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MECHANISMS OF INCREASED ERYTHROPOIETIN LEVELS DURING PHYSICAL EXERCISE: A SYSTEMATIC REVIEW

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Abstract. Mechanisms of increased erythropoietin levels during physical exercise: a systematic review. Putra D.P., Utami D.A., Sundari L.P.R.,Arohman A.S.B. *Erythropoietin levels rising during exercise is a significant physiological reaction that helps the body adjust to higher oxygen demands. By triggering biochemical pathways sensitive to variations in oxygen levels, physical activity, especially at high intensities or in hypoxic environments, might increase the production of erythropoietin. This adaptive response enhances erythropoiesis, thus improving oxygen transport capacity to meet the increased metabolic demands during exercise. Furthermore, elucidating the molecular pathways responsible for exercise-induced erythropoietin production may provide valuable insights for optimizing exercise interventions in both athletic and clinical settings. The association between exercise and elevated erythropoietin has been studied extensively, but the underlying molecular mechanisms are still unknown. The aim of this study was to determine the effect of physical exercise on human erythropoietin levels. We reviewed several literature databases, including Scopus, PubMed, Web of Science, and Science Direct, for our systematic review investigation. The search was conducted for articles published between 2015 and 2025 that discussed physical exercise and erythropoietin. Using the Scopus, Web of Science, PubMed, and Science Direct databases, 704 published publications were identified. For this systematic review, ten papers meeting the inclusion criteria were selected and reviewed. This study evaluated standard operating procedures using the preferred reporting items for systematic reviews and meta-analyses criteria. Based on 10 reviewed papers, it has been shown that physical exercise can significantly increase erythropoietin levels. Erythropoietin levels have been demonstrated to rise with physical activity. This rise is a natural reaction to physical activity, especially when there is hypoxia. The body's adaptive reaction to the elevated oxygen requirement is this rise. Exercise therefore contributes to the formation of red blood cells and the expansion of oxygen transport capacity.*

Реферат. Механізми підвищення рівня еритропоетину під час фізичних вправ: систематичний огляд. Путра Д.П., Утамі Д.А., Сундарі Л.П.Р., Арохман А.С.Б. *Підвищення рівня еритропоетину під час фізичних навантажень є важливою фізіологічною реакцією, яка допомагає організму адаптуватися до підвищеної*

потреби в кисні. Шляхом активації біохімічних шляхів, чутливих до коливань рівня кисню, фізична активність – особливо високої інтенсивності або в умовах гіпоксії – може стимулювати вироблення еритропоетину. Ця адаптивна відповідь посилює еритропоез, покращуючи тим самим здатність транспортування кисню для забезпечення підвищених метаболічних потреб під час тренувань. Окрім того, з'ясування молекулярних механізмів, відповідальних за індуковане фізичними навантаженнями вироблення еритропоетину, може надати цінні дані для оптимізації тренувальних програм як у спортивній, так і в клінічній практиці. Взаємозв'язок між фізичними вправами та підвищеним рівнем еритропоетину досліджувався досить широко, проте основні молекулярні механізми й досі залишаються невідомими. Метою цього дослідження було визначити вплив фізичних вправ на рівень еритропоетину в людини. Для проведення систематичного огляду ми здійснили пошук у кількох літературних базах даних, зокрема Scopus, PubMed, Web of Science та Science Direct. Пошук охоплював статті, опубліковані в період з 2015 до 2025 року, у яких розглядалися фізичні вправи та еритропоетин. За допомогою баз даних Scopus, Web of Science, PubMed і Science Direct було знайдено 704 опубліковані праці. Для цього систематичного огляду було відібрано та проаналізовано десять статей, які відповідали критеріям включення. У цьому дослідженні стандартні операційні процедури оцінювалися згідно з критеріями PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). На основі 10 проаналізованих статей було доведено, що фізичні вправи здатні суттєво підвищувати рівень еритропоетину. Рівень еритропоетину демонструє тенденцію до зростання внаслідок фізичної активності. Це зростання є природною реакцією на фізичне навантаження, особливо за умов гіпоксії. Подібне підвищення є адаптивною реакцією організму на підвищену потребу в кисні. Отже, фізичні вправи сприяють утворенню еритроцитів та розширенню здатності транспортування кисню.

Because altitude enables physiological adaptation, athletes frequently engage in physical training there to enhance their physical performance [1]. When oxygen levels fall below average, it's called hypoxia. This condition has drawn attention due to its possible positive physiological consequences and is frequently employed as a means of enhancing physical performance [2]. Long-term exposure to hypoxia, which frequently occurs when arterial oxygen saturation drops below 90%, triggers a variety of physiological responses and adaptations that enhance exercise performance [3]. Over decades of scientific study and athletic practice, numerous strategies for training at high altitudes and hypoxia have been devised.

One of the primary physiological benefits of training in hypoxic environments is an increase in hemoglobin and red blood cell concentration, which is crucial for transferring oxygen from the lungs to the tissues and has a significant influence on enhancing aerobic performance [4]. During exercise, oxygen is transferred from the lung to the muscles via the binding of hemoglobin, an iron-containing protein found in red blood cells [5]. Consequently, hemoglobin mass has a strong association with maximum oxygen consumption and is a valid indicator of blood oxygen-carrying ability [6]. Previous studies have demonstrated that the distinct hypoxic environment at specific altitudes and training load intensities will cause the body to experience a "double" hypoxic stimulation [7]. Erythropoietin (EPO) is one of the vital and advantageous hormones in this system [8].

The vital function of EPO, an evolutionarily conserved hormone mostly produced in the kidney, in erythropoiesis has been well-documented [9]. EPO is a member of the type 1 cytokine superfamily and consists of four α helices formed by 165 amino acids [10]. Because of its high glycosylation rate, EPO generated by kidneys has a plasma half-life of 5-6 hours in humans. The renal tubules' interstitial cells sense relative hypoxia when the red blood cell count falls, and they use a traditional endocrine pathway to release EPO into the bloodstream [9]. Following its migration to the bone marrow, EPO stimulates erythropoiesis via binding to the homodimeric EPO receptor (EPOR) 2 on erythroid progenitors. Small levels of EPO in human serum, controlled by a traditional negative feedback loop, can preserve erythropoiesis homeostasis because of the high affinity of (EPOR) 2 [11].

Many investigations conducted in the last few years have demonstrated that EPO has effects that go far beyond erythropoiesis. EPO has a crucial function in tissue protection and repair at the border surrounding the injury site, where it is produced by numerous tissues under hypoxic, traumatic, or inflammatory conditions [9]. This impact was previously thought to be mediated by reduced apoptosis and suppression of proinflammatory cytokines [12]. Furthermore, previous studies have verified and demonstrated that physical activity or sports training has been found to increase erythropoietin (EPO) in athletes [13]. The exact chemical mechanisms at play, however, are still up for debate and need more research. Thus, the purpose of this study was to ascertain how exercise raised EPO levels and what that meant for people, specifically in terms of enhancing physical performance and ability.

MATERIALS AND METHODS OF RESEARCH

The design of this study was a systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA 2020 guidelines. The literature search was performed using four electronic databases: PubMed, ScienceDirect, Web of Science, and Scopus. These

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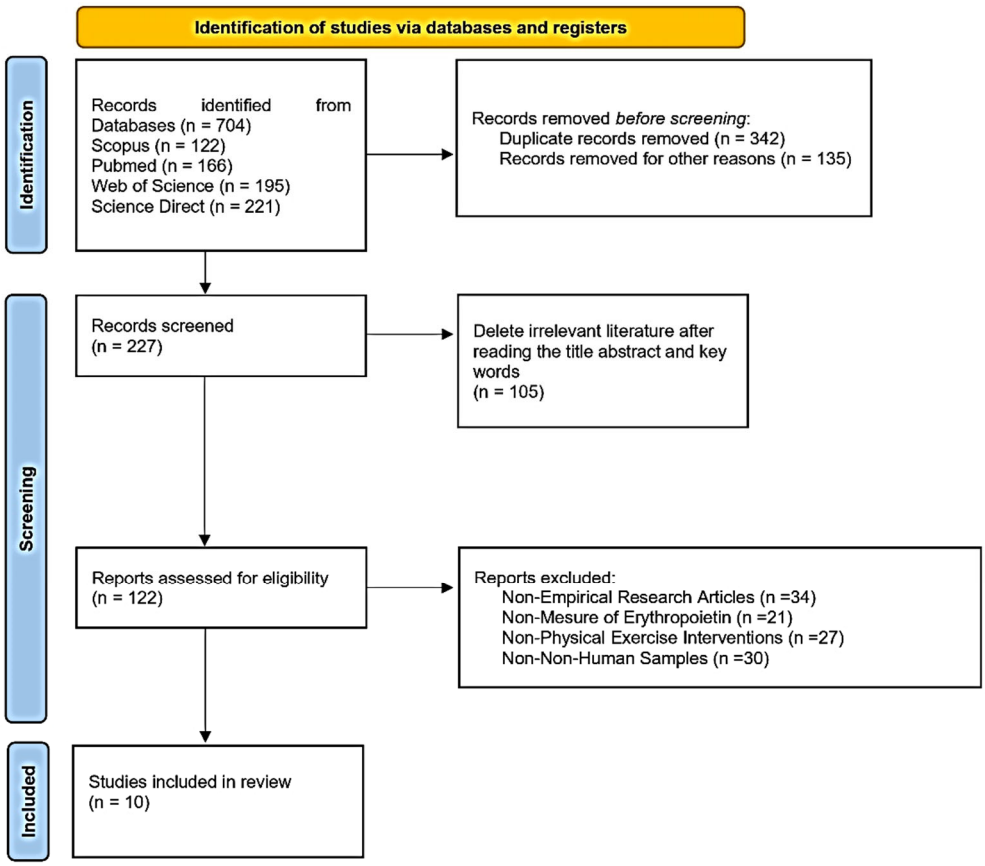
databases were selected because they provide comprehensive coverage of peer-reviewed publications in the fields of exercise physiology, sports medicine, hematology, and biomedical sciences.

A predefined search strategy was applied across all databases to identify relevant studies investigating the effects of physical exercise on erythropoietin levels in humans. Duplicate records were removed before the screening process using reference management software. Subsequently, all retrieved articles were screened independently based on predefined inclusion and exclusion criteria, and eligible studies were selected for qualitative synthesis. The study selection process followed the PRISMA 2020 flow diagram to ensure transparency and reproducibility throughout the review process.

The inclusion criteria for this study were created considering papers published from 2015 to 2025 that discussed the effects of physical activity on erythropoietin. Furthermore, our analysis did not include publications that did not meet the standards for scientific validity or that were not included in reputable search indexes such as Scopus, Web of Science, Pubmed, or Science Direct.

Following preliminary review and approval, each paper's complete text, abstract, and title were added to the Mendeley database. Using the Scopus, Science Direct, Pubmed, and Web of Science databases, 704 papers were located in the first phase. 227 eligible papers were chosen for the second screening stage following the title appropriateness screening. 122 papers were chosen for the third round after the title, abstract, and keywords were examined. Each publication was examined, and we concluded that it satisfied the inclusion criteria, which were as follows: the study had to be unique, the parameter had to be an erythropoietin biomarker, the intervention had to be any kind of physical activity, and the sample had to be human. At this stage, we arranged the things according to their general appropriateness. Following a rigorous review and scrutiny procedure, ten papers that satisfied the inclusion criteria were chosen for study. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Fig.) standards was one of the study's operational requirements. Furthermore, every publication complies with the Declaration of Helsinki and research standards.

Ethical approval was not required for this study because it is a literature review based exclusively on previously published data and does not involve human participants, animals, biological specimens, or identifiable personal data.



PRISMA flow chart of the article selection process

RESULTS AND DISCUSSION

Summary of the design and intervention of the studies

Author	Design	Participants	Participants Age	Intervention	Outcome
(Montero et al., 2017) [14]	Randomized controlled trials	9 healthy, previously untrained young individuals	18-35 years	Exercise Program Over the course of eight weeks, each person participates in 25 60-minute sessions of supervised bicycle ergometry (Monark E839) in our lab. During this time, people are trained three to four times a week, depending on their schedule	Following a physical activity intervention, EPO levels significantly increased
(Riberio et al., 2017) [15]	Randomized controlled trials	38 research participants	20 years	Exercise Program Weight training sessions included three sets of 12 repetitions and were conducted at an intensity of 60%, 70%, or 80% of the 1-RM. Each training session lasts roughly 30 minutes, with a one-minute break between sets. Every training session was held in the morning, from 8:30 to 11:00 AM	Following a physical activity intervention, EPO levels considerably increased
(Dziembowska, Bukowski et al., 2021) [16]	Randomized controlled trials	39 athletes	22-23 years	Exercise Program 5120.00 (3100.00–6300.00) for athletes undergoing physical training Physical activity is measured in MET × min/week. Athletes engage in high levels of physical exercise in the early season	Following a physical activity intervention, EPO levels significantly increased
(Azadan et al., 2021) [17]	Randomized controlled trials	15 participants	31 years	Exercise Program 14 participants in a different group underwent three 30-minute high-intensity cycling sessions following the administration of either a placebo, the non-preferential β1 + β2 antagonist nadolol, or the β1-adrenergic receptor (AR) antagonist bisoprolol	Following a physical activity intervention, EPO levels significantly increased
(Yatsutani et al., 2020) [18]	Randomized controlled trials	12 healthy males cycled	21 years	Exercise Program For 60 minutes, participants engaged in heat and hypoxia (H+H; fraction of inspired oxygen or FiO2: 14.5%, 32◦C), hypoxia (HYP; FiO2: 14.5%, 23◦C), and normoxia (NOR; FiO2: 20.9%, 23◦C) exercise at a constant workload (60% of their power output relative to their maximal oxygen intake in each conditions)	Following a physical activity intervention, EPO levels significantly increased
(Weng et al., 2021) [19]	Randomized controlled trials	6 swimmers	20 years	Exercise Program Every week, swimmers train for ten sessions. Land training, which consists of squats, running, bench presses, pull-ups, and other exercises, is done two to three times a week for an hour each. There are other types of in-water training, including elastic band training, which is done twice a week for thirty minutes each session	EPO levels increased significantly after physical exercise intervention

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Table (continued)

Author	Design	Participants	Participants Age	Intervention	Outcome
(Park et al., 2022) [20]	Randomized controlled trials	20 amateur Korean female runners	19-29 years	Exercise Program Based on their body composition and endurance training performance, interval training under normoxic conditions and hypoxic training groups were suitable for interval training under hypobaric hypoxia conditions at a simulated altitude of 3000 m. A 120-minute training session that included a 20-minute warm-up, 60-minute interval training, and a 20-minute cool-down was completed by all participants. For six weeks, the training course was held three days a week. For twenty minutes, the warm-up and cool-down phases were conducted at 60% of Hrmax	EPO levels increased significantly after physical exercise intervention
(Fernandez-Lazaro et al., 2022) [3]	Randomized controlled trials	24 male athletes	25-26 years	Exercise Program To improve performance, athletes add altitude training to their regular training regimen. Intermittent hypoxic exercise (IHE) in addition to altitude training for eight weeks	EPO levels increased significantly after physical exercise intervention
(Wang et al., 2022) [21]	Randomized controlled trials	6 male cross-country skiers participated	21 years	Exercise Program Including travel time from the high-altitude camp to the laboratory, exercise performance was assessed three days prior to and four days following the high-altitude field training. Following a treadmill and a gas analyzer (COMED Quark CPET, Italy), the exercise load test was conducted following the Bruce protocol. The incline was increased by 2% every three minutes after the initial 1.7 mph speed and 10% incline. The pace was then increased from 0.8 to 0.9 mph until the treadmill speed could no longer be maintained and the maximum heart rate exceeded 90% of the target heart rate (THR)	EPO levels increased significantly after physical exercise intervention
(Man et al., 2021) [2]	Randomized controlled trials	10 endurance-trained athletes	20 years	Exercise Program The athletes trained for the following three periods: during the first phase, the participants trained for 21 days at an altitude of about 2000 meters in Piatra Arsă. The participants in the second phase followed the same training regimen by the sea in Mamaia-Constant (~0 m) on the Black Sea coast. Lastly, the third training cycle was held at an altitude of about 600 meters in Blaj	EPO levels increased significantly after physical exercise intervention

The purpose of this study was to determine the effect of physical exercise on increasing EPO levels. The results showed that physical exercise significantly increased EPO levels. This is consistent with a previous study in which individuals received an ergometry exercise intervention of 25 sessions over 8 weeks, with three to four sessions per week, which significantly increased EPO levels [14]. According to additional study, training with three sets of 12 repetitions and weight training at intensities of 60%, 70%, or 80% of one repetition maximum significantly increases EPO levels [15]. Other research conducted on athletes undergoing early season training at high levels also showed a significant increase in EPO levels [16].

In a prior study, fourteen individuals completed three 30-minute high-intensity cycling sessions, and the results demonstrated a substantial effect on raising EPO levels [17]. Exercise in hypoxic environments significantly increases EPO levels, according to other research findings [18]. According to earlier studies, swimmers who had completed 10 training sessions per week in addition to land training performed squats, runs, bench presses, pull-ups, and other exercises two to three times a week for an hour each. Twice a week, for 30 minutes each, different types of in-water training were conducted, including elastic band exercise. The study's findings demonstrated a noteworthy influence on rising EPO levels [19].

A 120-minute training program that includes a 20-minute warm-up, 60 minutes of interval training, and a 20-minute cool-down has been shown to be effective when conducted under hypoxic conditions. In addition, the training course runs for six weeks, three days a week. The findings demonstrated that this training had a major effect on EPO levels [20]. According to the findings of another study, athletes who trained for eight weeks at high altitudes had a rise in EPO levels, which may have led to an improvement in their physical performance [3]. The results of other studies demonstrate that exercise at high elevations significantly increases EPO levels [21]. The altitude at which athletes participated in study activities for 21 days was also found to have a substantial effect on raising EPO levels [2]. So, various studies have clearly proven and shown that physical exercise has an impact and influence on increasing EPO levels which will affect athletes' physical performance and aerobic capacity.

Physiological Mechanisms of Physical Exercise in Increasing Erythropoietin Levels

To shed light on the beneficial effects of exercise on EPO levels, it is crucial to talk about and thoroughly investigate the molecular mechanisms behind exercise-induced EPO increase. Exercise and hypoxia are both powerful metabolic stresses. The total blood aggregation rate is greatly increased when these elements are combined. Exercise stimulates the sympathetic nervous system and the HPA axis [22]. The body will also contract its muscles 100 times faster than normal [23]. Energy requirements rise sharply and quickly after this increase in shrinkage [24]. The body searches for ways to obtain oxygen and distribute it throughout the body more rapidly and thoroughly through physiological processes because physical exertion causes hypoxia, or a lack of oxygen [25]. The body's hypoxic phase will cause HIF-1α to be expressed genetically [26]. Furthermore, a steady HIF-1α component is essential for the activation of downstream target genes involved in a number of biological activities, including angiogenesis, glucose metabolism, cell proliferation, and survival. This is accomplished by attaching to the HRE and then transferring to the nucleus to create a heterodimer with HIF-1β [27].

Under the control of HIF-1α, hypoxia can increase EPO secretion [28]. However, proinflammatory factors as MPO, TNF-α, IL-1, or IL-6 can rise in response to acute exercise or severe hypoxia circumstances. Hematological adaptability and the EPO response may be impeded by these situations [29]. A key component of this reaction is hematologic adaptation to extended hypoxia and breathing. The hematologic response is the result of elevated hemoglobin (Hb) and red blood cell levels caused by enhanced EPO production by the kidneys [26]. The body will try to preserve homeostasis while providing energy to the cells if hypoxia is induced [6]. The body will react to hypoxia by producing more erythropoietin [6]. Erythropoiesis is triggered by this hormone [30]. Erythrocyte levels will rise as a result of the body going through this erythropoiesis mechanism [30]. The distribution of oxygen to the cells is increased when the hemoglobin level rises in tandem with the erythrocyte level [31].

Together with red blood cells, hemoglobin is crucial for supplying oxygen to all bodily tissues [32]. The capacity of the heart, lungs, and blood to carry out physical exercise is significantly impacted by VO_2max [8]. Therefore, improving the blood's capacity to bind oxygen can also raise VO_2max while exercising [8]. Increased blood EPO levels speed up the rate and quantity of colony-forming units (CFU-E) that differentiate into red blood cells, which in turn promotes erythropoiesis in the bone marrow. Increased red blood cell mass has the effect of reducing the stimulation for the generation of EPO. When there is a higher demand for oxygen, such as during exercise, inflammation, or heat, the amount of oxygen in tissue decreases, a condition known as metabolic hypoxia [33]. Hypoxia is thought to be the most significant stimulus for EPO release, and EPO

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mRNA expression is strongly correlated with renal oxygen concentration [34].

According to recent studies, elite athletes' EPO concentrations peak after six days of intermittent hypoxia exposure [35]. Prior research also demonstrated a connection between erythropoiesis and muscle mass [36]. The idea that EPO improves exercise performance by activating EPO receptor subtypes in non-hematopoietic tissues, such as skeletal muscle, is supported by certain data [16]. According to recent research, endogenous EPO regulates skeletal muscle mitochondrial biogenesis through EPO receptors on myocytes [37]. Nijholt et al. demonstrated that the absence of EPO receptors in non-hematopoietic tissues led to decreased myocyte development and exercise capacity in response to voluntary exercise in mice, as well as poor mitochondrial content in skeletal muscle [37]. Therefore, it can be hypothesized that the kidneys may not be the only source of erythropoietin released into the bloodstream as a result of physical activity; the working skeletal muscles may also be involved, at least in the early phases of exercise [37].

Every physical activity session helps to release androgens, cortisol, and noradrenaline [38], It is a hormone that promotes the release of EPO, which increases the bone marrow's erythropoietic activity [34]. By raising the quantity of EPO receptors, testosterone can potentially have a direct impact on erythroblasts [38]. Recent research has also shown that noradrenaline interacts intricately with the bone marrow, which explains why the erythropoietic response depends on exercise length and intensity as well as the stress reaction that goes along with it [38, 39]. Review studies reveal that while prolonged and intense physical exertion (such as ultramarathon running) temporarily raises EPO levels in both trained and untrained men, short-term exercise has no discernible effect on EPO levels [14]. Due to a significant increase in physical effort relative to the person's typical level of physical activity, a brief increase in EPO concentration seems to have adaptive importance.

Strength and Limitations. This systematic review has the advantage of focusing solely on randomized controlled trials, the most trustworthy source of scientific data and removing the potential for ambiguous cause-and-effect correlations. Additionally, the collected samples are human-focused, exhibit consistent data, and aren't mixed with samples from other categories, such as animal samples.

We acknowledge that this systematic review has limitations because it only examined the detailed relationship between exercise and erythropoietin levels. Although the researchers acknowledge the intricacy of the physiological processes taking place within the body, their discussion of physiological reactions and their mechanisms may seem in-depth. Experimental research is required to investigate other biomarkers, such as how erythropoietin levels occur during exercise. Additionally, a thorough analysis of the differences between high- and low-intensity exercise is required; Consequently, more research is advised to address this matter.

CONCLUSIONS

1. According to several related studies we found, regular exercise has been shown to significantly increase human erythropoietin levels.
2. Erythropoietin levels during exercise play an important role in increasing erythropoiesis and improving physical performance in humans or athletes.

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Utami D.A. – conceptualization, writing – review & editing, data curation;

Sundari L.P.R. – conceptualization, writing – original draft;

Arohman A.S.B. – conceptualization, writing – original draft.

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