






## Review Article

## Physical Exercise at High Altitudes Increases Erythropoietin Hormone Secretion: A Systematic Review

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## Abstract

**Objective:** To investigate and quantify the mechanism by which exercise at high altitude increases the release of the erythropoietin hormone. **Methods:** This study examines many journal databases, such as Pubmed, Embase, Web of Science, and Scopus. Among the criteria considered in this study were articles published within the last five years, as well as those on erythropoietin, physical activity, and high-altitude training. We only rejected publications published in anonymous journals for inclusion in this analysis. We successfully identified 2510 papers in total using the Embase, Web of Science, Pubmed, and Scopus databases. We have looked at and reviewed approximately ten papers that address the requirements for this systemic breakthrough. We developed standard operating procedures for the current investigation using the Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA). **Results:** The systemic analysis reveals that physical activity at altitude elevates the hormone erythropoietin, leading to an increase in erythrocyte count. Furthermore, it can improve physical performance by increasing oxygen delivery to cells, thereby potentially triggering energy system function. **Conclusions:** Anaerobic physical exercise at an altitude of 4000-5000 m for a minimum of four weeks can have a real impact on increasing levels of the hormone erythropoietin. For further research and analysis, it is advisable to find out what genes trigger the release of the hormone erythropoietin.

**Keywords:** Erythropoietin, High-Altitude, Hormone, Physical exercise.

ممارسة الرياضة البدنية على ارتفاعات عالية يزيد من إفراز هرمون الإريثروبويتين: مراجعة منهجية

الخلاصة

**الهدف:** التحقيق وتحديد الآلية التي تزيد بها التمارين على ارتفاعات عالية من إفراز هرمون الإريثروبويتين. **الطريقة:** تبحث هذه الدراسة في العديد من قواعد بيانات المجالات ، مثل Pubmed و Embase و Web of Science و Scopus. من بين المعايير التي تم النظر فيها في هذه الدراسة كانت المقالات المنشورة خلال السنوات الخمس الماضية قد تم النظر فيها في هذه الدراسة ، وكذلك تلك المتعلقة بالإريثروبويتين والنشاط البدني والتدريب على ارتفاعات عالية. لقد رفضنا فقط المنشورات المنشورة في مجلات مجهولة لإدراجها في هذا التحليل. لقد نجحنا في تحديد 2510 ورقة في المجموع باستخدام قواعد بيانات Embase و Web of Science و Pubmed و Scopus. لقد نظرنا وراجعنا ما يقرب من عشر أوراق نتناول متطلبات هذا الاختراق المنهجي. قمنا بتطوير إجراءات تشغيل قياسية للتحقيق الحالي باستخدام بنود الإبلاغ المفضلة للتحليل المنهجي والتلوي (PRISMA). **النتائج:** يكشف التحليل الجهازي أن النشاط البدني على ارتفاعات يرفع هرمون الإريثروبويتين، مما يؤدي إلى زيادة عدد كرات الدم الحمراء. علاوة على ذلك، يمكن أن يحسن الأداء البدني عن طريق زيادة توصيل الأكسجين إلى الخلايا، وبالتالي يحتمل أن يؤدي إلى تحفيز وظيفة نظام إنتاج الطاقة. **الاستنتاجات:** يمكن أن يكون للتمرين البدني اللاهوائي على ارتفاع 4000-5000 متر لمدة لا تقل عن أربعة أسابيع تأثير حقيقي على زيادة مستويات هرمون الإريثروبويتين. لمزيد من البحث والتحليل، ينصح بمعرفة الجينات التي تؤدي إلى إطلاق هرمون الإريثروبويتين.

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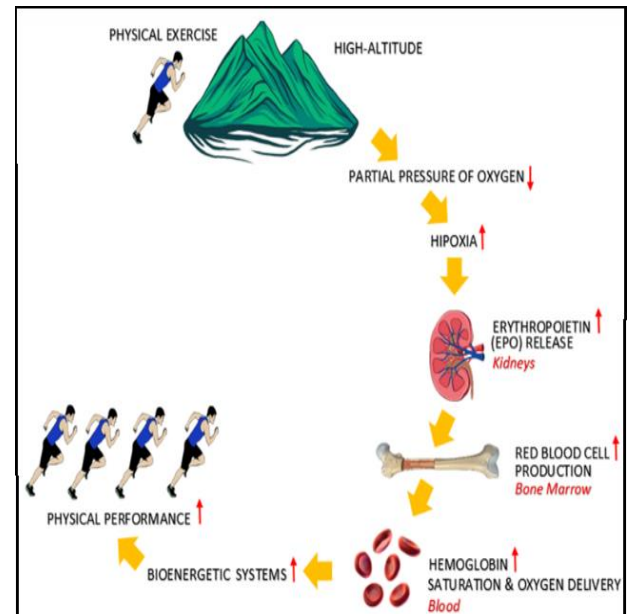
## INTRODUCTION

Athletes frequently engage in physical training at altitude to enhance their physical performance since it allows their bodies to adjust physiologically [1]. Hypoxemia is a condition in which oxygen levels are below normal limits. Chronic exposure to high altitude will cause the release of erythropoietin (EPO) into the circulation if hypoxemia lasts longer than 12 hours per day. EPO usually

accelerates erythropoiesis and increases hemoglobin mass, increasing the carrying capacity of the oxygen storage system [2]. Another technique that has received less attention but has the potential to improve physical performance without having certain detrimental physiological effects is hypoxic conditioning [3]. One of the primary training techniques to improve aerobic capacity is altitude physical training, which includes lactate tolerance training, interval training, and resistance training [4]. When arterial oxygen saturation falls below

90%, prolonged exposure to hypoxia, which frequently happens during high-altitude training, causes a number of physiological reactions and adaptations that improve exercise performance [5]. Numerous approaches for altitude and hypoxia training have been developed throughout decades of scientific inquiry and sports practice. Athletes commonly employ fundamental techniques including "intermittent hypoxic training" (IHT), "live high-train low" (LH-TL), and "live high-train high" (LH-TH) [6]. Living and training at altitude is the premise of the "live high, train high" approach. Athletes train in hypoxic environments while in a normoxic state during IHT. The LH-TL approach exposes athletes to hypoxia for 8–14 hours per day, primarily during sleep, while training takes place in a normoxic environment. The strategy known as "live high, base train high, interval train low" or "HiHiLo" is one of the several variations of altitude training that combines low-intensity base training in hypoxia with the traditional LH-TL approach [6]. Elite athletes and coaches utilize altitude training extensively to enhance physical performance. In order to be ready for a big tournament, athletes usually live and train at an altitude of two to four weeks using the altitude training method known as live high-train high (LHTH) [7]. It has been demonstrated that this kind of exercise alters hematopoiesis, particularly in athletes. Previous research has demonstrated that swimmers' hemoglobin (Hb) mass can increase when exposed to intermediate elevations (1800–2500 m) [8]. A decrease in the amount of oxygen (O<sub>2</sub>) or pressure inside cells is referred to as hypoxia [9]. There are two kinds of hypoxia: normobaric hypoxia, which has a barometric pressure of 760 mmHg and a FiO<sub>2</sub> less than 20.9%, and hypobaric hypoxia, which is defined as an atmospheric pressure lower than 760 mmHg [10]. Results from research conducted by González-Ravé *et al.* (2023) demonstrate that boosting physical performance with an increased hemoglobin concentration is not as beneficial [11]. An increase in the concentration of hemoglobin and red blood cells, which are in charge of carrying oxygen from the lungs to the tissues, is one of the primary physiological impacts of training at altitude and has a major impact on enhancing aerobic performance [12]. Hemoglobin, a protein in red blood cells that contains iron, binds to oxygen during exercise to move it from the lungs to the muscles [13]. Therefore, hemoglobin mass is a reliable measure of the blood's oxygen-carrying capacity and has a high correlation with maximum oxygen consumption [14]. Research by Hobbins *et al.* (2021) demonstrated that the body will experience a "double" hypoxic stimulus due to the unique hypoxic environment at high altitude and the intensity of a particular training load. This will alter arterial oxygen content, which will directly affect oxygen delivery, and hypoxic training will present even more special challenges to the body's cardiovascular system. It has been demonstrated that hypoxic training at altitude enhances hematological markers, cardiopulmonary function, and overall health without putting additional strain on the body's bones and muscles [15]. Originally intended to serve as adaptive training for athletes preparing for altitude events, intermittent hypoxia exposure is now more frequently employed as a training aid for elite athletes seeking to enhance their overall athletic performance and adaptability. Additionally, by

altering the training altitude, intermittent hypoxia exposure offers novel stimuli in a hypoxic environment, further enhancing physical function [16]. Resistance and/or aerobic capacity are important components of sports performance for long-distance athletes, hence ingredients that enhance oxygen transport and use at the muscle level are particularly important. However, the mechanism by which physical exercise at altitude increases physical performance is still not completely clear. Therefore, this systematic review will explain how the physiological mechanisms of physical exercise at altitude can improve physical performance through increasing secretion of the hormone erythropoietin (Figure 1).



**Figure 1:** Mechanisms of physical exercise at high altitudes that increased erythropoietin hormone secretion.

## METHODS

### Study design

As part of a systematic review process, this study examines many journal databases, such as Pubmed, Embase, Web of Science, and Scopus.

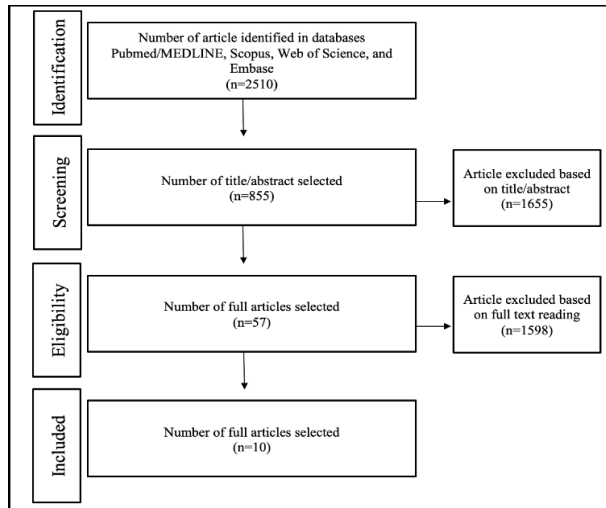
### Eligibility criteria

Studies on erythropoietin hormone, physical activity, and high-altitude training published in the preceding five years met the inclusion criteria for this study. Among the papers excluded from the study were those published in journals with a poor reputation.

### Procedure

Verified and approved, complete texts, abstracts, and article titles were added to the Mendeley database. In the first phase, 2510 publications were found using the databases Embase, Web of Science, Pubmed, Scopus, and Web of Science. Eight hundred and fifty-five items were assessed in the second stage according to how well the abstract and title complied with the guidelines. The third

phase consisted of verifying 57 articles for further processing. We now filter according to 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 2).



**Figure 2.** PRISMA flowchart of the article selection process.

## RESULTS

The experimental design, setting, and outcomes of the evaluated articles are summarized in Table 1.

## DISCUSSIONS

Significant increases in EPO, Hb, and VO<sub>2</sub>max were demonstrated by the results of a study conducted on ten athletes who had trained for running at sea level on sand and at altitude [3]. According to the findings of another study, Indian volunteers who were transported by air from Delhi to Bishkek at an altitude of 3000 m for four days and then transported by road at an altitude of 4111 m for twenty-one days had a rise in erythropoietin hormone levels [17]. The findings of a study involving ten athletes who completed three physical training sessions at varying elevations—2000 m for the first session, 2200 m for the second, and 300 m for the final session—showed that training in the 2200 m plains significantly increased the hormone erythropoietin [1]. The two most important factors for coaches to take into account when trying to improve athletes' physical performance are periodization and responsiveness to altitude training [20]. A state of altitude hypoxia is brought on by exercise at an altitude that is characterized by a drop in blood oxygen saturation [21]. Nonetheless, as coaches place a strong emphasis on anaerobic metabolism, it is crucial for athletes to increase their anaerobic endurance [21]. An artificial simulation mechanism was used to prepare seven active individuals to experience an altitude of 3000 m for a duration of 12 hours. The study's findings demonstrated a considerable rise in the hormone erythropoietin [2]. Of the 34 cyclists

who took part in the study, four training groups were formed: the control group (CN, normoxic training), the IHT group ("live high - base train high - interval train low procedure"), the HiHiLo group ("procedure live high - base train high - interval train low"), and the LH-TL group ("live high-train low"). For four weeks, each group underwent three sessions of physical activity. The study's findings revealed that the HiHiLo intervention group ("live high - base train high - interval train low procedure") had significantly higher erythropoietin hormone levels [6]. Another study finding showed that 12 participants in aerobic and anaerobic IHE (Exposure to Intermittent Hypoxia) training who had been trained to be at an altitude of 4000–5000 m had higher levels of erythropoietin hormone [18]. Athletes who received intermittent hypoxia exposure (IHE) therapy for eight weeks showed a rise in erythropoietin hormone levels [5]. The anaerobic capacity of athletes can be significantly increased by physical training at altitude [1]. The hypoxic state of the organism allows for physiological adjustments that improve athletic performance [22]. Subsequent research indicates that erythropoietin levels rise significantly at an altitude of 3000 m following a 12-hour hypoxic period [2]. The research result of Sanz-Quinto *et al.* (2022) demonstrated that after 8 days at an elevation of 3,900 meters, the erythropoietin hormone levels in a 36-year-old professional wheelchair marathon runner increased significantly [19]. Many coaches try to use training methods at high altitudes to support athletes' physical improvements. Training modification and periodization provide athletes with physiological adaptations that have beneficial effects on their performance. The mechanism by which physical exercise increases erythropoietin hormone levels is as follows: When you do physical exercise, the body activates the sympathetic nervous system to work, which will increase the hormone cortisol and increase energy needs [23]. When such conditions occur, the body automatically tries to meet energy needs through physiological mechanisms in order to maintain body homeostasis [24]. Engaging in physical training at altitude, under conditions of low partial pressure of oxygen, can lead to remarkable physiological adaptations in the body. Inducing hypoxia will prompt the body to strive for maintaining homeostasis while supplying energy to the cells [14]. When hypoxia occurs, the body will respond by increasing levels of the hormone erythropoietin [14]. This hormone functions to trigger erythropoiesis [25]. When the body experiences this erythropoiesis mechanism, it will have an impact on increasing erythrocyte levels [25]. If erythrocyte levels rise, hemoglobin levels also rise, increasing the distribution of oxygen to cells [26]. In the human body, hemoglobin plays a crucial role in delivering oxygen to every bodily tissue, together with red blood cells [27]. VO<sub>2</sub>max has a significant impact on the heart's, lungs', and blood's capacity to do physical exercise [26]. As a result, increasing the blood's ability to bind oxygen can also raise VO<sub>2</sub>max when engaging in physical activity [26].

## Study limitations

The limitation of this study is that it solely focuses on how different types of altitude can increase erythropoietin

hormone levels, and it only provides a general explanation of how training at altitude can enhance physical

performance by increasing erythrocytes, which are triggered by the erythropoietin hormone.

**Table 1:** Results of a review of the effects of physical exercise at high altitudes on erythropoietin hormone secretion.

Author	Sample Characteristics	Study Design	Intervention	Results
(Man <i>et al.</i> , 2021) [3]	10 healthy male endurance athletes participated in this study	Experimental	Jogging for 21 days at 2000 m is physical training. The second and third training levels are 0 m and 600 m, respectively.	There was a significant increase in erythropoietin hormone levels during exercise at an altitude of 2000 respectively.
(Gaur <i>et al.</i> , 2020) [17]	20 people of Indian ethnicity and 20 people of Kyrgyz ethnicity participated in this study	Experimental	The 7th day of research was done in Bishkek after Indian participants arrived by flight from Delhi. Participants acclimatized to 3000 m altitude for 4 days. They then traveled by road for 21 days to 4111 m.	On the seventh day of adaptation, at a plateau of 4111 m, erythropoietin hormone levels significantly increased in both groups. Still, the Indian group grew considerably faster than the Kyrgyz group.
(Dragos <i>et al.</i> , 2022) [1]	10 male endurance athletes participated in this study	Experimental	The runners completed 30 days of 2000-meter training, two months at 2200 meters, and three months at 300 meters. Each phase comprises 50 training sessions.	Erythropoietin hormone levels significantly increased while training at an altitude of 2200 meters in athletes who were at an altitude of 1850 meters.
(Baranauskas <i>et al.</i> , 2022) [2]	7 physically active men and women participated in this study	Experimental	The sample is in a place with simulated conditions such as being at an altitude of 3000 m for 12 hours	Erythropoietin hormone levels increased significantly after 12 hours in a simulated location with an altitude of 3000 m
(Wiśniewska <i>et al.</i> , 2020) [6]	The study included 34 cyclists in 4 training groups: control group (normoxic training), the IHT, the HiHiLo, and the LH-TL.	Experimental	Each group received physical exercise three times a week for four weeks. Each training session lasts 30 minutes in the first week, 35 minutes in the second, and 40 minutes in the third	At an altitude of 1900 meters, the HiHiLo group ("live high - base train high - interval train low") experienced a considerable rise in erythropoietin hormone levels
(Fernández-Lázaro <i>et al.</i> , 2020) [18]	Twelve (n=12) top men from the Spanish National Team and the Soria Center of High Training and Promotion of Sports took part in this study.	Experimental	For 4 wks, the sample rested and sat comfortably. Daily IHE sessions involved breathing through a portable mask for 90 min. In hypoxia, intermittent breathing was administered for 5 min. For 5 min, the air was normoxic. Due to hypoxia, samples must be placed at "HA" (4,000–5,000 m) and "VHA" (> 5,000 m). After this adjustment, samples tested their anaerobic and aerobic endurance on a treadmill.	There was a significant increase in erythropoietin hormone levels after simulating altitude adaptation
(Fernández-Lázaro <i>et al.</i> , 2022) [5]	The study had 24 male athletes in good health who were split into two groups: the Intermittent Hypoxia Exposure (IHE) group (HA, n = 12) and the Intermittent Normoxia group (NA, n = 12)	Experimental	IHE intervention group (HA) athletes attended 90-min IHE sessions one hr after morning practice for 8 wks. The control group (NA) athletes attended daily 90-min treatment simulation sessions one hr after morning practice for 8 wks. Simulation treatment used an altitude hypoxia apparatus that cycled between normobaric normoxic air and room air for 5 min, like in the HA group.	Erythropoietin hormone levels significantly increased following training in the IHE group.
(Sanz-quinto <i>et al.</i> , 2022) [19]	A male competitive wheelchair marathon runner with quadriplegia-tetraparesia was diagnosed with Charcot Marie Tooth, the most common neuromuscular illness. The research participant has 13 world records.	Experimental	In a 36-year-old professional wheelchair marathon runner, this case study intends to describe blood markers and resting RR changes at sea level, throughout 5 wks of physical training at an altitude of 3,900 m, and after returning to sea level.	After eight days at a high altitude, erythropoietin hormone levels significantly increased
(Wang <i>et al.</i> , 2022) [4]	Six South Korean skiers took part in this investigation.	Experimental	Blending is used for altitude training. Workout at 1609 me. The intensity of treadmill workouts increases. It includes high-intensity interval training (12–15%) and low-intensity activities (70–80%). The overall workout for this trial was: 75.19% was LIT, 2.32% MIT, 6.2% HIT, 11.62% strength training, and 4% jogging.	Elevated levels of the hormone erythropoietin are observed following physical activity at altitude.

## Conclusion

Physical exercise at altitude has been proven to increase levels of the hormone erythropoietin, based on an analysis of research results. This increase in the hormone erythropoietin will trigger erythropoiesis, thereby increasing erythrocytes and hemoglobin. The increase in erythrocytes and hemoglobin has an impact on increasing oxygen distribution to cells during physical exercise and competition. Researchers recommend anaerobic physical exercise at an altitude of 4000-5000 m for a minimum of four weeks to increase the levels of the hormone

erythropoietin. Researchers recommend further research and analysis to identify the genes that trigger the release of the erythropoietin hormone, in order to gain a comprehensive understanding of its secretion in hypoxic conditions.

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**Conflict of interests**

No conflict of interests was declared by the authors.

**Funding source**

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**Data sharing statement**

Supplementary data can be shared with the corresponding author upon reasonable request.

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