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Review Article

Molecular Mechanism of Physical Exercise Enhances Angiogenesis Through Vascular Endothelial Growth Factor Expression: A Systematic Review

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Abstract

Objective: The aim of this study was to examine how exercise affects human VEGF levels through a review of molecular mechanisms. ***Methods***: This study used a systematic review method, where we searched for original articles in Scopus, PubMed, Web of Science, and Science Direct for analysis. Papers on VEGF and physical activity from 2020 to 2025 were searched. Furthermore, the sample included men and women aged 20 to 80 years. After a comprehensive review and observation, ten publications that met the inclusion criteria were analyzed. Ten studies found that exercise substantially increased VEGF expression. ***Results***: This comprehensive study found that regular exercise significantly increased VEGF expression, which promotes angiogenesis. Activation of the HIF-1α pathway, stimulation of tissue hypoxia, and enhancement of signal transduction associated with blood vessel development are key molecular mechanisms involved. ***Conclusions***: These results indicate that exercise has functional benefits and a significant impact on the molecular regulation of new blood vessel production, which aids physiological adaptation in a number of diseases, such as metabolic and cardiovascular disorders. By modifying VEGF expression, exercise is a successful non-pharmacological strategy to improve blood vessel health, according to the study.

Keywords: Angiogenesis; Hypoxia; Physical exercise; Physical fitness.

الآلية الجزيئية للتمارين البدنية تعزز تكوين الأوعية من خلال تعبير عامل نمو بطانة الأوعية الدموية: مراجعة منهجية

الخلاصة

الهدف: دراسة كيفية تأثير التمارين على مستويات VEGF في الإنسان من خلال مراجعة الآليات الجزيئية. **الطرائق**: استخدمت هذه الدراسة طريقة مراجعة منهجية، حيث بحثنا عن مقالات أصلية في Scopus وPubMed وWeb of Science وScience Direct للتحليل. تم البحث في أوراق حول VEGF والنشاط البدني من 2020 إلى 2025. علاوة على ذلك، شملت العينة رجالا ونساء تتراوح أعمارهم بين 20 و80 عاما. بعد مراجعة شاملة وملاحظة، تم تحليل عشرة منشورات استوفت معايير الإدراج. وجدت عشر دراسات أن التمارين الرياضية زادت بشكل كبير من تعبير VEGF. **النتائج**: وجدت هذه الدراسة الشاملة أن التمارين المنتظمة زادت بشكل ملحوظ من تعبير VEGF، مما يعزز تكوين الأوعية. تنشيط مسار HIF-1α، وتحفيز نقص الأكسجين في الأنسجة، وتعزيز نقل الإشارات المرتبطة بتطور الأوعية الدموية هي آليات جزيئية رئيسية متدخلة. **الاستنتاجات**: تشير هذه النتائج إلى أن التمارين لها فوائد وظيفية وتأثير كبير على تنظيم إنتاج الأوعية الدموية الجديدة الجزيئي، مما يساعد على التكيف الفسيولوجي في عدد من الأمراض مثل اضطرابات الأيض وأمراض القلب والأوعية الدموية. من خلال تعديل تعبير VEGF، تعد التمارين استراتيجية غير دوائية ناجحة لتحسين صحة الأوعية الدموية، وفقا للدراسة.

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INTRODUCTION

Globally, a growing public health problem is non-communicable diseases (NCDs). A recent study on the global burden of disease found that chronic non-communicable diseases (NCDs), such as diabetes, hypertension, and cardiovascular disease (CVD), are the leading causes of death globally [1]. In addition to burdening already overburdened health care systems and being the primary cause of early death in many nations, this disease has a significant negative economic impact on nations through decreased productivity and slowed economic growth [2]. The risk of NCDs, which typically start early in life and affect health throughout one's life, is raised by risk factors including smoking, eating poorly, being sedentary, and being overweight or obese [3]. Even in low- and middle-income countries, where health systems are least prepared to recognize and treat these silent killers, the burden of NCDs will increase unless action is taken [4]. Ischemic heart disease remains the most prevalent despite the development of novel treatment options, such as medication and invasive procedures [5]. The initial sign of ischemic heart disease may be myocardial infarction (MI) [6]. It should be noted that ischemic heart disease is commonly described as a condition in which the heart muscle does not receive enough blood flow. This condition is primarily brought on by blood clots or constriction, as well as atherosclerotic plaques that develop on the walls of the coronary arteries [7]. Furthermore, if ischemic heart disease worsens, scar

tissue production, myocardial remodeling, and myocardial hypertrophy can result in MI and ultimately heart failure after MI [8]. Angiogenesis is the process of forming new blood vessels from pre-existing ones. Physiological or pharmacological stimulation of angiogenesis can promote neovascularization and hasten the development of collateral circulation [9]. The process of endothelial migration and proliferation of smooth muscle cells, which is crucial to angiogenesis, involves several components, including VEGF [7]. Hypoxia triggers the angiogenesis process, while elevated shear stress triggers the arteriogenesis process [10]. Among the most researched angiogenic growth factors, VEGF is used to treat ischemic heart disease. Increased vascular permeability, plasminogen activator production, cell survival, migration, and proliferation are all VEGF actions that are linked to angiogenesis [11]. In animal models, it has been demonstrated that VEGF deficiency impairs myocardial angiogenesis, leading to heart failure. 12 Low plasma VEGF levels were linked to a markedly higher risk of further detrimental cardiovascular and cerebrovascular events in MI patients [13]. The association between plasma VEGF levels and long-term prognosis in patients with acute myocardial infarction was investigated using logistic regression analysis. The findings demonstrated that these patients' VEGF levels were significantly low [14]. Consequently, to maximize the rise in VEGF expression, therapeutic measures are required. The best non-pharmacological treatment for enhancing general health is exercise. Due to its many health-promoting advantages and its use as a non-pharmacological treatment strategy to save nerve cells and other organs, physical exercise has attracted a lot of interest in recent decades [15]. The human body produces more free radicals when exercising because it adapts physiologically to physical activity [16]. Exercise will also raise enzymatic antioxidants, including catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD) [17]. Previous research results have indicated that exercise can help improve decreased myocardial VEGF expression in heart dysfunction in patients with diabetes mellitus [18]. However, it is still not known for certain how the underlying mechanism of physical exercise is increasing VEGF expression. Consequently, this systematic review's goal is to investigate in depth how physical exercise influences VEGF expression and what the underlying mechanism is.

METHODS

Studi design

This study employed a systematic review method, where researchers conducted an extensive search of journal databases such as PubMed, Science Direct, Web of Science, and Scopus, spanning 2020–2025. These databases are considered among the world's best for collecting high-impact publications with a strong scientific foundation, ensuring their legitimacy and validity. Using this first-result search approach, duplicate entries were removed. Using pre-defined inclusion and exclusion criteria, the search results were then further refined.

Eligibility criteria

The inclusion criteria for the study were developed by examining publications that discussed VEGF expression and physical activity from 2020 to 2025. Additionally, articles that did not match the criteria for scientific validity or that were not listed in reliable search indexes such as Scopus, Web of Science, PubMed, or Science Direct were not included in our analysis.

Procedure

The full text, abstract, and title of each paper were added to the Mendeley database after initial evaluation and confirmation. In the first phase, 2,102 publications were identified using Scopus, Science Direct, PubMed, and Web of Science. After title compatibility screening, 846 suitable papers advanced to the second screening phase. Following title, abstract, and keyword analysis, 324 papers were selected for the third round. The study had to be unique, the parameter had to be a VEGF biomarker, the intervention had to involve physical activity, and the sample had to be human, according to the inclusion criteria we evaluated after reviewing each publication. At this point, we organized the items based on their overall suitability. Ten papers meeting the inclusion criteria were selected for analysis after a thorough review and scrutiny process. The operational requirements for this study were the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All reviewed articles met ethical standards as per the Helsinki Declaration guidelines (Figure 1).

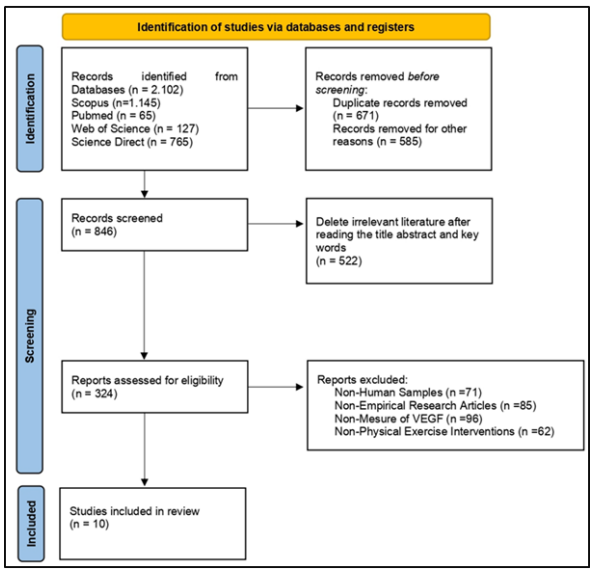

Figure 1: PRISMA flowchart of the article selection process.

RESULTS

Table 1 Summarizes of the design and intervention of the studies selected for synthesis of data presented in this study.

Table 1: Summary of the design and intervention of the studies

Author	Design	Participants	Age (year)	Intervention	Outcome
Ramadhan *et al*. (2025) [19]	Randomized controlled trials	Twenty-two participants	60 – 80	Two intervention groups were formed from the participants. For six weeks, the exercises were done twice a week. The moderate intensity group performed workouts to develop their quadriceps femoris with ankle weights (≥ 40–60% 1RM). Three sets of eight to twelve repetitions were performed in each session, with a two-minute break in between. The BFR group performed low-intensity quadriceps femoris strengthening exercises with ankle weights (20–30% 1RM) in addition to blood flow restriction (BFR). Each session consisted of four sets of exercises, with a 30-second rest period between each set. The first set consisted of 30 repetitions, while sets 2-4 included 15 repetitions.	In the exercise group combined with BFR, there was a significant increase in VEGF expression.
Liu *et al*. (2025) [20]	Randomized controlled trials	15 participants	22	A bicycle ergometer was used to execute high-intensity interval training, which included a 2-minute warm-up at 40% VO2max, an 8-minute high-intensity workout at 80% VO2max, a 7-minute active rest at 40% VO2max, and a 3-minute recovery rest at 40% VO2max. Using a bicycle ergometer, moderate intensity continuous exercise was also carried out. It included a two-minute warm-up at 20% VO2max, thirty minutes of exercise at 60% VO2max, and three minutes of recovery rest at 20% VO2max. Both training procedures produced the same amount of power overall during the training period. For an hour, participants in the rest control (CON) session continued to be inactive.	In both HIIE and MICE groups, there was a significant increase in VEGF expression. The HIIE group had the highest VEGF expression from both the MICE and control groups.
Kim *et al*. (2023) [21]	Randomized controlled trials	Forty-three older women	65-75	The study participants were split up into three groups: control, resistance, and aerobic exercise groups. For 16 weeks, all exercise interventions lasted 60 minutes each day, three times a week. The aerobic exercises included the following: walk, knee-up, low front kick, low back kick, one-step, two-step, side touch, march, turn, change, grapevine step, step-touch (one-step, side-step), open step, lunge, mambo, chachacha, and chassé (two-step, triple-step). Resistance training encompasses the following types of exercises: Thera-band knee exercises include eversion and inversion, leg push, knee extension, knee flexion, ankle dorsiflexion, and ankle plantar flexion. hip: flexion, extension, adduction, and abduction Hyperextension of the back; flexion, extension, abduction, and adduction of the hips in the abdomen; arm exercises: lunge, side bend, stiff-leg dead lift, dumbbell lateral raise, bent-over dumbbell raise, elbow flexion, elbow extension, and dumbbell shrug and internal rotation.	In the resistance exercise group, there was a significant increase in VEGF expression.
Suhr *et al*. (2021) [22]	Randomized controlled trials	Twelve male subjects	23	In a random order, each subject conducted four rigorous cycle tests to individual exhaustion at elevations of 2000, 3000, 4000, and normoxia. The athletes underwent a 10-minute warm-up program with a 70 Watt (W) output and varied pedaling frequencies following the initial venous blood sample. The power was increased by 30 W per minute until each person reached their limit, starting at 100 W.	Following physical activity intervention, VEGF levels at an elevation of 4000 meters above sea level significantly increased.
Huang *et al*. (2025) [23]	Randomized controlled trials	Sixty-three sedentary participants	-	All research participants were split up into four groups: control, RE, MICT, and HIIT. People used a bicycle ergometer to practice HIIT and MICT. The HIIT group warmed up for two minutes at 50% VO2max, worked out for one minute at 90% VO2max, and then actively recovered for one minute at 50% VO2max. This was performed ten times, and a 3-minute cool-down at 50% VO2max marked the end of the workout. After a two-minute warm-up at 20% VO2max, the MICT group cycled for thirty-five minutes at 60% VO2max before cooling down for three minutes at 20% VO2max. To develop their core muscles and upper and lower limbs, the RE group performed six exercises: dumbbell bench press, high pull-down, barbell squat, dumbbell pull-up, stability ball flat support, and V-pass stability ball. Each exercise was performed twelve times at 60% of one's one-repetition maximum (1RM), with a 3-minute and 90-second rest period between sets. Members of the control group continued to engage in their typical sedentary behaviors.	There was an increase in VEGF expression in all physical exercise intervention groups.
Gorna *et al*. (2025) [24]	Randomized controlled trials	44 patients	63-68	Moderate intensity continuous training (MICT) and low intensity continuous training (LICT) were the two groups into which all research participants were split. For three weeks (a total of twelve training sessions), exercise was done four times a week on a bicycle ergometer. Both groups' participants rode a bicycle ergometer for thirty minutes at a target cadence of sixty revolutions per minute (RPM). The exercise intensity matched 50–60% of maximum oxygen uptake (VO2max) for the LICT group and 70–80% of VO2max for the MICT group.	There was an increase in VEGF expressions in the group with MICT intervention.

Sofiatun *et al*. (2025) [25]	Randomized controlled trials	30 settled women participated in this study	18-26	Aerobic exercise consists of walking on a treadmill for 30 minutes at moderate intensity. Weight training consists of 40 minutes of strength training consisting of three sets of ten exercises each, such as triceps pushdown, seated row, shoulder press, chest press, lateral pull-down, abdominal crunch, leg press, leg extension, and sitting bicep curl. Each weight training exercise was performed according to the National Strength and Conditioning Standards. Each exercise involved 8–10 repetitions in 3 sets, with a 5–10 minute rest period between each set.	There was a significant increase in VEGF levels after aerobic physical exercise intervention.
Kim *et al*. (2023) [21]	Randomized controlled trials	43 respondents participated in this study	65-75	All participants in the exercise groups performed their respective exercises for 60 min/day, three days/week, for 16 weeks. The intensity of aerobic and resistance exercises was determined using the individual heart rate reserve (40–60%) and RPE (12–13), respectively.	Aerobic exercise significantly increases VEGF levels.
Volga Fernandes *et al*. (2022) [26]	Randomized controlled trials	Twenty-four males	21	LL (low-load exercise), LL-BFR (low-load exercise with blood-flow restriction), and HL (high-load exercise) were the three participant groups that were created. For the LL-BFR group, the pneumatic cuff was inflated to 80% of the arterial occlusion pressure. Each participant performed bilateral knee extension exercises twice a week for eight weeks. The LL and LL-BFR groups finished three to four sets of fifteen repetitions at 20% 1RM, whereas the HL group finished three to four sets of eight to ten repetitions at 80% 1RM with a 60-second break in between sets.	Both the LL-BFR and HL groups showed an increase in VEGF gene expression, but LL-BFR's effect was noticeably larger than LL's.
Kuhne *et al*. (2021) [27]	Randomized controlled trials	Fifty healthy participants	20–40	Participants were divided into two groups: one for cardiovascular cycling exercise and the other for stretching. The BIKE group used a bicycle ergometer (Taurus Indoor Bike IC50) to perform cardiovascular exercise while following video-based indoor cycling instructions (CyberFitness GmbH2). Participants in the videos exercised for 45 to 55 minutes at their target heart rate, determined by a cardiorespiratory fitness test, after a quick, low-impact warm-up. Toning and Stretching (STRETCH) Training sessions were taught to the STRETCH group using videos selected from an online fitness platform. During training sessions, a variety of low-impact exercises were used. Stretching, relaxation methods, low-impact exercises like push-ups or sit-ups, posture and posture guidelines, and back pain prevention activities were among them.	Following physical activity intervention, VEGF expression significantly increased in the BIKE group.

DISCUSSION

The purpose of this research was to ascertain the impact of physical exercise on increasing VEGF expression. Based on the results of the analysis of 10 reviewed articles, it was shown that all physical exercise can significantly increase VEGF expression. The results of previous studies comparing moderate-intensity exercise and a combination of exercise with blood flow restriction (BFR) carried out 2x a week for 6 weeks proved that exercise with blood flow restriction (BFR) significantly increased VEGF expression [19]. Other research results, specifically comparing moderate intensity continuous exercise (MICE) and high intensity interval exercise (HIIE), demonstrated that both types of exercise increased VEGF expression, but HIIE was found to have significantly higher VEGF expression than MICE and the control group [20]. So, it is proven that vigorous workouts have a real impact on increasing VEGF expression. The findings of earlier research indicated that participants were elderly people aged 65-75 years who compared the aerobic training and resistance training groups on VEGF expression by intervening three times a week for 16 weeks. The results of the study demonstrated that resistance training significantly increased VEGF expression [21]. The results of this study demonstrate that resistance training is highly beneficial for the elderly, as it significantly increases VEGF expression. The following other data compares the type of altitude to the increase in VEGF expression. The study subjects were given a physical exercise intervention at normoxic altitudes of 2,000 m, 3,000 m, and 4,000 m above sea level, and the results of the study proved significant in increasing VEGF expression at an altitude of 4,000 m above sea level [22]. When it occurs at a high altitude, the oxygen condition becomes thinner, which triggers hypoxia. It can be concluded that making the body experience hypoxia triggers a significant increase in VEGF expression based on the results of this study. The data strengthens the evidence that physical exercise, both moderate and high intensity, has been proven to increase VEGF expression [23]. The results of the next study involved elderly people who participated in an intervention that included both low-intensity and moderate-intensity exercise types, conducted four times a week for 3 weeks, resulting in a total of 12 exercise sessions using a 30-minute cycling ergometer per session. The results of the study proved that moderate-intensity exercise significantly increased VEGF expression [24]. Other research results also compared the two types of exercise, namely cardiorespiratory cycling exercise and only stretching and tightening exercises. The results of the study proved that cardiorespiratory exercise through cycling provided a significant increase in VEGF expression [27]. Based on the studies analyzed, various types of physical exercise have been reported to have a positive effect on increasing VEGF expression. Studies consistently show that both moderate- and high-intensity aerobic

exercise increase VEGF levels by enhancing tissue oxygen demand and activating angiogenesis pathways. Furthermore, resistance training has also been reported to increase VEGF expression, primarily through mechanical adaptations in muscle tissue that stimulate angiogenesis. Several studies have also shown that exercise with blood flow restriction (BFR) produces a higher VEGF response than low-intensity exercise without BFR, likely due to greater local hypoxia during exercise. Meanwhile, high-intensity interval training (HIIT) has been reported to produce a higher VEGF response than moderate-intensity continuous exercise in several studies. Overall, these findings suggest that various exercise modalities can increase VEGF expression, although the magnitude of the response is influenced by the characteristics of the exercise and the population studied. This means that exercise can significantly increase VEGF levels.

Physiological Mechanisms of Increasing VEGF Expression

We are all aware that the most effective non-pharmacological therapy for enhancing population health is physical exercise. We are all aware that the most effective non-pharmacological treatment for enhancing public health is physical activity. Exercise, both acute and chronic, has the potential to alleviate obesity, type 2 diabetes, and cardiovascular disease by expressing exerkines [28]. The scientific literature emphasizes how interdisciplinary approaches, including pharmaceutical, dietary, exercise, and psychological treatments, are crucial to the treatment of obesity [29]. Engaging in physical exercise increases skeletal muscle contractions. Exercise causes mechanical and physiological changes in human muscle that allow it to adapt to stress [30]. Exercise causes mechanical and physiological changes that allow human muscles to adapt to stress. Skeletal muscles now serve as signal transducers that act as endocrine organs, secreting transcription factors and cytokines into the bloodstream to regulate the function of other organs in addition to producing force and movement [31]. Furthermore, as the body adapts to physical activity, the contraction of skeletal muscles during exercise will result in an increase in free radical production [16]. This phenomenon is indeed intriguing because the human body was created so extraordinarily in carrying out the process of physiological adaptation. Vasculogenesis and angiogenesis are the two processes that lead to the development and arrangement of blood vessels. While vasculogenesis is the creation of a capillary network because of pluripotent mesenchymal cells maturing into hemangioblasts, angiogenesis is the process by which new blood vessels form from existent ones [32]. Vasculogenesis and angiogenesis are important because they play a homeostatic role in supplying tissues and organs with nutrients and oxygen while also eliminating waste products. Therefore, vascular and angiogenesis are necessary for physiological processes, including embryonic development, growth, hematopoiesis, tissue remodeling, and wound healing, as well as pathological conditions like cancer, inflammation, atherosclerosis, or diabetic retinopathy [33]. These activities are coordinated by contact between different endothelial and non-endothelial cell types, as well as by cell responses to angiogenic or anti-angiogenic stimuli [34]. Since oxygen and nutrients are essential building blocks for tissue anabolic activity, angiogenesis also plays a significant role in the physiology of human tissue repair [35]. Through the PI3K/Akt pathway, exercise-induced hypoxia and mechanical stress primarily trigger the transcription of vascular endothelial growth factor (VEGF), a proangiogenic factor that is crucial for endothelial cell survival and improved capillary germination [36]. Resistance and endurance training raises VEGF expression in the heart, brain, skeletal muscle, and bone, according to several studies. 37 In the skeletal muscle of individuals with peripheral myopathy linked to heart failure, HIIT training increased the expression levels of VEGF and VEGF receptor-2 (VEGFR2) overall. This increased muscle capillarization, and the skeletal muscle genes that were differentially expressed suggested that the PI3K/Akt signaling pathway is activated in response to HIIT [38]. When doing physical exercise, the body is in a condition that requires a lot of oxygen as quickly as possible to meet the needs of energy production. Under these conditions, exercise physiologically increases the expression of HIF-1 alpha [39]. Hypoxia-inducible factor-1 (HIF-1) is a key regulator of the molecular response to low oxygen levels. It controls the expression of target genes that are important for angiogenesis, blood cell growth, energy metabolism, and apoptosis. It also controls a number of physiological and cellular processes that are important for oxygen uptake. 40 Following its translocation into the nucleus, stabilized HIF-1α forms an active HIF-1 complex by dimerizing with HIF-1β (ARNT), a conservative and oxygen-insensitive subunit [41]. This complex starts the transcription of genes involved in adaptive processes by attaching itself to hypoxia-responsive regions in target gene promoters. These target genes promote cellular survival by enhancing stress tolerance and regulating apoptosis, metabolic reprogramming, which includes a switch to glycolytic pathways, and angiogenesis, for instance, by inducing vascular endothelial growth factor (VEGF) [42]. This complex regulatory system is crucial to the body's reaction to oxygen deprivation because it enables cells to adjust to hypoxic environments and preserve homeostasis. Furthermore, PGC-1 alpha expression rises in response to the effects of exercise on molecular responses. Increased biogenesis in mitochondria as a result of this reaction boosts energy output [43]. The VEGFs are a family of heparin-binding proteins that affect the angiogenesis, lymphopoiesis, and lymphangiogenesis processes, as well as how cells respond to inflammation and oxidative stress and control lipid metabolism [44]. Vascular permeability and the growth, differentiation, and survival of endothelial cells are the main functions of the multifunctional protein known as vascular endothelial

growth factor, or VEGF [45]. Regular exercise eventually increases the body's sensitivity to VEGF, which leads to more effective blood vessel creation [46]. Additionally, it helps stop blood vessel function from declining because of aging or leading an unhealthy lifestyle. Exercise-induced VEGF also contributes to blood pressure and heart health maintenance. Exercise of even moderate intensity is sufficient to raise muscle VEGF levels. Consequently, VEGF is one of the key processes in the vascular system's adaptation to exercise. By exercising regularly, you will maintain your body's condition, allowing it to function properly, including through the angiogenesis process, which helps increase the distribution of oxygen to cells for energy production (Figure 2).

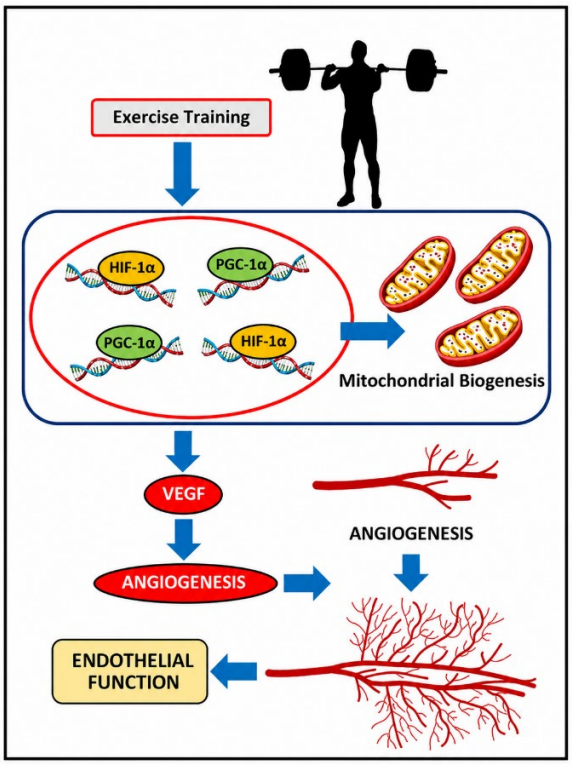

Figure 2: The mechanism by which physical exercise increases VEGF expression.

Strength and Limitations

This systematic review's advantage is that it just examines randomized controlled trials, which eliminate the chance of unclear cause-and-effect linkages and are the most trustworthy form of scientific data. Furthermore, the samples collected are human-focused, exhibit consistent data, and aren't combined with samples from other categories, like animal samples. We are aware of the limitations of researchers in this systematic review; we only focus on conducting an in-depth analysis of how physical exercise affects the increase in VEGF expression. Researchers know that the body's physiological mechanisms are complex, so their discussion of them may seem less in-depth. To examine in depth how the VEGF stages occur during physical exercise, experimental research is needed. In addition, the comparison between high- and low-intensity physical exercise also needs to be studied in depth; therefore, further research is recommended to resolve this issue. Furthermore, the studies included in this review varied in subject characteristics, such as age, health condition, and fitness level, as well as in the type, intensity, frequency, and duration of exercise interventions. This heterogeneity may contribute to the variation in VEGF responses reported across studies. Therefore, one should interpret the results of this review while considering these differences in characteristics across studies.

Conclusion

Based on the studies analyzed in this systematic review, physical exercise is consistently associated with increased VEGF expression, although the magnitude of the response may vary depending on subject characteristics and the type of exercise intervention. Available evidence suggests that increased VEGF plays a role in angiogenesis through the activation of various molecular pathways related to exercise adaptation. These findings support the potential of physical exercise as a non-pharmacological strategy to improve vascular function. However, given the variation in study designs and intervention protocols across the included studies, interpretation of the results should be approached with caution, and further research with more consistent methodology is needed to strengthen the existing evidence.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. Champion KE, Parmenter B, McGowan C, Spring B, Wafford QE, Gardner LA, et al. Effectiveness of school-based eHealth interventions to prevent multiple lifestyle risk behaviours among adolescents: a systematic review and meta-analysis. *Lancet Digit Heal*. 2019;1(5):e206-e221. doi: 10.1016/S2589-7500(19)30088-3.
2. Abdu A, Bakrey H, Hamed M, Idris T. Non-communicable diseases in Eritrea: a review of challenges, risk factors and public health strategies. *Discov Public Health*. 2025;22(1). doi: 10.1186/s12982-025-00449-1.
3. Long KQ, Ngoc-Anh HT, Phuong NH, Tuyet-Hanh TT, Park K, Takeuchi M, et al. Clustering lifestyle risk behaviors among Vietnamese adolescents and roles of school: A Bayesian multilevel analysis of global school-based student health survey 2019. *Lancet Reg Health - West Pac*. 2021;15:100225. doi: 10.1016/j.lanwpc.2021.100225.
4. Biswas T, Townsend N, Huda MM, Maravilla J, Begum T, Pervin S, et al. Prevalence of multiple non-communicable diseases risk factors among adolescents in 140 countries: A

population-based study. *eClinicalMedicine*. 2022;52:101591. doi: 10.1016/j.eclinm.2022.101591.
5. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: A compass for future health. *J Am Coll Cardiol*. 2022;80(25):2361-2371. doi: 10.1016/j.jacc.2022.11.005.
6. Manfroi WC, Peukert C, Berti CB, Noer C, Gutierres D de A, Silva FT. Acute myocardial infarction: the first manifestation of ischemic heart disease and relation to risk factors. *Arq Bras Cardiol*. 2002;78(4):392-395. doi: 10.1590/S0066-782X2002000400006,
7. Florek K, Mendyka D, Gomułka K. Vascular endothelial growth factor (VEGF) and its role in the cardiovascular system. *Biomedicines*. 2024;12(5):1-15. doi: 10.3390/biomedicines12051055.
8. Swaroop G. Post-myocardial infarction heart failure: A review on management of drug therapies. *Cureus*. 2022;14(6):14-19. doi: 10.7759/cureus.25745.
9. Weckbach LT, Preissner KT, Deindl E. The role of midkine in arteriogenesis, involving mechanosensing, endothelial cell proliferation, and vasodilation. *Int J Mol Sci*. 2018;19(9). doi: 10.3390/ijms19092559.
10. Wang J, Song Y, Xie W, Zhao J, Wang Y, Yu W. Therapeutic angiogenesis based on injectable hydrogel for protein delivery in ischemic heart disease. *iScience*. 2023;26(5):106577. doi: 10.1016/j.isci.2023.106577.
11. Uemura A, Fruttiger M, D'Amore PA, De Falco S, Joussen AM, Sennlaub F, et al. VEGFR1 signaling in retinal angiogenesis and microinflammation. *Prog Retin Eye Res*. 2021;84:100954. doi: 10.1016/j.preteyeres.2021.100954.
12. Braile M, Marcella S, Cristinziano L, Galdiero MR, Modestino L, Ferrara A, et al. VEGF-A in cardiomyocytes and heart diseases. *Int J Mol Sci*. 2020;21(15):1-18. doi: 10.3390/ijms21155294.
13. Lai JYM, Riley DR, Anson M, Henney A, Cuthbertson DJ, Hernadez G, et al. Cardiovascular outcomes with intravitreal anti-vascular endothelial growth factor therapy in patients with diabetes: A real-world data analysis. *Diabetes Ther.* 2024;15(4):833-842. doi: 10.1007/s13300-024-01544-3.
14. Niu J, Han X, Qi H, Yin J, Zhang Z, Zhang Z. Correlation between vascular endothelial growth factor and long-term prognosis in patients with acute myocardial infarction. *Exp Ther Med*. 2016;12(1):475-479. doi: 10.3892/etm.2016.3286.
15. Wibawa JC, Setiawan A, Pratiwi DJ, Yunitasari I, Puspitaningsih F, Dzikryet LF, al. Increased activity of the catalase enzyme after physical exercise as a signal for reducing hydrogen peroxide (H_2O_2): a systematic review. *Fizjoterapia Pol*. 2024;2024(5):232-238. doi: 10.56984/8ZG020C7GDL.
16. Ayubi N, Wibawa JC, Callixte C. The mechanism of physical exercise increases heat shock protein 70 (HSP70): A systemic review. *Medicni Perspekt*. 2024;29(4):14-22. doi: 10.26641/2307-0404.2024.4.319168.
17. Wibawa JC, Febrianto N, Fudin MS, Ockta Y, Festiawan R. The mechanism of physical exercise increasing glutathione peroxidase as an endogenous antioxidant: a systematic review. *Retos*. 2025;63:610-619. doi: 10.47197/retos.v63.108856.
18. Muhammed Al-Jarraha, Nour Erekatb AAK. Upregulation of vascular endothelial growth factor expression in the kidney could be reversed following treadmill exercise training in type I diabetic rats. *World J Nephrol Urol*. 2014;3(1):25-29. doi: 10.14740/wjnu153e.
19. Ramadhan NA, Tinduh D, Nugraheni N, Subadi I, Narasinta I, Melaniani S. Vascular endothelial growth factor levels: moderate versus low-intensity flow-restricted exercise. *Retos*. 2025;2025:254-262. doi: 10.47197/retos.v64.110307
20. Liu Z, Huang J, Hu M, Cui X, Leng L, Wang K, et al. Acute high-intensity interval exercise is superior to moderate-intensity continuous exercise in enhancing endothelial function and its associated biomarkers in sedentary young individuals: the possible involvement of lactate. *J Exerc Sci Fit*. 2025;23(1):60-68. doi: 10.1016/j.jesf.2024.12.006.
21. Kim HB, Seo MW, Jung HC. Effects of aerobic vs. resistance exercise on vascular function and vascular endothelial growth factor in older women. *Healthc*are. 2023;11(18):1-9. doi: 10.3390/healthcare11182479.
22. Suhr F, Knuth S, Achtzehn S, Mester J, De Marees M. Acute exhaustive exercise under normoxic and normobaric hypoxic conditions differentially regulates angiogenic biomarkers in humans. *Medicine*. 2021;57(7). doi: 10.3390/medicina57070727.
23. Huang J, Leng LU, Hu M, Cui X, Yan XU, Liu Z, et al. Comparative effects of different exercise types on cardiovascular health and executive function in sedentary young individuals. *Med Sci Sports Exerc*. 2025;0:1110-1122. doi: 10.1249/MSS.0000000000003645.
24. Górna S, Podgórski T, Kleka P, Domaszewska K. Effects of different intensities of endurance training on neurotrophin levels and functional and cognitive outcomes in post-ischaemic stroke adults: A randomised clinical trial. *Int J Mol Sci*. 2025;26(6):1-20. doi: 10.3390/ijms26062810.
25. Sofiatun, Putra DP, Rossa M, Meilani E, Dewi AK, Prayitno DA, et al. Acute effects of resistance and aerobic exercise on HIF-1α erythropoietin, and VEGF levels in women with a sedentary lifestyle: A randomized controlled trial. *J Sport Heal Res*. 2025;17(Supl 2):117-140.
26. Volga Fernandes R, Tricoli V, Garcia Soares A, Haruka Miyabara E, Saldanha Aoki M, Laurentino G. Low-load resistance exercise with blood flow restriction increases hypoxia-induced angiogenic genes expression. *J Hum Kinet*. 2022;84(1):82-91. doi: 10.2478/hukin-2022-0101.
27. Kuhne LA, Ksiezarczyk AM, Braumann KM, Reer R, Jacobs T, Röder B, et al. The effects of acute cardiovascular exercise on memory and its associations with exercise-induced increases in neurotrophic factors. *Front Aging Neurosci*. 2021;13:1-17. doi: 10.3389/fnagi.2021.750401.
28. dos Santos LL, de Castro JBP, Linhares DG, dos Santos AOB, Cordeiro LS, Borba-Pinheiro CJ,et al. Effects of physical exercise on hepatic biomarkers in adult individuals: A systematic review and meta-analysis. *Retos*. 2023;49:762-774. doi: 10.47197/retos.V49.98939.
29. de Sousa TR, da Silva Alexandrino WG, Souza A, Faúndez-Casanova C, Pascoini MJS, Awada MAM, et al. Effects of physical activity in adults with severe obesity: a systematic review. *Retos*. 2024;53(424):671-680. doi: 10.47197/retos.V53.102511.
30. Marinho DA, Ferraz R, Toubekis AG, Neiva HP. Editorial: Musculoskeletal adaptations to training and sports performance: Connecting theory and practice. *Front Physiol*. 2022;13:866895. doi: 10.3389/fphys.2022.866895.
31. Vargas-Ortiz K, Pérez-Vázquez V, Macías-Cervantes MH. Exercise and sirtuins: A way to mitochondrial health in skeletal muscle. *Int J Mol Sci*. 2019;20(11):1-11. doi: 10.3390/ijms20112717.
32. Venkatakrishnan G, Parvathi VD. Decoding the mechanism of vascular morphogenesis to explore future prospects in targeted tumor therapy. *Med Oncol*. 2022;39(11):1-14. doi: 10.1007/s12032-022-01810-z.
33. Ribatti D, Pezzella F. Overview on the different patterns of tumor vascularization. *Cells*. 2021;10(3):1-13. doi: 10.3390/cells10030639.
34. Lorenc P, Sikorska A, Molenda S, Guzniczak N, Dams-Kozlowska H, Florczak A. Physiological and tumor-associated angiogenesis: Key factors and therapy targeting VEGF/VEGFR pathway. *Biomed Pharmacother*. 2024;180:117585. doi: 10.1016/j.biopha.2024.117585.
35. Zhang J, Muri J, Fitzgerald G, Gorski T, Gianni-Barrera R, Masschelein E, et al. Endothelial lactate controls muscle regeneration from ischemia by inducing M2-like macrophage polarization. *Cell Metab*. 2020;31(6):1136-1153.e7. doi: 10.1016/j.cmet.2020.05.004.
36. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, et al. Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol*. 2018;59(2):455-467. PMID: 30173249.
37. Wazzani R, Pallu S, Bourzac C, Ahmaïdi S, Portier H, Jaffré C. Physical activity and bone vascularization: A way to explore in bone repair context? *Life*. 2021;11(8):1-12. doi: 10.3390/life11080783.
38. Tryfonos A, Tzanis G, Pitsolis T, Karatzanos E, Koutsilieris M, Nanas S, et al. Exercise training enhances angiogenesis-related gene responses in skeletal muscle of patients with chronic heart failure. *Cells*. 2021;10(8). doi: 10.3390/cells10081915.
39. Niazi S, Tayebi SM, Costa PB, Mirdar S, Hamidian G. Effects of six weeks of high-intensity interval training on HIF-1α protein expression in lung tissues and apoptosis of pulmonary system in male Wistar rats. *Ann Appl Sport Sci*. 2023;11(1):1-7. doi: 10.52547/aassjournal.1203.

40. Pullamsetti SS, Mamazhakypov A, Weissmann N, Seeger W, Savai R. Hypoxia-inducible factor signaling in pulmonary hypertension. *J Clin Invest*. 2020;130(11):5638-5651. doi: 10.1172/JCI137558.
41. Pan J, Zhang L, Li D, Li Y, Lu M, Hu Y, et al. Hypoxia-inducible factor-1: Regulatory mechanisms and drug therapy in myocardial infarction. *Eur J Pharmacol*. 2024;963:176277. doi: 10.1016/j.ejphar.2023.176277.
42. Albadari N, Deng S, Li W. The transcriptional factors HIF-1 and HIF-2 and their novel inhibitors in cancer therapy. *Expert Opin Drug Discov*. 2019;14(7):667-682. doi: 10.1080/17460441.2019.1613370.
43. Mozaffaritabar S, Koltai E, Zhou L, Bori Z, Kolonics A, Kujach S, et al. PGC-1α activation boosts exercise-dependent cellular response in the skeletal muscle. *J Physiol Biochem*. 2024;80(2):329-335. doi: 10.1007/s13105-024-01006-1.
44. Dabravolski SA, Khotina VA, Omelchenko AV, Kalmykov VA, Orekhov AN. The role of the VEGF family in atherosclerosis development and its potential as treatment targets. *Int J Mol Sci*. 2022;23(2). doi: 10.3390/ijms23020931.
45. Apte RS, Chen DS, Ferrara N. VEGF in signaling and sisease: Beyond discovery and development. *Cell*. 2019;176(6):1248-1264. doi: 10.1016/j.cell.2019.01.021.
46. Ross M, Kargl CK, Ferguson R, Gavin TP, Hellsten Y. Exercise-induced skeletal muscle angiogenesis: impact of age, sex, angiocrines and cellular mediators. Eur J Appl Physiol. 2023;123(7):1415-1432. doi: 10.1007/s00421-022-05128-6.