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THE EFFECT OF PHYSICAL EXERCISE IN INCREASING HYPOXIA-INDUCIBLE FACTOR-1 ALPHA: A SYSTEMATIC REVIEW

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Abstract. The effect of physical exercise in increasing hypoxia-inducible factor-1 alpha: a systematic review. Yulfadinata A., Ayubi N., Wibawa J.C., Rizki A.Z., Afandi A., Jr P.B.D. *The human body during physical exercise triggers various molecular reactions, one of which is the activation of hypoxia-inducible factor-1 alpha (HIF-1α), a transcription factor that plays a role in cellular responses to hypoxic conditions. Hypoxia is a condition in which the body experiences a lack of oxygen. Although it is known that physical exercise can increase HIF-1α expression, until now there is still inconsistency in the results of studies related to the impact of physical exercise on HIF-1α expression.In addition, the underlying mechanism of increased HIF-1α during physical exercise is not fully understood. The lack of a deep understanding of the causal relationship between physical exercise and HIF-1α expression is a challenge in efforts to unravel the underlying mechanisms. Therefore, more systematic studies are needed to evaluate the specific effects of physical exercise on HIF-1α regulation and its impact on physiological adaptation. The aim of this study was to investigate and measure the mechanism of physical exercise on increasing the expression of hypoxia-inducible factor 1-alpha (HIF-1α). Several journal databases, including Embase, Pubmed, Web of Science, and Scopus, were searched for this study. The study considered several criteria, including studies published in the last five years and those related to erythropoietin, physical activity, and HIF-1α. The only papers excluded from inclusion in this analysis were those published in non-reputable journals.Using databases from Embase, Web of Science, Pubmed, and Scopus, a total of 1578 publications were identified. Ten carefully screened and peer-reviewed papers addressed what is needed for this systemic change. The current standard operating procedure for investigations was established using Systematic and Meta-Analysis Preferred Reporting Items (PRISMA). The results of this systemic analysis show that physical exercise has been shown to increase HIF-1α expression. Increased HIF-1α causes the hormone erythropoietin to be secreted and an increase in erythrocytes count which then affects hemoglobin and VO_2max and ultimately increases the athlete's physical performance.*

Реферат. Вплив фізичних вправ на збільшення індукованого гіпоксією фактора-1 альфа: систематичний огляд. Юлфадіната А., Аюбі Н., Вібава Дж.К., Різкі А.З., Афанді А., Дж П.Б.Д. *Під час фізичних вправ в організмі людини відбуваються різні молекулярні реакції, однією з яких є активація індукованого гіпоксією фактора-1 альфа (HIF-1α), транскрипційного фактора, який відіграє роль у клітинних реакціях на гіпоксичні умови. Гіпоксія – це стан, при якому організм відчуває нестачу кисню. Хоча відомо, що фізичні вправи можуть збільшити експресію HIF-1α, досі існує суперечливість у результатах досліджень, пов'язаних з впливом фізичних вправ на експресію HIF-1α. Крім того, основний механізм підвищення HIF-1α під час фізичних вправ до кінця не*

вивчений. Відсутність глибокого розуміння причинно-наслідкового зв'язку між фізичними вправами та експресією HIF-1α є перешкодою для спроб щодо розкриття основних механізмів. Тому необхідні більш систематичні дослідження для оцінювання специфічного впливу фізичних вправ на регуляцію HIF-1α та її вплив на фізіологічну адаптацію. Метою цього дослідження було дослідити та виміряти механізм впливу фізичних вправ на збільшення експресії індукованого гіпоксією фактора-1 альфа (HIF-1α). Для цього дослідження було проведено пошук у кількох базах даних журналів, включаючи Embase, Pubmed, Web of Science та Scopus. У дослідженні враховувалися кілька критеріїв, зокрема дослідження, опубліковані за останні п'ять років, та ті, що стосуються еритропоетину, фізичної активності та HIF-1α. Статтями, виключеними з цього аналізу, були ті, що опубліковані в неавторитетних журналах. Використовуючи бази даних Embase, Web of Science, Pubmed та Scopus, було виявлено загалом 1578 публікацій. Десять ретельно відібраних та рецензованих статей присвячені необхідним для цього системного дослідження питанням. Поточна стандартна операційна процедура для досліджень була розроблена з використанням переважних звітних елементів систематичного та метааналізу (PRISMA). Результати цього системного аналізу показують, що фізичні вправи, як було показано, збільшують експресію HIF-1α. Підвищення рівня HIF-1α приводить до секреції гормону еритропоетину та збільшення кількості еритроцитів, що впливає на гемоглобін та VO_2max, що зрештою підвищує фізичну працездатність спортсмена.

The body goes through a phase of hypoxia, or reduced oxygen levels when exercising, which has a variety of effects on cells, including alterations to mitochondrial biogenesis and angiogenesis both during and after exercise [1]. Another novel therapy approach to improve general health in overweight and obese people is the combination of physical exercise with exposure to hypoxia [2]. Exercise on a regular basis has been shown to benefit human health [3]. Factor that induces hypoxia in transcription of 100 different enzymes and proteins involved in physiological responses to hypoxia are transcriptionally regulated by HIF-1α [4]. Living above sea level causes people to have greater heart rates, increased peripheral oxygen saturation, lower pulmonary hypertension, and a decreased ventilatory response to hypoxia [5].

Regular exercise, regardless of the kind, reduces inflammation in both healthy people and those with metabolic diseases [6]. Furthermore, it has been suggested that hypoxic exercise training is a useful method for enhancing body composition, insulin sensitivity, and other functions linked to better health [7]. Hypoxia inducible factor (HIF) is a heterodimeric protein consisting of an oxygen-sensitive α subunit (HIF-1α, HIF-2α, and HIF-3α) and a constitutively generated β component[8].HIF-1α, one of the three HIFα homologs found in higher metazoans, controls glycolysis in response to hypoxia [8]. In 1992, HIF-1α was identified as a transcription factor for the human erythropoietin (EPO) protein gene [9]. Vascular endothelial growth factor (VEGF) is the most potent endothelial mitogen, and over two percent of human genes are now involved either directly or indirectly in the manufacture of HIF-1α in arterial endothelial cells [9].

Transcription factor HIF-1α is a key player in the hypoxia response, controlling target gene expression linked to angiogenesis, erythropoiesis, energy metabolism, and cell survival [10]. Low oxygen availability prevents mitochondrial respiration and ATP synthesis, which results in a lack of energy [11]. Therefore, in order to adapt to low oxygen levels and to shield themselves from related risks, cells, tissues, and organisms need efficient systems [12]. A single exercise session causes a rise in HIF-1α protein levels in skeletal muscle, and PGC-1α's effects on HIF-1α may extend HIF-1α activity, enabling a persistent adaptive response to exercise [10]. Hypoxia-inducible factors (HIF), transcription factors, chemosensors, and signaling molecules all play a role in the regulation of gene expression and the activity of their enzymatic products [12].

Conversely, toxic byproducts of oxygen consumption impair tissue and cellular function and are implicated in the etiology of several illnesses as well as the natural aging process [13].Because mitochondria need oxygen, they are also important producers of harmful byproducts, especially reactive oxygen species (ROS) within the mitochondria [13]. This happens in both physiological and normoxic settings, but it gets worse in some pathological situations and/or hypoxia because of biological compartment-specific hypoxia, hypoxia "caused by critical functions," or decreased oxygen delivery because of decreased oxygen availability in the surrounding environment [14]. Effective mechanisms are therefore needed by cells, tissues, and organisms to enable adaptation in situations where oxygen is in short supply and to offer defense against related risks.

Nontranscriptional mechanisms, such as cardiorespiratory reactions for the control of gene expression and enzyme activity, are used in this tactic [15]. Numerous activities alter mitochondrial function, and they also have the reverse consequence of regulating mitochondrial HIF. Comprehending the regulation of mitochondrial HIF interactions in both health and sickness is crucial for mitigating risks and optimizing hypoxia-based therapies for use in clinical settings or boosting performance, as adaptation to hypoxia may induce resistance or pathological changes [16]. There is

growing evidence that physical activity improves overall health outcomes, such as immune system function, general metabolism, cardiovascular fitness, and the avoidance of chronic illnesses including cancer and cardiovascular disease [17]. We still don't fully understand how the integrative response to exercise is linked to health advantages, despite the identification of several signaling pathways as part of this response[17]. And there is still much confusion about how exercise responds to HIF-1α expression. Thus, the physiological process of physical activity that increases the expression of hypoxia-induced factor-1α (HIF-1α) will be discussed in this comprehensive investigation. Therefore, the purpose of this systematic observation is to discuss and examine in depth how physical exercise affects and how its mechanism increases the gene expression of HIF-1α.

MATERIALS AND METHODS OF RESEARCH

This study uses a systematic literature review method. As part of the systematic review process, this study examines many journal databases, such as Pubmed, Embase, Web of Science, and Scopus [18].

Research on hypoxia-inducible factor-1 alpha (HIF-1α), exercise, and erythropoietin were published from 2019-2024 that met the inclusion criteria for this study. Among the papers excluded from this study were those published in non-reputable journals and not published in predetermined databases according to the inclusion criteria.

Verified and approved, complete texts, abstracts, and article titles were added to the Mendeley database. In the first phase, 1578 publications were found using the databases Embase, Web of Science, Pubmed, Scopus, and Web of Science. 485 items were assessed in the second stage according on how well the abstract and title complied with the guidelines. The verification of 45 articles for additional processing constituted the third phase. We now filter according on whether the topic is appropriate throughout. Ten publications that satisfied the inclusion criteria were chosen in the end and carefully examined for this systematic review. For this systematic review, ten papers in total that met the inclusion criteria were selected and thoroughly scrutinized. The evaluation of standard operating procedures according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is supported by this study. Figure 1. PRISMA flow chart of the article selection process.

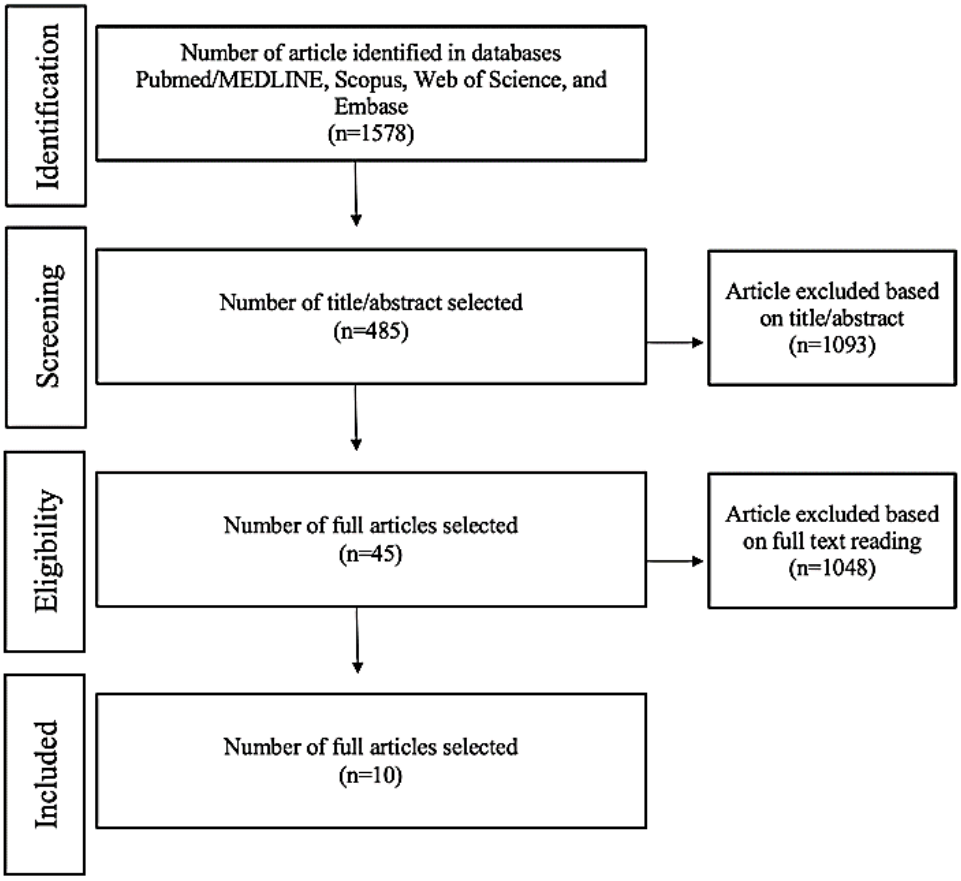

Fig. 1. PRISMA flow chart of the article selection process

RESULTS AND DISCUSSION

Results of the effect of physical exercise in increasing hypoxia-inducible factor-1α

Author	SampleCharacteristics	Study Design	Intervention	Results
(Song et al., 2020) [19]	Fifty male rats were used in this investigation and divided into five groups: MIE treated with 2-methoxyestradiol (2ME2; MIE + 2ME2, n = 9), MIE treated with PBS (MIE + PBS, n = 9), the myocardial infarction group (n = 9), the MI-with-ET group (n = 9), and the sham-operated group (n = 8). The rats in each group were given the same care	Experimental	For four weeks, doing 60 minutes of treadmill exercise five days a week	The Myocardial Infarction + Exercise group shoved the greatest rise in HIF-1α expression
(Baygutalp et al., 2021) [20]	In this study, 23 athletes who reside at an elevation of 1850 meters and have an average age of 21 years were included	Experimental	The study sample engaged in four training sessions: session 1, which involved rest; session 2, which involved exercising for thirty minutes at 50% VO2max; session 3, which involved exercising for seventy-five minutes at 75% VO2max; and session 4, which involved exercising at 100% VO2max until tiredness	At 75% VO_2 Max, the greatest rise in HIF-1α was seen during exercise
(Soori et al., 2020) [10]	Eight male top runners took part in the research	Experimental	The athletes train for four weeks at altitude (TH+2500m) and subsequently for four weeks as residents in normoxia circumstances (LL+1200m). After that, they trained under normoxia circumstances (LL+1200m) for four weeks. Following that, they trained at see level (TH+0) for three weeks. The program consists of interval, plyometric, endurance, speed, and strength training with different volume and intensity levels. Over four weeks at altitude and three weeks at sea level, the runners completed sixteen training sessions each week (two or three sessions per day at 06.00, 10.00, and 16.00)	Throughout post-TL, HIF-1α expression increased
(Tian et al., 2020) [21]	Four groups were formed out of the 140 jantan, namely the palsu type of liar (WT-sham), the ET type of liar (WT-ET), the ET type of liar (WT-ET), and the ET type of liar (WT-ET). In the first group, we have the type group TAC (WT-TAC) and the group latihan TAC + type liar (WT-TAC + E). In the second group, we have three groups: the group knockout sham	Experimental	For eight weeks, mice undertook a moderate intensity exercise training routine (about 60% of their maximum aerobic speed) on a treadmill. The training program was set up for 30 minutes a day at a speed of 11 m/min during the first two weeks of the program, with a 0% rate. Each day, the intensity and length were raised to achieve 60	The ET exercise training group showed an increase in HIF-1α expression

Author	SampleCharacteristics	Study Design	Intervention	Results
	HSF1 (HSF1KO-sham), the group knockout TAC HSF1 (HSF1KO-TAC), and the group latihan KO HSF1 TAC + (HSF1KO-TAC + ET)		minutes of training at a speed of 13 m/min, a 0% rate. Each training phase consists of five days of moderately intense additional training. In order to avoid the acute effects of exercise, all post-exercise sessions were held two days following the previous exercise session. Over the training period, the mice in the other four groups did not move	
(D. Wu et al., 2020) [22]	Ten female mice took part in the investigation	Experimental	Mice were put in aquariums with 15-20 cm of warm, sterile water in them. Three forms of exercises were utilized: (1) Heavy Intensity Exercise (HE): rats swam for 1.5 hours with a load equal to 5% of their body weight attached; (2) Moderate Exercise (ME, SWIM): rats swam for 30 minutes willingly; and (3) Prolonged Exercise (LE): mice swim voluntarily for three hours or until exhausted. When the mice took five seconds to get to the top of the water to breathe, it was decided that they were exhausted. Rats that were sedentary (SED) served as the controls (CON)	HIF-1α was upregulated in mice that received exercise training
(Tryfonos et al., 2021)[23]	Thirteen male patients with chronic heart failure (age: 51 ± 13 years; BMI: 27 ± 4 kg/m2) were randomly assigned to receive one of two 3-month exercise programs: HIIT (N = 6) or COM (N=7)	Experimental	Every participant received three months of weekly sessions of athletic instruction. Before engaging in 14 minutes of strength training, patients in the COM group exercised for 3 minutes at 50%VO_2peak + 2× (4 minutes at 80%VO_2peak + 3 minutes at 50%VO_2peak) and the HIIT group's patients exercised for 3 minutes at 50%VO_2peak + 4× (4 minutes at 80%VO_2peak + 3 minutes at 50%VO_2peak). Leg curls and leg extensions were the two exercises used in strength training, and each limb was worked independently for two to four sets of 10 to 12 repetitions with a 30-second break in between at 60 to 70% of 1-RM	Following training, there was an increase in HIF-1α expression
(Torabimehr et al., 2019) [9]	The study involved the selection of 48 female rats, divided into six groups of eight rats each: (1) cadmium; (2) endurance training; (3) endurance training combined with cadmium consumption;	Experimental	For three weeks, five sessions a week of resistance training were conducted by groups 2, 3, 4, and 5. Furthermore, drinking water containing 400 mg of dissolved cadmium chloride	HIF-1α expression was higher in the resistance training + cadmium group

Author	SampleCharacteristics	Study Design	Intervention	Results
	(4) endurance training; (5) endurance training combined with cadmium consumption; and (6) restraint/control		per liter was given to groups 1, 3, and 5. Resistance training lasted 30 minutes on the first day, and 60 minutes on the third week after a progressive increase in training time. Additionally, by increasing speed to 20 m/min in the first week and 30 m/min in the last week, excessive training loads that increase training volume are controlled. Furthermore, during three weeks, five times a week, groups 2 and 3 engaged in resistance training with a load of 30 to 50% body weight	
(Płoszczyca et al., 2022) [24]	Twenty-four men cyclists with training were split into two groups, G1 and G2	Experimental	To ascertain VO_2max and lactate threshold (LT) values, subjects underwent an incremental exercise test in a normobaric hypoxic environment (FiO2 = 16%; about 2500 m). Further tests were conducted in a normobaric hypoxia chamber (AirZone 25, Air Sport, Warsaw, Poland) and with an Excalibur Sport cycle ergometer (Lode, Groningen, The Netherlands). To improve the investigation's dependability, a number of atmospheric parameters were maintained throughout the test series, including temperature (19 ◦C), humidity (50%), carbon dioxide (700–800 ppm), and oxygen (FiO2 = 16%) concentrations. To measure the levels of HIF-1α after exercise, venous blood was drawn once again after the test	Exercise was followed by an increase in HIF-1α expression
(Kamada et al., 2023) [25]	Male eight-week-old rats were split into three groups at random (N = 6 per group): the hypoxic sedentary group (Hypo-no), the normoxia sedentary group (Normo-no), and the hypoxic treadmill running group (Hypo-ex)	Experimental	From day 28 to day 42, only the Hypo Exercise group was required to run on a treadmill for five times a week, twelve meters per minute, and thirty minutes each day. To examine the short-term effects of treadmill running in a hypoxic environment, CIA rats were split into three groups and given a single treadmill workout on day 2. Day 44: last workout on the treadmill	The Hypo Exercise group had elevated levels of HIF-1α expression
(Volga Fernandes et al., 2022) [26]	Three groups of twenty-four men were assigned to different activities: high-load exercise (HL), low-load exercise (LL), and low-load	Experimental	For the LL-BFR group, the pneumatic cuff was inflated to 80% of the arterial occlusion pressure. Every participant performed bilateral knee extension	The LL-BFR group had a considerable rise in HIF-1α levels

Author	SampleCharacteristics	Study Design	Intervention	Results
	exercise with blood flow restriction (LL-BFR)		exercises twice a week for eight weeks. The LL and LL-BFR groups performed three to four sets of fifteen repetitions at 20% 1RM, whereas the HL group performed three to four sets of eight to ten repetitions at 80% 1RM with a 60-second rest interval in between sets	

The aim of this study was to determine the mechanism of HIF-1α increase during physical exercise. We know that physical exercise increases the occurrence of oxidative stress as a physiological response to exercise [27]. When mice had daily treadmill exercise for 60 minutes, five times a week for four weeks, their levels of HIF-1α increased [19]. Four training sessions were conducted with the research sample, according to another research result. The first session consisted of rest; the second included thirty minutes of exercise at 50% VO_2max; the third included seventy-five minutes of exercise at 75% VO_2max; and the fourth session involved training at 100% VO_2max until fatigue. The findings of the study demonstrate that HIF-1α is most expressed at 75% VO_2max [20]. HIF-1α levels increased in runners who trained for four weeks at altitude and three weeks at sea level, according to another study finding. Every week, the runners trained for sixteen hours (two or three sessions each day at 06.00, 10.00, and 16.00) [10]. Strength training, in particular, has been found to be beneficial for enhancing insulin sensitivity, heart health, bone density, muscle mass, and metabolic health [28]. Exercise causes the body to go into a hypoxic phase, which triggers the activation of hypoxia-induced factor (HIF-1), a transcription factor that controls metabolism and helps the body adjust to hypoxic conditions [29].

Other research' findings indicated that mice receiving regular physical exercise intervention for eight weeks at a moderate intensity (about 60% of their maximal aerobic speed) on a treadmill had an increase in HIF-1α expression [21]. HIF-1α levels were found to be increased in mice used in another study that trained them to swim at a moderate intensity and kept them in an aquarium with 15-20 cm of sterile warm water [22]. After receiving strength training and HIIT therapies, males showed an increase in HIF-1α expression [23]. Research result Płoszczyca et al., 2022. Increased expression of HIF-1α was also seen in twenty-four male cyclists who trained under normobaric hypoxic conditions and used ergometers. It has been demonstrated that physical exercise, when used as a therapeutic intervention, increases young people's attentiveness and produces higher stimulation of cerebral metabolism [30]. SpO_2 saturation can range from 90% to 94%, which can exacerbate and cause hypoxia when engaging in daily physical activity like walking, taking a shower, or using the restroom [31]. Hematological adaptation to prolonged hypoxia and ventilation are important factors in this response. The increased production of erythropoietin (Epo) by the kidneys causes an increase in red blood cells and hemoglobin (Hb) content, which is known as the hematological response [32]. Below we present the molecular mechanism of physical exercise increasing HIF-1α gene expression as shown in Figure 2 below.

Thus, sports medicine was the first to identify intermittent hypoxic training (IHT) as a potentially helpful tactic for enhancing athletes' exercise performance. It enhances IHT's physical performance and has preclinical protective effects as well[33]. According to other research, exercising under hypobaric or normobaric hypoxia increases the vasodilatory response in lung tissue, which can help avoid pulmonary arterial hypertension brought on by hypoxia [32]. In a recent research, Semenza et al. disclosed the molecular mechanisms underlying the "discovery of how cells sense and adapt to changes in oxygen". Furthermore, they were awarded the 2019 Nobel Prize in Physiology or Medicine for their contributions to a better understanding of how oxygen levels affect cell metabolism and physiological function [34]. Additionally, it has been demonstrated that pertinent studies on molecular pathways have an impact on the management of a number of human illnesses, such as cancer and anemia [34]. In this regard, during the hypoxia induction of hepatocellular carcinoma (HCC) cell lines, Semenza et a1. identified HIF-1, a transcription factor associated with the regulation of cellular adaptation to ambient hypoxia. HIFs are a family of transcription factors that are critical for regulating how cells respond to hypoxic stress [35]. Of these, it is now known that three HIFs HIF-1, HIF-2, and HIF-3 are the most significant proteins active in hypoxia [36].

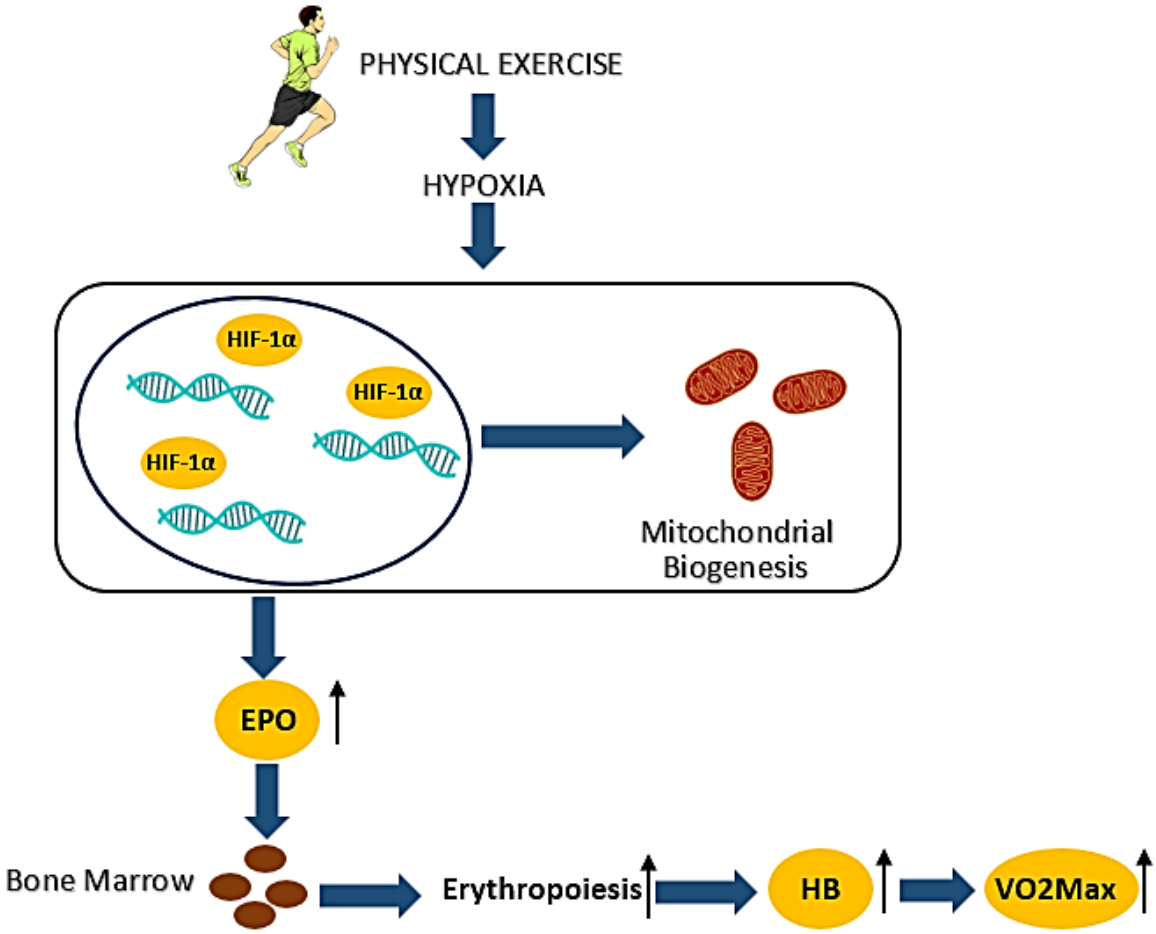

Fig. 2. Mechanisms of Physical Exercise in Increasing Hypoxia-Inducible Factor-1 Alpha

The HPA axis and the sympathetic nervous system will both be activated by physical activity [37]. In addition, the body will contract its muscles 100 times faster than usual [38]. Following this increase in constriction, the need for energy rises significantly and quickly [39]. Because the body is hypoxic that is, lacking oxygen during physical activity, it searches for ways to get oxygen and distribute it throughout the body more quickly and thoroughly through physiological processes [40]. The hypoxic phase that the body goes through will trigger HIF-1α genetic expression [32]. Furthermore, activating downstream target genes involved in several biological processes, such as angiogenesis, glucose metabolism, cell proliferation, and survival, is largely dependent on the stable HIF-1a component. It accomplishes this by attaching itself to the HRE and moving to the nucleus to combine with HIF-1b to create a heterodimer [8].

Particularly, experimental data indicate that HIF-1α, an essential transcription factor for hypoxia adaptation, may regulate the expression of more than 100 downstream genes, including four target gene categories that are inextricably connected to the development of tumors and the synthesis of proteins: Vascular endothelial growth factor (VEGF), glycolytic enzymes and glucose transporter (GLUT) [41], tumor invasion and metastasis-related factors, and proteins connected to tumor development and death [34]. Hypoxia, or low oxygen levels, trigger this gene transcription factor, which in turn causes the body to generate the hormone erythropoietin [42]. Therefore, the erythropoiesis process in the bone marrow will be activated by the presence of Epo [43]. Thus, this process will result in a rise in red blood cells [43]. An increase in red blood cells will also result in an increase in hemoglobin levels, which will bind more oxygen [44]. Additionally, this will affect VO_2max capacity, which will assist and enhance physical capacities [45]. Nevertheless, the analysis of this study has limitations because it only looks at how the body's condition in the hypoxic phase during physical exercise can cause HIF-1α expression, and it only looks at how this can increase the erythropies mechanism by increasing the hormone erythropietin. The next analysis, according to researchers, should provide a clearer picture of how HIF-2 or HIF-3 is

expressed during physical activity. It may also shed light on how exercise might improve one's health or perhaps be a justification for suggesting it as a treatment for a sickness. There might have a significant effect on public knowledge.

CONCLUSIONS

1. Physical exercise has been shown to increase HIF-1α expression.
2. The increase in this gene will trigger the secretion of the hormone erythropoietin.
3. So that there is an increase in the formation of erythrocytes. Hb also increases and has a positive impact on increasing VO_2max.

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Contributors:

Yulfadinata A. – conceptualization, validation, resources, funding acquisition;

Ayubi N. – methodology, formal analysis;

Wibawa J.C. – conceptualization, writing – original draft;

Rizki A.Z. – data curation, visualization;

Afandi A. – supervision, project administration;

Jr P.B.D. – writing – review & editing.

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