Physical Activity and Hormones (J Physic Act Horm)
Vol. 6 Autumn 2025

The effect of 8 weeks of aerobic training and vitamins E & C supplementation on the plasma levels of MMP-1 and MMP-3 and TIMP-4 in patients with Coronary artery disease

Elham Karami[1]
Department of Physical Education and Sports Sciences, Ra.C., Islamic Azad University, Rasht, Iran

Ramin Shabani[2]
Department of Physical Education and Sports Sciences, Ra.C., Islamic Azad University, Rasht, Iran

Farhad Rahmani-Nia[3]
Professor of Department of Exercise Physiology, Faculty of Sport Sciences, University of Guilan, Rasht, Iran

Alireza Elmiye[4]
Department of Physical Education and Sports Sciences, Ra.C., Islamic Azad University, Rasht, Iran

Mahdi Rezagholizadeh[5]
Department of Physical Education and Sports Science, Za.C., Islamic Azad University, Zanjan, Iran

ABSTRACT

Introduction: The family of matrix metalloproteinases (MMPs) and its inhibitors play an important role in cardiovascular diseases and vascular wall regeneration. The effect of sports training along with vitamin supplements on heart diseases due to the change of MMPs is not clear. Therefore, the aim of the present study is investigating the effect of eight weeks of aerobic training with vitamin E & C supplementation on the plasma levels of MMP-1 and MMP-3 and TIMP-4 in patients with coronary artery disease (CAD).

Material & Methods: 60 patients with CAD (53.84±5.49 years old mean ± SD) participated in this study., All the subjects were randomly divided into 4 equal groups (n=15): (1) control (C), (2) aerobic training (A), (3) supplement (S) and (4) aerobic training + supplement (AS) according to their aerobic capacity: and Groups 3 and 4 received 1000 mg of D-alpha tocopherol and 1000 mg acid ascorbic tablets daily. . The training program was also carried out for eight weeks (three sessions per week) with an intensity of 40 to 80% of the reserve heart rate for 45 minutes. 48 hours after the last session of training, blood samples were taken to analyze MMPs levels by using ELISA. The data were analyzed using analysis of covariance and paired t-test at a significance level of $P<0.05$.

Results: The plasma levels of MMP-1 (P=0.001) and MMP-3 (P=0.000) in the AS were significantly lower than the A group. TIMP-4 concentration in the AS group were significantly higher than in the A group (P=0.000). In addition, plasma MMP-1 and MMP-3 levels in patients with CAD in the AS group were significantly lower than in the S group (P=0.000) and C group (P=0.000). Also, plasma MMP-1 and MMP-3 levels in patients with CAD in the T group were significantly lower than in the C group (P=0.000). However, plasma MMP-1 (P=0.068), MMP-3 (P=0.069), and TIMP-4 (P=1.000) levels in patients with CAD in the T group were not significantly different from those in the S group. Also, plasma MMP-1 (P=0.055), MMP-3 (P=0.392), and TIMP-4 (P=0.405) levels in patients with CAD in the S group were not significantly different from those in the C group. In addition, plasma TIMP-4 levels in patients with CAD in the AS group were significantly higher than in the supplement (P=0.000) and control (P=0.000) groups. Also, plasma TIMP-4 levels in patients with CAD in the A group were significantly higher than in the C group (P=0.021).

Conclusion: combined aerobic training and taking vitamin E and C supplements can affect the plasma levels of the mentioned indicators to a greater extent and cause them to improve, which displays the higher efficiency of training at the same time as the supplement.

Keywords: Cardiac artery diseases, Aerobic training, Rehabilitation, Vitamins E & C supplementation.

***Correspondence:** Raminshabani@iau.ac.ir
Received: Jul 2025; **Revised:** Sept 2025; **Accepted:** Oct 2025.

DOI: https://doi.org/10.71878/jpah.2025.1212279

1. Introduction

Coronary artery disease (CAD) is a worldwide medical problem that is the leading cause of death in both developed and developing countries, especially in older people (1). Several studies have shown that the traditional risk factors, such as high blood lipids, diabetes, hypertension and obesity play crucial roles in the initiation and perpetuation of CAD. However, it is accepted that genetic component has an essential role in the development of CAD (2-5). Researches have suggested that family aggregation of CAD is not unusual, and genetic association investigations revealed that the average heritability of CAD is more than 50% (3, 6). Epidemiological studies have found many genetic variants especially single-nucleotide polymorphism (SNP) in association with an increased risk of CAD (7). The exact mechanism underlying the influence of polymorphism on the pathogenesis of CAD is not fully understood. Nevertheless, polymorphisms in numerous genes involved in inflammation, metabolism of lipid and glucose, blood clotting, and homocysteine may affect susceptibility to CAD (8, 9). The atherosclerotic lesion is formed due to lipoprotein particles accumulation in the intima of the coronary artery wall and gradually develops into the fibrous plaque, which is rich in extracellular matrix (ECM) proteins. It has now been well established that among many proteases, matrix metalloproteinases (MMPs) are the key enzymes in the transformation of the ECM in physiological and pathological conditions that involve inflammatory processes, such as arthritis, cancer, periodontal diseases, and cardiovascular disease (CVD)(10).

The matrix metalloproteinase family (MMPs) consists of more than 20 secretases or ectocellular enzymes that degrade extracellular matrix proteins, coagulation factors, lipoproteins, latent growth factors, chemokines, and cell adhesion molecules (11). Dysregulated extracellular matrix (ECM) metabolism is of significance in vascular remodeling during the progression and complication period of atherosclerosis (12). MMP3 not only degrades ECM components, but also activates MMP1 and other family members (13). Evaluation of the role of the remaining major fibrillar collagenase in atherosclerotic plaque development, namely MMP1, has lagged over the past 2 decades as an early prevailing view was that there was no functional homolog of MMP1 in mice, and that transgenic overexpression of human MMP1 in mouse macrophages led to paradoxical reductions in plaque size (14). With the advanced progression achieved on DNA technologies, MMP3 gene polymorphisms in the promoter region have been identified. In particular, MMP3 5A/6A is closely related to multiple pathological states. In the MMP3 promoter, a common functional variant (rs3025039) has been reported, in which one allele has a run of six adenosines (6A), while the other has only five (5A).22 MMP3 promoters containing the 5A allele have approximately 50% higher activity compared with those with the 6A allele because a putative transcriptional repressor protein preferentially binds to the promoter containing the 6A sequence and reduces gene expression (15). The activity of MMPs is regulated mostly by the endogenous tissue inhibitors of metalloproteinases (TIMPs), which bind to the active site of MMPs and block access to extracellular matrix substrates. This family consists of four membrane-associated structural members: TIMP-1, TIMP-2, TIMP-3, and TIMP-4, which are expressed by various cell types and are influenced by factors such as stretch, injury, inflammation, and immune activation (16). TIMP-4 has been reported to inhibit the activity of MMP-1, MMP-3, and MMP-9, and its expression levels in the cardiac tissue of adult individuals are notably high. The balance between MMPs and their tissue inhibitors plays a crucial role in maintaining the integrity of healthy tissues (17).

One of the most important and effective methods for improving the quality of life in patients with heart disease is cardiac rehabilitation. Cardiac rehabilitation is a complex intervention offered to patients diagnosed with heart disease, which includes components of health education, advice on cardiovascular risk reduction, physical activity and stress management. Evidence that cardiac rehabilitation reduces mortality, morbidity, unplanned hospital admissions in addition to improvements in exercise capacity, quality of life and psychological well-being is increasing, and it is now recommended in international guidelines (18). Another factor that can be effective in the prevention and improvement of cardiovascular diseases is an appropriate dietary approach. The consumption of fruits and vegetables rich in vitamins, or dietary supplements containing vitamins, can contribute to this effect. One of the vitamin supplements that is commonly used today is Vitamin E. Vitamin E is a fat-soluble antioxidant vitamin that protects lipids from peroxidation in vitro (19). Increasing evidence supports a central role for lipid oxidation in the development and progression of atherosclerosis (20). Therefore, vitamin E has been postulated to attenuate the process of atherosclerosis and reduce the risk of cardiovascular disease. Several observational studies showed that higher vitamin E intake from dietary sources or supplements was associated with a lower risk of cardiovascular disease (CVD) (21-23). Dietary or supplemental vitamin E intake as measured by food frequency questionnaires may not be well correlated with serum vitamin E concentrations, or reflect the lifelong vitamin E exposure. Moreover, the protective effects of vitamin E against CVD might be due to the combination of various antioxidants and nutritional substances contained in daily food. Some studies examining the association of serum vitamin E with the risk of CVD showed inconsistent results (24- 26), with some study showing a cardioprotective effect (27, 28), while some reporting vitamin E has no effect on CVD (24, 25, 26). Vitamin C (ascorbic acid), which is water soluble and present in the cytosolic compartment of the cell, serves as an electron donor to vitamin E radicals generated in the cell membrane during oxidative stress (12). Plasma vitamins E and C and uric acid, all of which have potential antioxidant activity, have been reported to

increase after exercise (10, 13-15). In rats, acute submaximal exercise has been shown to decrease vitamin E concentrations in skeletal muscle (16).

In research conducted, it has been reported that the gene expression of MMP-1 (collagenase-1) and TIMP-1, the protein expression of MMP-1, MMP-2 (gelatinase-A), TIMP-1 and TIMP-2 as well as the enzyme activity of MMP-1 and MMP-2 were examined. AGR (α-glucosylrutin) and vitamins C and E were shown to reduce MMP expression and activity, whereas 8-prenylnaringenine appeared to be responsible for the opposite effect (29). It has been shown that high-dose oral vitamin E supplementation for 12 weeks among diabetic nephropathy patients had favorable effects on biomarkers of kidney damage, inflammation, and oxidative stress (30). Based on the results, interaction between antioxidant supplements and exercise reduced the glucose concentration and improved the mitochondrial biogenesis of heart tissue, while the combination of these two interventions compared to the effect of each alone, the effect has more (31).

Today, invasive methods such as angioplasty, open-heart surgery, and pharmacological interventions are primarily used to treat coronary artery disease. However, various studies support the implementation of exercise programs during the recovery phase post-surgery and such interventions. Nevertheless, there has been less focus on the effects of physical activity on the molecules involved in the process of re-endothelialization of damaged arteries, as well as on their expression levels and arterial activity. Additionally, the impact of supplementation with major antioxidant vitamins on the activity of these molecules in patients with coronary artery disease (CAD) is a topic that has not been addressed in the existing literature. Furthermore, previous research has rarely examined the simultaneous effects of both vitamins in conjunction with physical exercise, and the findings reported have been inconsistent. Therefore, the present study aims to investigate whether an eight-week regimen of regular aerobic training, both alone and in conjunction with the long-term administration of vitamins E and C, has an effect on the expression and production levels of MMP-1, MMP-3, and TIMP-4 in the blood of patients with coronary artery disease (CAD).

2. Methodology

2.1. Materials and methods

This experimental study with a pre-test and post-test design conducted at cardiac rehabilitation center of Bahman Hospital, located in Zanjan city, in the year 2022. This study is registered under the clinical trial number IRCT20240418061518N1 and bears the ethics code IR.IAU.Z.REC.1403.005

2.2. Participants

For this purpose, based on the physician's recommendations (which included comprehensive blood tests, echocardiography, exercise stress test, and angiography) and the inclusion criteria for the study diagnosis of coronary artery disease with at least 50% stenosis in a minimum of two major coronary vessels, subsequent angioplasty treatment performed by an interventional cardiologist, absence of antioxidant medication, lack of exercise activity, no cognitive or psychiatric disorders, no stable angina, no myocardial infarction in the past month, personal readiness for physical activity, and age range of participants between 40 and 60 years, 60 men and women were selected using a convenient and purposive sampling method. The exclusion criteria included severe respiratory distress during exercise, and the occurrence of complications such as renal failure or pulmonary embolism during the study period. Subsequently, the participants were randomly divided into 4 equal groups (n=15): (1) control (C), (2) aerobic training (A), (3) supplement (S) and (4) aerobic training + supplement (AS), with approximately two-thirds of them being male and one-third female.

2.3. Measurements

The study's dependent variables, encompassing anthropometric measurements such as weight, height, BMI, and WHR, as well as fasting blood samples to quantify MMP-2 and MMP-9 levels, were assessed both 48 hours before the experimental period began and 48 hours after it ended. were measured with participants in surgical scrubs and bare feet. Height was measured to the nearest 0.1 cm via a wall-mounted stadiometer and weight was measured to the nearest 0.1 kg using an electronic scale. BMI (kg/m2) was calculated using the weight/height ratio and WHR measured by waist-to-hip ratio. To account for dietary influences on blood variables, participants completed a food recall questionnaire three days prior to the pre-test and submitted it to the researcher. They were instructed to replicate this dietary intake for the 72 hours preceding the post-test. Both blood sampling and anthropometric evaluations were performed 48 hours following the final exercise session. Blood samples were collected twice during the study—once at the pre-test and again at the post-test—using 5 cc drawn from the right antecubital vein each time. Each sample was placed into test tubes containing EDTA as an anticoagulant and subsequently centrifuged at 3000 RPM for 10 minutes to separate plasma. The extracted plasma was stored in a freezer set to -80°C for later laboratory analysis. To measure MMP-1, MMP-3, and TIMP-4 concentrations, human ELISA kits manufactured by Biotech Cusabio, China, were employed. These kits had the following specifications: for MMP-1, a range of 0.312–20 ng/ml with a sensitivity of 0.078 ng/ml; for MMP-3, a range of

1.56–100 ng/ml with a sensitivity of 0.39 ng/ml; and for TIMP-4, a range of 0.313–20 ng/ml with a sensitivity of 0.005 ng/ml.

2.4. Intervention

Aerobic training was conducted over eight weeks with the following training load: Frequency: three days per week; Intensity: 40 to 80 percent of heart rate reserve or Karvonen formula; Progression: the intensity of the activity was increased every two weeks based on the participants' progress; Duration: the goal was to perform 45 minutes of continuous activity at the specified intensity on each device. The type of activity included running on a treadmill, cycling on a stationary bike, and using a hand ergometer (each for approximately 15 minutes) (32). It is important to note that participants engaged in a 15-minute warm-up involving light jogging and stretching before exercising and performed stretching exercises for 10 minutes at the end of the sessions to cool down.

Over the same eight-week period, participants in the supplementation groups were administered daily doses of specific vitamins as prescribed: 1000 mg of d-alpha-tocopherol (33)(Vitamin E, Lifespan) and 1000 mg of ascorbic acid (34)(Vitamin C, Omid Parsian Damavand). These supplements were provided to individuals in both the supplementation-only and aerobic training + supplementation groups under physician guidance.

2.5. Statistical Methods

The collected data were analyzed using SPSS27 software, employing statistical tests such as covariance analysis, Bonferroni post hoc tests, paired t-tests, Shapiro-Wilk tests, Levene's tests.

3. Results

Analysis of the findings utilizing the analysis of covariance test revealed a statistically significant difference in plasma MMP-1 levels ($F_{4,55}$=27.051, P=0.000, η^2=0.596). The results of the Bonferroni post hoc test indicated that the plasma MMP-1 levels of patients with coronary artery disease (CAD) in the AS group were significantly lower compared to those in the A group (P=0.001) (Figure 1). Furthermore, the analysis of the findings via the analysis of covariance test showed a significant difference in plasma MMP-3 levels ($F_{4,55}$=31.200, P=0.000, η^2=0.630). The results from the Bonferroni post hoc test indicated that the plasma MMP-3 levels of patients with CAD in the AS group with were significantly lower than those in the A group (P=0.000) (Figure 2). Additionally, the analysis of the findings using the analysis of covariance test indicated a significant difference in plasma TIMP-4 levels ($F_{4,55}$=13.955, P=0.000, η^2=0.432). The results of the Bonferroni post hoc test demonstrated that the plasma TIMP-4 levels of patients with CAD in the AS group were significantly higher than those in the A group (P=0.000) (Figure 3).

In addition, plasma MMP-1 and MMP-3 levels in patients with CAD in the AS group were significantly lower than in the S group (P=0.000) and C group (P=0.000). Also, plasma MMP-1 and MMP-3 levels in patients with CAD in the T group were significantly lower than in the C group (P=0.000). However, plasma MMP-1 (P=0.068), MMP-3 (P=0.069), and TIMP-4 (P=1.000) levels in patients with CAD in the T group were not significantly different from those in the S group. Also, plasma MMP-1 (P=0.055), MMP-3 (P=0.392), and TIMP-4 (P=0.405) levels in patients with CAD in the S group were not significantly different from those in the C group. In addition, plasma TIMP-4 levels in patients with CAD in the AS group were significantly higher than in the supplement (P=0.000) and control (P=0.000) groups. Also, plasma TIMP-4 levels in patients with CAD in the A group were significantly higher than in the C group (P=0.021).

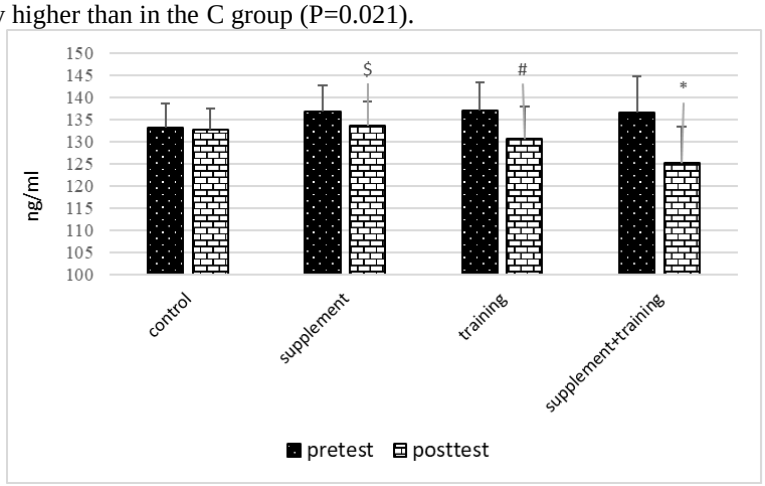

Figure 1. Plasma MMP-1 changes

*: Significant difference compared to other groups and pre-test
#: significant difference compared to the control group and pre-test
$: significant difference compared to the pre-test

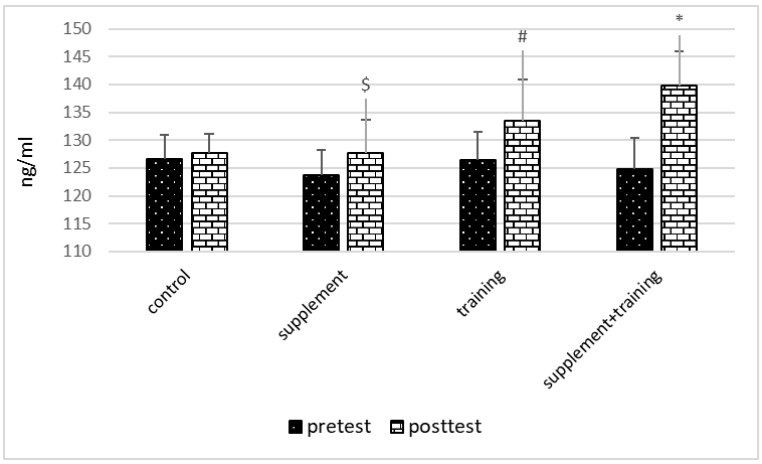

Figure 2. Plasma MMP-3 changes

*: Significant difference compared to other groups and pre-test
#: significant difference compared to the control group and pre-test
$: significant difference compared to the pre-test

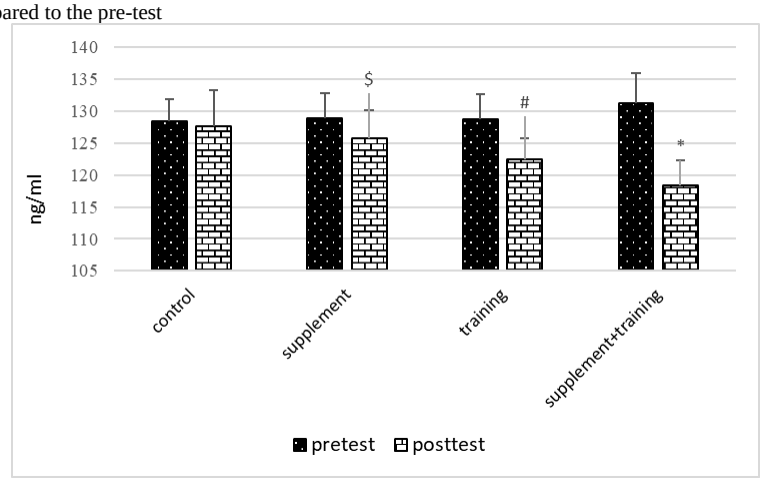

Figure 3. Plasma TIMP-4 changes

*: Significant difference compared to other groups and pre-test
#: significant difference compared to the supplement and control and pre-test groups
$: significant difference compared to the control group and pre-test

4. Discussion

Overall, the findings of the present study indicated that the plasma levels of MMP-1 and MMP-3 in patients with CAD in the aerobic training group supplemented with vitamins E and C were significantly lower than those in the aerobic training group alone. Conversely, the plasma levels of TIMP-4 in patients with CAD in the aerobic training group supplemented with vitamins E and C were significantly higher than those in the aerobic training group alone.

Given that cardiovascular diseases are among the leading causes of mortality worldwide, various rehabilitation methods have been proposed. One such method involves engaging patients in appropriately intense physical activity. Implementing rehabilitation programs can enhance both physical and psychological outcomes, reduce the risk of sudden death and heart attacks, and be beneficial for patients (35). Training at suitable intensities can improve cardiovascular function (36). The adaptations that occur following physical training enable other organs to achieve optimal performance. Among the crucial adaptations stemming from training are increased blood flow, enhanced metabolism of organs, and the removal of waste products (37). In addition to the factors mentioned, nutrition is another intervention that can improve cardiovascular function. Adopting a suitable dietary program rich in vitamins and nutrients can help enhance cardiac efficiency. Vitamin E supplementation, often combined with vitamin C due to their synergistic antioxidant effects, is commonly utilized. Vitamin E is a fat-soluble vitamin that includes four tocopherols and four tocotrienols, with alpha-tocopherol being the most biologically available form. It acts as a potent antioxidant capable of donating hydrogen atoms to free radicals, including superoxide and hydroxyl radicals, thereby converting them into more stable forms and preventing lipid peroxidation and membrane damage. Similarly, vitamin C, a water-soluble vitamin, protects against free radical production by neutralizing free radicals. Vitamins E and C work synergistically, with vitamin C assisting in the recycling of vitamin E to its reduced form, enabling it to continue oxidizing free radicals (38). Furthermore, they

prevent the oxidative degradation of cell membrane phospholipids, which can help prevent LDL-C oxidation and the onset of cardiovascular diseases (39). Additionally, vitamins C and E act as strong inhibitors of reactive oxygen species, which are activators of matrix metalloproteinases (MMPs). They play a critical role in preventing excessive MMP activity, which can be associated with the progression of various diseases. Therefore, these vitamins may be beneficial in the prevention and management of certain pathologies related to MMP regulation disorders (40). Moreover, the response of MMPs to training, depending on the training load, can create favorable conditions for individuals (41). Consequently, it can be concluded that the use of vitamin supplements alongside physical activity is advantageous in improving the health status of patients. Given that there is limited research on the effects of vitamin supplementation on the specified indices, a review of related studies will be conducted. It has been reported in related research that the consumption of black tea significantly reduces serum levels of MMP-3 in women with rheumatoid arthritis (42). Additionally, it has been noted that supplementation with S-equol leads to a significant decrease in levels of MMP-1 and MMP-3 in women with osteoarthritis (43). Furthermore, a significant increase in TIMP-4 was observed in diabetic mice treated with likogliflozin, which contributed to the improvement of diabetic cardiomyopathy (44). Moreover, it has been reported that zingiberine inhibits Pi-induced vascular calcification by modulating the AMPK/TIMP4 signaling cascade in vascular smooth muscle cells (45). Additionally, one study reported that 12 weeks of copper supplementation, with effects on TIMP-3, assists in improving cardiac function in a cardiomyopathic heart (46).

In general, the protective effects of vitamins E and C in preventing cardiovascular disease have been demonstrated in several contexts; however, a definitive correlation has not been universally established. Under certain conditions, L-ascorbic acid and α-tocopherol may exhibit antioxidant properties, potentially reducing the formation of oxidized small molecules, proteins, and lipids, which could contribute to cellular dysregulation. Nevertheless, non-antioxidant effects have also been proposed to play a role in the prevention of atherosclerosis. Vitamins E and C can modulate signal transduction and gene expression, thereby influencing various cellular responses such as smooth muscle cell proliferation, cell-adhesion expression, extracellular matrix molecules, NADPH oxidase production, platelet aggregation, and inflammatory responses. Vitamins E and C may affect the extracellular matrix environment by influencing the expression of connective tissue proteins involved in vascular remodeling, as well as maintaining the integrity of the vascular wall. Moreover, during the progression of atherosclerosis, cholesterol transfer as oxLDL activates a signaling cascade upon recognition by the CD36 receptor, which includes mitogen-activated protein kinase (MAPK), the c-Jun N-terminal kinase (JNK) pathway, and matrix metalloproteinases (MMPs), thereby stimulating inflammation through monocyte infiltration. It has been reported that α-tocopherol reduces c-Jun phosphorylation mediated by JNK1 (47).

Limitations of the present study include the lack of daily activity monitoring for the subjects, the absence of control over emotional states and psychological conditions, and insufficient control over nutrition during the training period.

Considering that this study observed the efficacy of vitamin supplementation alongside aerobic training in the subjects, it is recommended that future research related to this study be conducted in separate groups of women and men. Additionally, the impact of each vitamin individually, as well as the combination of both types of vitamins used in this study, should be examined for more precise results.

5. Conclusion

Overall, the review of the conducted studies indicates that the consumption of antioxidant supplements, both alone and in conjunction with training, leads to improvements in research indices. The findings of the present study also suggest improvements in blood indices alongside anthropometric measures and maximal oxygen consumption. Therefore, it appears that there is a positive relationship between aerobic training and the intake of vitamins E and C on anthropometric indices, which contributes to positive effects on MMPs and TIMP-4.

6. Acknowledgment

This research is the result of a doctoral dissertation in Exercise Physiology at the Islamic Azad University, Rasht Branch, conducted at the personal expense of the student and with the support of the university's Research Vice Presidency.

Conflict of interests: The authors declare that there is no conflict of interest regarding this article.

References

1. Sharma K, Gulati M. Coronary artery disease in women: a 2013 update. Global heart. 2013;8(2):105-12. https://doi.org/10.1016/j.gheart.2013.02.001.
2. Sanjadi M, Rezvanie Sichanie Z, Totonchi H, Karami J, Rezaei R, Aslani S. Atherosclerosis and autoimmunity: a growing relationship. International journal of rheumatic diseases. 2018;21(5):908-21. https://doi.org/10.1111/1756-185X.13309.

3. Mayer B, Erdmann J, Schunkert H. Genetics and heritability of coronary artery disease and myocardial infarction. Clinical Research in Cardiology. 2007;96(1):1-7. https://doi.org/10.1007/s00392-006-0447-y.
4. Mack M, Gopal A. Epidemiology, traditional and novel risk factors in coronary artery disease. Heart failure clinics. 2016;12(1):1-10. DOI: 10.1016/j.hfc.2015.08.002.
5. Giannakoulas G, Dimopoulos K, Engel R, Goktekin O, Kucukdurmaz Z, Vatankulu MA, et al. Burden of coronary artery disease in adults with congenital heart disease and its relation to congenital and traditional heart risk factors. The American journal of cardiology. 2009;103(10):1445-50. https://doi.org/10.1016/j.amjcard.2009.01.353.
6. Evans A, Van Baal GCM, McCarron P, DeLange M, Soerensen TI, De Geus EJ, et al. The genetics of coronary heart disease: the contribution of twin studies. Twin Research and Human Genetics. 2003;6(5):432-41. https://doi.org/10.1375/twin.6.5.432.
7. Sayols-Baixeras S, Lluís-Ganella C, Lucas G, Elosua R. Pathogenesis of coronary artery disease: focus on genetic risk factors and identification of genetic variants. The application of clinical genetics. 2014:15-32. https://doi.org/10.2147/TACG.S35301.
8. Onrat ST, Akci Ö, Söylemez Z, Onrat E, Avşar A. Prevalence of myocardial infarction polymorphisms in Afyonkarahisar, Western Turkey. Molecular biology reports. 2012;39:9257-64. https://doi.org/10.1007/s11033-012-1799-1.
9. Lusis AJ, Mar R, Pajukanta P. Genetics of atherosclerosis. Annu Rev Genomics Hum Genet. 2004;5(1):189-218. https://doi.org/10.1146/annurev.genom.5.061903.175930.
10. Mogharrabi M, Rahimi HR, Hasanzadeh S, Dastani M, Kazemi-Oskuee R, Akhlaghi S, et al. The effects of nanomicelle of curcumin on the matrix metalloproteinase (MMP-2, 9) activity and expression in patients with coronary artery disease (CAD): A randomized controlled clinical trial. ARYA atherosclerosis. 2020;16(3):136. https://doi.org/10.22122/arya.v16i3.1938.
11. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. Annual review of cell and developmental biology. 2001;17(1):463-516. https://doi.org/10.1146/annurev.cellbio.17.1.463.
12. Wenwang L. Susceptibility of MMP3 gene polymorphism to coronary artery disease: A meta-analysis. Journal of Medical Biochemistry. 2023;42(4):685. https://doi.org/10.5937/jomb0-43315.
13. Mittal B, Mishra A, Srivastava A, Kumar S, Garg N. Matrix metalloproteinases in coronary artery disease. Advances in clinical chemistry. 2014;64:1-72. https://doi.org/10.1016/B978-0-12-800263-6.00001-X.
14. Fletcher EK, Wang Y, Flynn LK, Turner SE, Rade JJ, Kimmelstiel CD, et al. Deficiency of MMP1a (matrix metalloprotease 1a) collagenase suppresses development of atherosclerosis in mice: translational implications for human coronary artery disease. Arteriosclerosis, thrombosis, and vascular biology. 2021;41(5):e265-e79. https://doi.org/10.1161/ATVBAHA.120.315837.
15. Pleskovic A, Letonja MS, Vujkovac AC, Starcevic JN, Caprnda M, Curilla E, et al. Matrix metalloproteinase-3 gene polymorphism (rs3025058) affects markers atherosclerosis in type 2 diabetes mellitus. Vasa. 2017;46(5):363-9. https://doi.org/10.1024/0301-1526/a000637.
16. Fragão-Marques M, Miranda I, Martins D, Barroso I, Mendes C, Pereira-Neves A, et al. Atrial matrix remodeling in atrial fibrillation patients with aortic stenosis. BMC Cardiovascular Disorders. 2020;20:1-13. https://doi.org/10.1186/s12872-020-01754-0.
17. Kuliczkowski W, Radomski M, Gąsior M, Urbaniak J, Kaczmarski J, Mysiak A, et al. MMP-2, MMP-9, and TIMP-4 and Response to Aspirin in Diabetic and Nondiabetic Patients with Stable Coronary Artery Disease: A Pilot Study. BioMed research international. 2017;2017(1):9352015. https://doi.org/10.1155/2017/9352015.
18. Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. Bmj. 2015;351. https://doi.org/10.1136/bmj.h5000.
19. Clarke MW, Burnett JR, Croft KD. Vitamin E in human health and disease. Critical reviews in clinical laboratory sciences. 2008;45(5):417-50. https://doi.org/10.1080/10408360802118625.
20. Navab M, Ananthramaiah G, Reddy ST, Van Lenten BJ, Ansell BJ, Fonarow GC, et al. Thematic review series: the pathogenesis of atherosclerosis the oxidation hypothesis of atherogenesis: the role of oxidized phospholipids and HDL. Journal of lipid research. 2004;45(6):993-1007. https://doi.org/10.1194/jlr.R400001-JLR200.
21. Lee C-H, Chan RS, Wan HY, Woo Y-C, Cheung CY, Fong CH, et al. Dietary intake of anti-oxidant vitamins A, C, and E is inversely associated with adverse cardiovascular outcomes in chinese—A 22-years population-based prospective study. Nutrients. 2018;10(11):1664. https://doi.org/10.3390/nu10111664.
22. de Oliveira Otto MC, Alonso A, Lee D-H, Delclos GL, Bertoni AG, Jiang R, et al. Dietary Intakes of Zinc and Heme Iron from Red Meat, but Not from Other Sources, Are Associated with Greater Risk of Metabolic Syndrome and Cardiovascular Disease3. The Journal of nutrition. 2012;142(3):526-33. https://doi.org/10.3945/jn.111.149781.
23. Wang T, Xu L. Circulating vitamin E levels and risk of coronary artery disease and myocardial infarction: a Mendelian randomization study. Nutrients. 2019;11(9):2153. https://doi.org/10.3390/nu11092153.
24. Goyal A, Terry MB, Siegel AB. Serum antioxidant nutrients, vitamin A, and mortality in US adults. Cancer Epidemiology, Biomarkers & Prevention. 2013;22(12):2202-11. https://doi.org/10.1158/1055-9965.EPI-13-0381.
25. Karppi J, Laukkanen JA, Mäkikallio TH, Kurl S. Low serum lycopene and β-carotene increase risk of acute myocardial infarction in men. The European Journal of Public Health. 2012;22(6):835-40. https://doi.org/10.1093/eurpub/ckr174.
26. Nagao M, Moriyama Y, Yamagishi K, Iso H, Tamakoshi A. Relation of serum α-and γ-tocopherol levels to cardiovascular disease-related mortality among Japanese men and women. Journal of epidemiology. 2012;22(5):402-10. https://doi.org/10.2188/jea.JE20120002.
27. Wright ME, Lawson KA, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, et al. Higher baseline serum concentrations of vitamin E are associated with lower total and cause-specific mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. The American journal of clinical nutrition. 2006;84(5):1200-7. https://doi.org/10.1093/ajcn/84.5.1200.
28. Mezzetti A, Zuliani G, Romano F, Costantini F, Pierdomenico SD, Cuccurullo F, et al. Vitamin E and lipid peroxide plasma levels predict the risk of cardiovascular events in a group of healthy very old people. Journal of the American Geriatrics Society. 2001;49(5):533-7. https://doi.org/10.1046/j.1532-5415.2001.49110.x.
29. Hantke B, Lahmann C, Venzke K, Fischer T, Kocourek A, Jack Windsor L, et al. Influence of flavonoids and vitamins on the MMP-and TIMP-expression of human dermal fibroblasts after UVA irradiation. Photochemical & Photobiological Sciences. 2002;1:826-33. https://doi.org/10.1039/b207731k.
30. Khatami PG, Soleimani A, Sharifi N, Aghadavod E, Asemi Z. The effects of high-dose vitamin E supplementation on biomarkers of kidney injury, inflammation, and oxidative stress in patients with diabetic nephropathy: A randomized, double-blind, placebo-controlled trial. Journal of clinical lipidology. 2016;10(4):922-9. https://doi.org/10.1016/j.jacl.2016.02.021.
31. Heidarnia E, Taghian F, Dehkordi KJ, Moghadasi M. The effect of combined training and consumption of e and C antioxidant supplements on mitochondrial function and biogenesis in the heart tissue of diabetic rats. 30 January 2022, Vol. 21, No. 5, fa323-fa332, en333 ref. 42 ref. https://ijdld.tums.ac.ir/article-1-6093-en.html.
32. Fitzhugh EC, Thompson DL. Leisure-time walking and compliance with ACSM/AHA aerobic-related physical activity recommendations: 1999–2004 NHANES. Journal of Physical Activity and Health. 2009;6(4):393-402. https://doi.org/10.1123/jpah.6.4.393.
33. Mueller K, Hingst J. The athlete's guide to sports supplements: Human Kinetics; 2013.

34. Jourkesh M, Ostojic SM, Azarbayjani M. The effects of vitamin E and vitamin C supplementation on bioenergetics index. Research in sports medicine. 2007;15(4):249-56. https://doi.org/10.1080/15438620701693249.
35. Pourghane P, Hosseini M-A, Mohammadi F, Ahmadi F, Tabari R. Patient's perception of cardiac rehabilitation after coronary artery bypass graft (CABG): A qualitative study. Journal of Mazandaran University of Medical Sciences. 2013;23(106):61-76. http://jmums.mazums.ac.ir/article-1-2196-en.html.
36. Moholdt TT, Amundsen BH, Rustad LA, Wahba A, Løvø KT, Gullikstad LR, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. American heart journal. 2009;158(6):1031-7. https://doi.org/10.1016/j.ahj.2009.10.003.
37. Olfert IM, Howlett RA, Wagner PD, Breen EC. Myocyte vascular endothelial growth factor is required for exercise-induced skeletal muscle angiogenesis. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2010;299(4):R1059-R67. https://doi.org/10.1152/ajpregu.00347.2010.
38. Higgins MR, Izadi A, Kaviani M. Antioxidants and exercise performance: with a focus on vitamin E and C supplementation. International journal of environmental research and public health. 2020;17(22):8452. https://doi.org/10.3390/ijerph17228452.
39. Holvoet P. Obesity, the metabolic syndrome, and oxidized LDL. The American journal of clinical nutrition. 2006;83(6):1438-9. https://doi.org/10.1093/ajcn/83.6.1438.
40. Vo HVT, Nguyen YT, Kim N, Lee HJ. Vitamin A, D, E, and K as matrix metalloproteinase-2/9 regulators that affect expression and enzymatic activity. International journal of molecular sciences. 2023;24(23):17038. https://doi.org/10.3390/ijms242317038.
41. Jaoude J, Koh Y. Matrix metalloproteinases in exercise and obesity. Vascular health and risk management. 2016:287-95. https://doi.org/10.2147/VHRM.S103877.
42. Mirtaheri E, Khabbazi A, Nazemiyeh H, Ebrahimi A-A, Hajalilou M, Shakibay Novin Z, et al. Stachys schtschegleevii tea, matrix metalloproteinase, and disease severity in female rheumatoid arthritis patients: a randomized controlled clinical trial. Clinical Rheumatology. 2022;41(4):1033-44. https://en.irct.ir/trial/11602.
43. Hu Y-C, Huang T-C, Huang L-W, Cheng H-L, Hsieh B-S, Chang K-L. S-Equol Ameliorates Menopausal Osteoarthritis in Rats through Reducing Oxidative Stress and Cartilage Degradation. Nutrients. 2024;16(14):2364. https://doi.org/10.3390/nu16142364.
44. Alblooshi AG. THE EFFECT OF LICOGLIFLOZIN (SGLT1/2 INHIBITOR) ON DIABETES AND CARDIAC COMPLICATIONS. 2022.
45. Lim Y-J, Min H-Y, Jang W-G. Zingerone attenuates pi-induced vascular calcification via AMPK-mediated TIMP4 expression. Journal of Lipid and Atherosclerosis. 2021;10(1):62. https://doi.org/10.12997/jla.2021.10.1.62.
46. Hughes WM, Rodriguez WE, Rosenberger D, Chen J, Sen U, Tyagi N, et al. Role of copper and homocysteine in pressure overload heart failure. Cardiovascular toxicology. 2008;8:137-44. https://doi.org/10.1007/s12012-008-9021-3.
47. Sozen E, Demirel T, Ozer NK. Vitamin E: Regulatory role in the cardiovascular system. Iubmb Life. 2019;71(4):507-15. https://doi.org/10.1002/iub.2020.