy for Modulating Lipid Metabolism and Energy Homeostasis. Nutrients. 2020 May 2;12(5):1299. doi: 10.3390/nu12051299. PMID: 32370170; PMCID: PMC7282259.

22. Carpio-Rivera E, Moncada-Jiménez J, Salazar-Rojas W, Solera-Herrera A. Acute Effects of Exercise on Blood Pressure: A Meta-Analytic Investigation. Arq Bras Cardiol. 2016 May;106(5):422-33. doi: 10.5935/abc.20160064. Epub 2016 May 6. PMID: 27168471; PMCID: PMC4914008.

23. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online ahead of print November 13, 2017].Hypertension. doi: 10.1161/HYP.0000000000000065.

24. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA; American College of Sports Medicine. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc. 2004 Mar;36(3):533-53. doi: 10.1249/01.mss.0000115224.88514.3a. PMID: 15076798.