REVIEWS
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PHYSIOLOGICAL IMPLICATIONS OF ERYTHROPOIETIN ON ENDURANCE SPORTS PERFORMANCE

FIZIOLOŠKE IMPLIKACIJE ERITROPOETINA NA IZVEDBU U SPORTOVIMA IZDRŽLJIVOSTI

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ABSTRACT

Erythropoietin (EPO) is a glycoprotein hormone primarily synthesized in the kidney that plays a critical role in regulating red blood cell production by stimulating erythropoiesis through erythropoietin receptors (EPOr) on bone marrow progenitor cells. Its production is induced under hypoxic conditions via hypoxia-inducible factors (HIFs). Beyond haematopoiesis, EPO demonstrates diverse effects, including neuroprotection, cardioprotection, immune modulation, and metabolic regulation. In endurance sports, one of the earliest strategies used to enhance erythropoiesis in athletes was exposing the organism to high-altitude environments. As such, altitude exposure became one of the foundational techniques in the realm of blood doping, serving as a non-pharmacological approach. Since its introduction in the late 1980s, recombinant human EPO (rHuEPO) has been widely misused for performance enhancement due to its capacity to increase oxygen delivery. This misuse has led to the development of sophisticated anti-doping measures, including direct detection of synthetic EPO isoforms and indirect monitoring of biological markers such as haemoglobin levels and reticulocyte counts through the Athlete Biological Passport (ABP). Emerging gene doping technologies, which involve the manipulation of genes to enhance EPO production, present future challenges for anti-doping efforts. These advances underscore the need for ongoing innovation in detection and regulation strategies to preserve integrity in sports.

Keywords: *erythropoietin, recombinant human erythropoietin, hypoxia-inducible factor; altitude training, blood doping*

SAŽETAK

Eritropoetin (EPO) je glikoproteinski hormon koji se primarno sintetizira u bubrezima i ima ključnu ulogu u regulaciji proizvodnje crvenih krvnih stanica stimulirajući eritropoezu putem eritropoetinskih receptora (EPOr) na progenitorskim stanicama koštane srži. Njegova se proizvodnja povećava u hipoksičnim uvjetima posredstvom čimbenika induciranih hipoksijom (HIF). Osim hematopoetske funkcije, EPO pokazuje širok spektar učinaka, uključujući neuroprotekciju, kardioprotekciju, modulaciju imunološkog sustava i regulaciju metabolizma. U sportovima izdržljivosti jedna od najranijih strategija za poticanje eritropoeze bila je izlaganje organizma visinskim uvjetima. Stoga je boravak na visini postao jedna od temeljnih tehnika u području krvnog dopinga, djelujući kao nefarmakološki pristup. Od svog uvođenja krajem 1980-ih, rekombinantni ljudski EPO (rHuEPO) široko se zloupotrebljava za poboljšanje performansi zbog svoje sposobnosti povećanja dostave kisika. Ova zloupotreba potaknula je razvoj sofisticiranih antidopinških mjera, uključujući izravnu detekciju sintetskih EPO izoformi i neizravno praćenje bioloških markera poput koncentracije hemoglobina i broja retikulocita kroz Biološku putovnicu sportaša (ABP). Nove tehnologije genskog dopinga, koje uključuju manipulaciju genima radi povećanja proizvodnje EPO-a, predstavljaju buduće izazove antidopinškim naporima. Ovi napreci naglašavaju potrebu za kontinuiranom inovacijom u detekciji i regulaciji kako bi se očuvala cjelovitost sporta.

Ključne riječi: *eritropoetin, rekombinantni humani eritropoetin, hipoksija inducibilni faktor, visinski trening, krvni doping*

1. INTRODUCTION: UNDERSTANDING THE ROLE OF ERYTHROPOIETIN

Erythropoietin (EPO) is an acidic N-linked glycoprotein hormone, composed of 165 amino acids with two disulfide bonds between cysteine residues (Cys 29– Cys 33 and Cys 7- Cys161) [1,42,47,55]. Its spatial structure consists of four α-helices linked A-D (via Cys7 and Cys161) and A-B (via Cys 29 and Cys 33). The mature glycoprotein has a molecular mass is ~30–34kDa of which (40-60%) is made up of CHO (carbohydrates) at three N-glycosylation sites at (Asn 24, Asn 38, Asn 83) and one O-glycosylation site at (Ser126). Primarily produced by peritubular interstitial cells in the kidney, although a small amount is also produced in the liver. Besides these tissues, recent research suggests that small amounts of this hormone are also produced in other cells, such as bone osteoblasts, brain astrocytes, and pericytes of capillaries and small venules [1,62,70,89].

During mammalian embryonic development EPO production begins in the neural crest, resulting in erythropoiesis and enabling oxygen transport to the embryo. The first site of erythrocyte production occurs in the yolk sac (blood islands), and during the later development of organ systems, the liver takes over EPO synthesis and erythropoiesis. As gestation enters its last third, the kidneys take over the final role of hormone synthesis [104], while the bone marrow participates in the overall haematopoiesis [41,64,65].

The importance of EPO and its receptor (EPOr) during gestation is indicated by studies on knockout mice lacking EPOr. It caused a decrease in erythropoiesis in hematopoietic tissues and abnormal heart development, which consequently caused severe anemia and death of mice during the fetal period [54,100,101].

2. METHODS

This article integrates literature sourced from major scientific databases including Scopus, Web of Science (WoS), and PubMed and provide a narrative synthesis of physiological mechanisms and training methods influencing EPO levels, highlighting their potential impact on athletic performance. The key terms used in our search were: “erythropoietin,” “altitude training,”, “hypoxic training”, “recombinant human erythropoietin”, “recreational athlete”, “EPO doping”, “doping affairs” All the studies were selected based on relevance to physiology, athletic performance, or doping practices. Taking into account documented cases of doping misuse from earlier decades, the search timeframe was extended to include publications dating from 1970 to the present.” This review is characterized by its descriptive and summative nature, with no statistical integration or primary data evaluation conducted. Paragraphs addressing doping incidents are presented in a more popularized style, as they are based on articles from local newspapers and lack scientific verification.

3. MOLECULAR BASIS OF HYPOXIA-INDUCIBLE FACTOR COMPLEX

It is the master regulator of red blood cell production in the body [36,88]. EPO production is regulated by an oxygen-dependent negative feedback loop via the transcription factor, hypoxia-inducible factor (HIF). The HIF complex consists of two subunits: HIF-α and HIF-β [84]. Under normal oxygen conditions (normoxia), the HIF-α subunit is unstable and undergoes rapid degradation shortly after synthesis by the currently known inhibitory factor HIF-1 (FIH-1) and prolyl hydroxylase domain (PhD). These enzymatic complexes are dependent on the partial pressure of oxygen, and PhD causes hydroxylation of HIF-α at two proline residues, then labelling and linking with Hippel-Lindau (pVHL) and E3 ligase, ubiquitination and proteasomal degradation [45,88,96]. Also, FIH1 causes hydroxylation of asparagine and disables the binding site for the p300 coactivator responsible for transcriptional regulation [28,49].

During a state of reduced oxygen partial pressure, oxygen-dependent enzymes are inactive and HIF-α avoids degradation, stabilizes and combines with the HIF-β subunit. Resulting heterodimer translocates to the nucleus and binds to the HIF binding site within the element responsible for hypoxia. Together with cAMP response element-binding protein/p300 (CBP/p300) regulates the expression of genes responsible for erythropoiesis. As the HIF-α subunit consists of HIF-1α and HIF-2α, recent research shows that HIF-2α is more responsible for the synthesis of EPO [69,85,94].

Under hypoxic conditions (ischemia, anemia, tissue injury, high altitude) EPO is released into the bloodstream [12,78,96], circulates in plasma and binds to EPOr on erythroid progenitor cells in the bone marrow. This stimulates the survival, proliferation, and terminal differentiation of erythroid progenitor cells to mature red blood cells (RBCs) [36,88,96]. As a result, the oxygen-carrying capacity of the blood is increased which will then suppress the further production of EPO and thus close the feedback loop [12,36,78,88,96].

Since EPOr is expressed on different types of cells, EPO also exhibits non-hematopoietic effects [12,43,46,56,67,88]. It is actively involved in neuroprotection [12,77,88] and cardioprotection [12,44,88], modulation of immune response and has anti-inflammatory properties [12,13,88]. Furthermore, EPO promotes wound healing of skeletal muscle injuries, stimulates bone remodelling, regulates energy metabolism and inhibits adipogenesis and obesity [12,87,88,92,93]. Owing to its pleiotropic effects, EPO has been a topic of investigation for several fields, including sports medicine and sports sciences.

4. NATURAL METHODS OF ERYTHROPOIETIN STIMULATION

Exposure to high altitudes where oxygen levels is reduced causes a natural stimulation of EPO in humans to increase total blood volume (tBV) and total haemoglobin

mass(tHb) [83]. Wiel et al. [97] concluded that 1600 meters above sea level represents a threshold, since the human PO_2 is 70 mmHg (9.3 kPa) corresponding to a SaO_2 of 95%, after which further ascent to higher altitudes causes a further decrease in SaO_2 and increased red blood cell mass production. When person experience acute hypoxia, plasma EPO levels rise rapidly, peaking within 48 hours before declining despite continued hypoxia. This decline occurs prior to significant increases in red cell mass or arterial oxygen content. However, erythropoiesis persists, stabilizing at higher haematocrit levels with near-normal EPO levels (EPO paradox).

Prolonged exposure to hypobaric environment will make the physiological response even more effective [22]. Polycythaemia in mountain dwellers is the result of chronic exposure to high altitude and genetic inheritance [5]. For example, measurements have shown that mountain dwellers have an 11% increase in total haemoglobin mass at altitudes of 2600 m and 14% at 3550 m [9,37], while Sanchez et al. reported an 83% increase in total Hb mass in some highlanders [79]. It is interesting to note that, unlike the Aymara highlanders living in the Andes, the Hb concentration in Tibetans is much lower, but their physiological adaptations to hypoxia are different in the form of an increased ventilation response [5].

Long-term adaptation includes enhanced erythropoietic sensitivity, involving upregulation of EPOr and antiapoptotic mechanisms in bone marrow erythroid progenitors. Consequently, red blood cell production outpaces destruction, maintaining elevated haematocrit during prolonged high-altitude exposure. Red blood cells (RBCs) have a lifespan of approximately three months, so during prolonged high-altitude exposure as we mentioned above their breakdown occurs much more slowly than their production. This allows a sustained higher haematocrit level. A soluble EPO receptor (sEPOr) modulates EPO activity by binding to EPO in the bloodstream, limiting its interaction with EPOr. Lower sEPOr levels increase free EPO availability, enhancing erythropoiesis [12,91,96].

Although studies investigating chronic exposure to hypoxia are lacking, the available data suggest that time spent at a given altitude plays a role in increasing tHb mass and thus more efficient oxygen transport. A stay in the Himalayas resulted in a substantial increase in Hb of 40% after 126 days at altitudes of 5500m or after 1 year at 4550m, while Boning et al. measured an increase of 14% after 6 weeks at 5000m [9]. On the other hand, modest increases have been described after 6 months of long-term intermittent hypoxia at 3550 m [37,68], while Sawka et al did not see any changes in Hb at altitudes below 4000m over a 3-week period [81].

4.1. Training effects on haemoglobin

As we have previously stated, living at high altitudes stimulates erythropoiesis and increases the oxygen transport mechanism, thus enabling individuals to perform muscular work despite reduced partial pressure of oxygen [63]. Using such a climate for sports training and improving aerobic capacity is the basis of altitude training. Since in endurance sports the total Hb mass is associated with better VO_{2max} at least in lowlands, athletes have been reported to have a higher Hb mass by 35% than the general population, while athletes living at higher altitudes have an additional 14% increase [83].

Whether the effect of EPO will have an advantage for athletic performance at higher altitudes in an untrained population remains questionable. In particular, Young et al showed that an untrained group did not have a better VO_{2max} than a control group after infusion of 97g of haemoglobin before climbing to 4300m, indicating that the oxygen transport system is not the limiting factor in these conditions, but rather muscle training and its metabolic capacity [103]. On the other hand, studies have shown that training in normoxic conditions does not lead to an increase in tHb mass in untrained individuals and recreational athletes [33,34,71,86].

The question arises whether the increased tHb mass is a response to training or is due to something else, such as genetic inheritance. A study conducted on 6 male subjects by Martino et al showed above-average values of blood volume (92.3 mL/kg) and VO_{2max} (+62.5 mL/kg/1/min) in those who had not previously engaged in any sports activity [59]. In a longitudinal study, Schmidt et al. reported no significant changes in tHb mass in competitive athletes during and after their careers and decrease of training loads. [82]. The results obtained indicate that there are differences in the adaptation of trained athletes and untrained populations in hypoxic response and athletic performance at high altitudes.

4.2. High altitude as a tool for EPO boost

Over the years, various strategies have been developed to use hypoxic conditions as an athletic performance enhancer [29].

These strategies consist of different concepts that combine natural environmental conditions and/or artificially simulated climates such as live-high, train-Low (LH-TL) and live high, train high (LH-TH) [10,29,52].

The concept of "LH-TL", presented by Levine and Stray-Gunderson [51] was based on the advantages of staying at high altitudes for the purpose of acclimatization, and performing high-intensity training in normoxia conditions to avoid the effects of hypoxia on the athletic performance [52]. This way of preparation has become one of the main strategies for promoting haematological and non-haematological parameters. Many athletes are subjected to such models in order to increase EPO production and ultimately improve their athletic performance.

The concept of "LH-TH" is another popular method that advocates staying and training at high altitudes. Opinions about how effective the methods are and which method is superior are not clear. Namely, before a possible conclusion

about the usefulness, several issues run through the studies that are up for and against. Although both concepts have a positive haematological effect, the question is to what extent they have on VO_{2max}. Another problem is the use of interest groups of subjects, elite athletes, or non-elite athletes. The use of a standard protocol for measuring VO_{2max}, as well as the individual response to hypoxia are some of the problems of the research and thus the answer is unclear.

Recommendation for the duration of these protocols is to stay or simulate altitude above 2100m, optimally 2000-2500m [61] for 3–4 weeks and daily exposure to hypoxia for a period of 14h/day. Protocols with similar durations have led to a significant increase in Hb by 8-10% [48,75,84,99]. Altitudes above 3000m may contribute to a stronger haematological response but also an increased risk of altitude sickness and reduced athletic performance [16,22,61].

In addition to the general parameters of altitude and duration of hypoxia exposure, the hypoxic dose from Garvican et al 2016 was also used [31]. To make things easier for coaches and athletes, they proposed a formula for calculating how much hypoxia exposure is needed to trigger erythropoiesis where: km.h =(m/1,000) Based on their findings, they came to a value of 500km.h, which correlates with other studies in which tHb and EPO were measured, and the mean hypoxic dose was 578km.h [8].

4.3. The influence of testosterone on the hematopoietic system

Normal haematocrit level in men is 41 to 50%, while in women it is 36 to 44%, which makes a difference of approximately 13 to 14%. The association between the male sex hormone testosterone and higher erythrocyte and Hb concentration [4,60] has long been recognized.

Patients with type 2 diabetes have been shown to have an increased risk of developing anemia, which may be attributed to low testosterone levels [35], however it is possible that its influence on erythropoiesis is not directly related to the stimulation of EPO [72]. Although it was thought that testosterone has a direct influence on EPO synthesis that involves the transcriptional activation of erythropoietin EPO by androgens [66], another study suggests that testosterone suppresses hepcidin—a key regulator of iron metabolism and a mediator in EPO synthesis—thereby promoting erythropoiesis pathway [3].

Consistent with this, recent studies reach the same conclusions, which is connected with use of more modern methodologies. Namely, using the ELISA method, several studies have shown that the administration of testosterone in patients leads to an increase in the level of Hb and haematocrit but not EPO, which indicates the effect of androgens on another independent pathway [18,58].

5. EPO DOPING - THE PAST

Blood doping has been a controversial practice in sports for several decades and, despite increased testing and regulations, is likely to persist. Following the 1968 Olympic Games in Mexico City, where athletes competed at a high altitude, scientific interest intensified around the role of Hb concentration and the total amount of Hb in determining VO_{2max} and endurance performance.

In two studies conducted by Ekblom et al, it was clearly shown that an increase in Hb concentration resulted in a higher VO_{2max} and enhanced athletic performance [25,26,57,78]. In fact, a correlation was presented between tHb mass, BV and VO_{2max}, where an increase in tHb mass by 1g/kg results in an increase in VO_{2max} by 4.4 mL/kg/min. On the other hand, a change in BV by 1 mL/kg increases VO_{2max} by 0.7 mL/kg/min [2,17,33,82].

Animal studies confirmed this result. Laboratory rats that received recombinant human erythropoietin (rHuEPO) showed increased tolerance to lactate, greater transport of O2 to the brain and increased utilization of fatty acids and glycogen [50]. Based on their research, Birkeland and Wilber estimated a 5-10% improvement during the use of rHuEPO [7,98]. In the 1970s, there have already been reports of athletes utilizing blood transfusions as part of their training and competition strategies [26,91]. In the 1980s, blood transfusions use became widespread, with the 1984 Olympic games scandal being the most known one. The USA cycling team has secured nine medals after seven out of the 24 members underwent homologous blood doping. All types of blood doping have officially banned since 1984.

However, the introduction of rHuEPO to the European market in 1987 quickly raised concerns within the sports community. Recognizing the significant advantage it could offer in endurance sports (and the potential for misuse) the International Olympic Committee (IOC) Medical Commission took action and by 1990, the IOC officially banned the use of rHuEPO [30,73]. Despite the imposed ban, the illicit use of rHuEPO has been implied in many deaths among top European cyclists, such as the unverified reports linked to deaths of Danish cyclists due to rHuEPO abuse in 1989 [15].

In the late 1990s during and after the 1998 Tour de France (TDF), there was a series of doping incidents (known as Festina affair) where the Festina team cyclists used different substances including erythropoietin. Subsequently, they were ejected from the race and criminally prosecuted [24].For example, in 16 TDF races (1998 to 2013), only four winners had a negative doping test in their careers, and in that period, 38% of the top 10 places were filled by riders who had a positive doping test and were sanctioned by an organization in the past.

In the 2000s, Lance Armstrong, one of the greatest cyclists of all time and seven times TDF winner, was stripped off all titles and banned for life by the United States Anti-Doping Agency (USADA) after evidence confirmed

usage of EPO and other prohibited substances [39]. The name of the late Italian racer and TDF winner Marco Pantani also surfaces, with reports repeatedly reporting a haematocrit level of over 50% (57.6%) and leading him to suspect EPO abuse [20].

In the Operation Puerto doping case, which involved many elite cyclists and other athletes such as tennis players and soccer players, illegal substances were discovered. A scandal that once again shook the world of professional sports, where in addition to the athletes themselves, their doctors were also involved. In this case, it is about Emilio Fuentes physician, who was arrested in the same operation in 2006, because 186 bags of blood plasma were found in his clinic that were tested for high doses of EPO, labelled for athletes.

In the world of women's skiing, three female competitors were disqualified during the 2002 Winter Olympic Games because of a positive result for "darbepoetin alfa", an analogue of rHuEPO with a longer half-life [27].

5.1. EPO doping – the present

The World Anti-Doping Agency (WADA) bans compounds as performance-enhancing drugs (PEDs) if they meet two out of three main criteria: they enhance athletic performance, they pose a risk to athlete health, or they contravene the principles or integrity of sport [95]. EPO doping remains a significant concern in endurance sports today, though advancements in testing have made it harder for athletes to use EPO and remain undetected (see Table 1).

EPO detection in anti-doping relies on both direct and indirect approaches. Direct method involves analysis of blood and urine samples to detect synthetic rHuEPO. This method exploits differences in the charge and structure of EPO isoforms, effectively distinguishing natural (endogenous) EPO produced by the body from synthetic (recombinant) rHuEPO introduced externally [19,38,39,74,102]. The indirect method introduced is the Athlete Biological Passport (ABP), which tracks changes in markers of erythropoiesis, such as haemoglobin levels and reticulocyte count, revealing potential doping through atypical fluctuations [6,80,90].

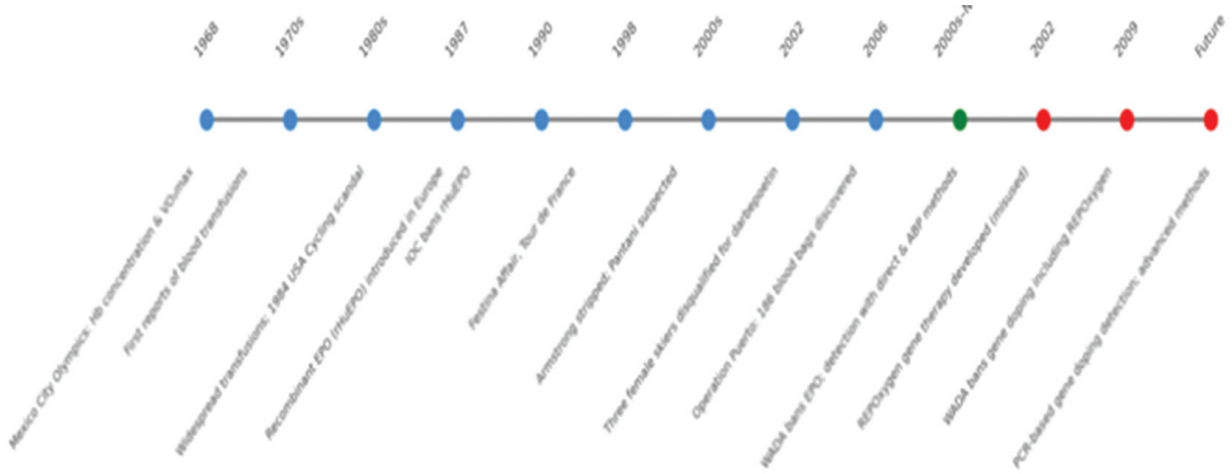
5.2. EPO doping – the future

EPO doping is expected to remain a challenge in sports due to its performance-enhancing effects, especially in endurance sports. With technological progress, the doping methods will become more advanced, with gene doping being the most prominent. In gene doping, the introduction of genetic material into cells and tissues is facilitated through the use of various delivery systems or vectors [11]. In 2002, REPOxygen was developed as a novel treatment modality for anemia in oncologic patients. The drug is administered through intramuscular injection and employs a viral vector to deliver a modified version of the human EPO gene. This gene is regulated by elements that oversee oxygen homeostasis, including HIF-1 and HIF-2. The expression of the EPO transgene is triggered when oxygen levels drop, promoting increased erythropoiesis to enhance oxygen transport in the body. Once oxygen concentrations return to normal, the transgene's activity is suppressed, effectively turning off further EPO production. In the early 2000s, it was administered in Germany to young female runners to maintain steady EPO expression in muscle cells. This drug has been banned by WADA in 2009 [11,14].

Apart from REPOxygen as a HIF-1 stabilizer, daprodustat, roxadustat, or vadadustat acts as prolyl hydroxylase inhibitors stabilizing HIF. With the completion

Table 1. Comparison of different erythropoietin (EPO) stimulation methods.
Tablica 1. Usporedba različitih metoda stimulacije eritropoetina (EPO)

Method	Natural Altitude-EPO	Synthetic EPO	Gene Doping
Mechanism	Hypoxia activates natural EPO via HIF	Injection of rHuEPO triggers erythropoiesis	Gene enhanced expression of EPO or HIF
Start and Duration	Slow, peaks after a day or two; effects last 3 to 4 weeks	Immediate increase in concentration, effects lasts several weeks	Maybe contiunous, life long?
Effects	Moderate, 3-5% in aerobic capacity?	Large, 5 to 10% in aerobic capacity?	The extent not known
Risks	In some: mountain sickness	Blood clots, hypertension	Still not known, in case of strong response possibility of blood clots
Ethics	allowed	banned	banned (still hard to detect)



Picture 1. EPO doping timeline; past – present – future.
Slika 1. Vremenska crta EPO dopinga: prošlost – sadašnjost – budućnost.

of Phase II clinical trials, this new class of oral agents offers an additional therapeutic option for patients suffering from anemia associated with chronic kidney disease [76].

Additional therapeutic alternatives exist that are not directly linked to erythropoietin (EPO) production but can still stimulate erythropoiesis—such as hepcidin antagonists. Since hepcidin regulates iron availability and thereby influences red blood cell formation [53], these agents could offer novel treatment pathways for iron deficiency disorders. However, their potential to enhance erythropoiesis also raises concerns about misuse in competitive sports."

The current and main approach for detecting doping genes in athletes' blood relies on polymerase chain reaction (PCR) techniques. This method targets specific, unique sequences found within doping genes. PCR assays are designed to detect complementary DNA (cDNA) of genes such as human erythropoietin (EPO), insulin-like growth factor-1 (IGF-1), growth hormone (GH), growth hormone-releasing hormone (GHRH), and follistatin [21]. However, additional approaches have been reported in the literature [23,53], predominantly considering the challenges related with detecting gene doping, as transgene-derived proteins are molecularly indistinguishable from their endogenous counterparts.

6. CONCLUSION

In conclusion, EPO plays a critical role in regulating red blood cell production and exhibits diverse biological functions beyond haematopoiesis. While its physiological importance is undeniable, the misuse of EPO and related biotechnological advancements, such as recombinant EPO and gene doping, pose significant ethical and regulatory challenges in sports. Current anti-doping efforts, including direct and indirect detection methods, have improved but face ongoing challenges due to technological innovations. Continued research and robust testing strategies are essential to address the evolving landscape of doping and maintain fairness in competitive sports.

References

1. Alnaeeli M et al. Erythropoietin in brain development and beyond. Anat Res Int. 2012;2012:953264.
2. Astrand, Per-Olof. Experimental studies of physical working capacity in relation to sex and age / Per-Olof Astrand Xerox University Microfilms Ann Arbor, Mich. 1952 p 39-59.
3. Bachman E et al. Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. J Clin Endocrinol Metab. 2010 Oct;95(10):4743-7.
4. Basaria S et al. Adverse events associated with testosterone administration. N Engl J Med. 2010 Jul 8;363(2):109-22.
5. Beall CM. Tibetan and Andean patterns of adaptation to high-altitude hypoxia. Hum Biol. 2000 Feb;72(1):201-28.
6. Bejder J et al. Detection of erythropoietin misuse by the Athlete Biological Passport combined with reticulocyte percentage. Drug Test Anal. 2016 Oct;8(10):1049-1055.
7. Birkeland KI et al. Effect of rhEPO administration on serum levels of sTfR and cycling performance. Med Sci Sports Exerc. 2000 Jul;32(7):1238-43.
8. Bonato G, Goodman SPJ, Tjh L. Physiological and performance effects of live high train low altitude training for elite endurance athletes: A narrative review. Curr Res Physiol. 2023 Nov 25;6:100113.
9. Böning D et al. Hemoglobin mass and peak oxygen uptake in untrained and trained residents of moderate altitude. Int J Sports Med. 2001 Nov;22(8):572- 8
10. Brocherie F et al. "Live High-Train Low and High" Hypoxic Training Improves Team-Sport Performance. Med Sci Sports Exerc. 2015 Oct;47(10):2140-9.
11. Brzeziańska E, Domańska D, Jegier A. Gene doping in sport - perspectives and risks. Biol Sport. 2014 Dec;31(4):251-9.
12. Bunn HF. Erythropoietin. Cold Spring Harb Perspect Med. 2013 Mar 1;3(3):a011619.
13. Cantarelli C, Angeletti A, Cravedi P. Erythropoietin, a multifaceted protein with innate and adaptive immune modulatory activity. Am J Transplant. 2019 Sep;19(9):2407-2414.
14. Cantelmo RA et al. Gene doping: Present and future. Eur J Sport Sci. 2020 Sep;20(8):1093-1101.
15. Catlin, D.H., Hatton, C.K., Lasne, F. (2003). Abuse of recombinant erythropoietins by athletes. In: Molineux, G., Foote, M.A., Elliott, S.G. (eds) Erythropoietins and Erythropoiesis. Milestones in Drug Therapy MDT. Birkhäuser Basel.
16. Chen X et al. Mechanism, prevention and treatment of cognitive impairment caused by high altitude exposure. Front Physiol. 2023 Sep 4;14:1191058.
17. Convertino VA. Blood volume: its adaptation to endurance training. Med Sci Sports Exerc 1991: 23: 1338–1348.
18. Coviello AD et al. (2008) Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab 93, 914–919.
19. Cox HD et al. Tracking immature reticulocyte proteins for improved detection of recombinant human erythropoietin (rhEPO) abuse. Am J Hematol. 2021 Dec 1;96(12): 1621-1629.
20. Dauncey and Hare 2003 The Tour de France 1903-2003: a Century of Sporting Structures, Meanings and Values, January 2003, Routledge.
21. de Boer EN et al. A next-generation sequencing method for gene doping detection that distinguishes low levels of plasmid DNA against a background of genomic DNA. Gene Ther. 2019 Aug;26(7-8):338-346.
22. Deng L et al. Impact of Altitude Training on Athletes' Aerobic Capacity: A Systematic Review and Meta-Analysis. Life (Basel). 2025 Feb 17;15(2):305.
23. Durussel J et al. Blood transcriptional signature of recombinant human erythropoietin administration and implications for antidoping strategies. Physiol Genomics. 2016 Mar;48(3):202-9.
24. Eichner ER. Blood doping : infusions, erythropoietin and artificial blood. Sports Med. 2007;37(4-5):389-91.
25. Ekblom B, Goldbarg AN, Gullbring B. Response to exercise after blood loss and reinfusion. J Appl Physiol. 1972 Aug;33(2):175-80.
26. Ekblom B, Wilson G, Astrand PO. Central circulation during exercise after venesection and reinfusion of red blood cells. J Appl Physiol. 1976 Mar;40(3):379-83.
27. Elliott S. Erythropoiesis-stimulating agents and other methods to enhance oxygen transport. Br J Pharmacol. 2008 Jun;154(3):529-41.
28. Fandrey J. Oxygen-dependent and tissue-specific regulation of erythropoietin gene expression. Am J Physiol Regul Integr Comp Physiol. 2004 Jun;286(6):R977-88.
29. Faulkner JA, Daniels JT, Balke B. Effects of training at moderate altitude on physical performance capacity. J Appl Physiol. 1967 Jul;23(1):85-9.
30. Fitch KD. Blood doping at the Olympic Games. J Sports Med Phys Fitness. 2017 Nov;57(11):1526-1532.
31. Garvican-Lewis LA, Sharpe K, Gore CJ. Time for a new metric for hypoxic dose? J Appl Physiol (1985). 2016 Jul 1;121(1):352-5.
32. Gong B et al. Glycosylation characterization of recombinant human erythropoietin produced in glycoengineered Pichia pastoris by mass spectrometry. J Mass Spectrom. 2013 Dec;48(12):1308-17.
33. Gore CJ et al. Vo2max and haemoglobin mass of trained athletes during high intensity training. Int J Sports Med 1997: 18:477–482.
34. Green HJ et al. Response of red cell and plasma volume to prolonged training in humans. J Appl Physiol (1985). 1991 Apr;70(4):1810-5.
35. Grossmann M et al. (2009) Low testosterone and anemia in men with type 2 diabetes. Clin Endocrinol (Oxf). 70, 547–553.
36. Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. Blood Rev. 2013 Jan;27(1):41-53.

37. Heinicke K et al. Blood volume and hemoglobin mass in elite athletes of different disciplines. Int J Sports Med. 2001 Oct;22(7):504-12.
38. Heiland CE et al. Optimizing detection of erythropoietin receptor agonists from dried blood spots for anti-doping application. Drug Test Anal. 2022 Aug;14(8):1377-1386.
39. Heuberger JAAC et al. Sensitivity and specificity of detection methods for erythropoietin doping in cyclists. Drug Test Anal. 2019 Sep;11(9):1290-1301.
40. Heuberger JAAC et al. Erythropoietin doping in cycling: lack of evidence for efficacy and a negative risk-benefit. Br J Clin Pharmacol. 2013 Jun;75(6):1406-21.
41. Ho MS et al. The dynamics of adult haematopoiesis in the bone and bone marrow environment. Br J Haematol. 2015 Aug;170(4):472-86.
42. Jacobs K et al. Isolation and characterization of genomic and cDNA clones of human erythropoietin. Nature. 1985 Feb 28-Mar 6;313(6005):806-10.
43. Jelkmann W. Physiology and pharmacology of erythropoietin. Transfus Med Hemother. 2013 Oct;40(5):302-9.
44. Kimáková P et al. Erythropoietin and Its Angiogenic Activity. Int J Mol Sci. 2017 Jul 13;18(7):1519.
45. Kobayashi H et al. Studies on novel HIF activators, A-503451sII: biological activities of A-503451A. J Antibiot (Tokyo). 2016 Oct;69(10):754-758.
46. Korzeniewski SJ, Pappas A. Endogenous Erythropoietin. Vitam Horm. 2017;105:39-56.
47. Lai PH et al. Structural characterization of human erythropoietin. J Biol Chem. 1986 Mar 5;261(7):3116-21.
48. Laitinen H et al. Acclimatization to living in normobaric hypoxia and training in normoxia at sea level in runners. Med Sci Sports Exerc 1995:27: 109
49. Lando D et al. FIH-1 is an asparaginyl hydroxylase enzyme that regulates the transcriptional activity of hypoxia-inducible factor. Genes Dev. 2002 Jun 15;16(12):1466-71.
50. Lavoie C et al. Erythropoietin (rHuEPO) doping: effects of exercise on anaerobic metabolism in rats. Int J Sports Med. 1998 May;19(4):281-6.
51. Levine BD, Stray-Gundersen J. A practical approach to altitude training: where to live and train for optimal performance enhancement. Int J Sports Med. 1992 Oct;13 Suppl 1:S209-12.
52. Levine BD, Stray-Gundersen J. "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. J Appl Physiol (1985). 1997 Jul;83(1):102-12.
53. Li R et al. Gene doping detection in the era of genomics. Drug Test Anal. 2024 Feb 25.
54. Lin CS et al. Differential effects of an erythropoietin receptor gene disruption on primitive and definitive erythropoiesis. Genes Dev. 1996 Jan 15;10(2):154-64.
55. Lin FK et al. Cloning and expression of the human erythropoietin gene. Proc Natl Acad Sci U S A. 1985 Nov;82(22):7580-4.
56. Lombardero M, Kovacs K, Scheithauer BW. Erythropoietin: a hormone with multiple functions. Pathobiology. 2011;78(1):41-53.
57. Lundby C, Robach P, Saltin B. The evolving science of detection of 'blood doping'. Br J Pharmacol. 2012 Mar;165(5):1306-15.
58. Maggio M et al. (2012). Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. Andrology, 1(1), 24–28.
59. Martino M, Gledhill N, Jamnik V. High VO2max with no history of training is primarily due to high blood volume. Med Sci Sports Exerc 2002: 34: 966–971
60. Merza Z et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. Int J Androl. 2006 Jun;29(3):381-91.
61. Millet GP, Brocherie F. Hypoxic Training Is Beneficial in Elite Athletes. Med Sci Sports Exerc. 2020 Feb;52(2): 515-518.
62. Nagai A et al. Erythropoietin and erythropoietin receptors in human CNS neurons, astrocytes, microglia, and oligodendrocytes grown in culture. J Neuropathol Exp Neurol. 2001 Apr;60(4):386-92.
63. Neya M et al. Increased hemoglobin mass and VO2max with 10 h nightly simulated altitude at 3000 m. Int J Sports Physiol Perform. 2013 Jul;8(4):366-72.
64. Palis J. Primitive and definitive erythropoiesis in mammals. Front Physiol. 2014 Jan 28;5:3.
65. Palis J, Koniski A. Functional Analysis of Erythroid Progenitors by Colony-Forming Assays. Methods Mol Biol. 2018;1698:117-132.
66. Pelekanou V et al. Testosterone membrane-initiated action in breast cancer cells: Interaction with the androgen signaling pathway and EPOR. Mol Oncol. 2010 Apr;4(2):135-49.
67. Peng B et al. Erythropoietin and its derivatives: from tissue protection to immune regulation. Cell Death Dis. 2020 Feb 3;11(2):79.
68. Prommer N et al. Total hemoglobin mass--a new parameter to detect blood doping? Med Sci Sports Exerc. 2008 Dec;40(12):2112-8.
69. Rankin EB et al. Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. J Clin Invest. 2007 Apr;117(4):1068-77.
70. Rankin EB et al. The HIF signaling pathway in osteoblasts directly modulates erythropoiesis through the production of EPO. Cell. 2012 Mar 30;149(1):63-74.
71. Ray CA, Cureton KJ, Ouzts HG. Postural specificity of cardiovascular adaptations to exercise training. J Appl Physiol (1985). 1990 Dec;69(6):2202-8.
72. Rishpon-Meyerstein N et al. The effect of testosterone on erythropoietin levels in anemic patients. Blood. 1968 Apr;31(4):453-60.
73. Robinson N et al. Erythropoietin and blood doping. Br J Sports Med. 2006 Jul;40 Suppl 1(Suppl 1):i30-4.

74. Rocca A et al. A fast screening method for the detection of CERA in dried blood spots. Drug Test Anal. 2022 May;14(5):820-825.
75. Rusko HK, Tikkanen HO, Peltonen JE. Altitude and endurance training. J Sports Sci. 2004 Oct;22(10):928-44; discussion 945.
76. Sackeyfio A et al. Comparison of outcomes on hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) in anaemia associated with chronic kidney disease: network meta-analyses in dialysis and non-dialysis dependent populations. Clin Kidney J. 2023 Dec 7;17(1):sfad298.
77. Sakanaka M et al. In vivo evidence that erythropoietin protects neurons from ischemic damage. Proc Natl Acad Sci U S A. 1998 Apr 14;95(8):4635-40.
78. Salamin O et al. Erythropoietin as a performance-enhancing drug: Its mechanistic basis, detection, and potential adverse effects. Mol Cell Endocrinol. 2018 Mar 15;464:75-87.
79. Sanchez-Medal L , L Duarte L, Labardini J. Hemolysis and Erythropoiesis. VI. A Comparative Study of the Utilization of Hemoglobin Iron and Transferrin Iron by the Erythropoietic Tissue, Blood,Volume 35, Issue 5,1970, Pages 721-726.
80. Saugy JJ, Schmoutz T, Botrè F. Altitude and Erythropoietin: Comparative Evaluation of Their Impact on Key Parameters of the Athlete Biological Passport: A Review. Front Sports Act Living. 2022 Jun 30;4:864532.
81. Sawka MN et al. Blood volume: importance and adaptations to exercise training, environmental stresses, and trauma/sickness. Med Sci Sports Exerc. 2000 Feb;32(2):332-48.
82. Schmidt W et al. Blood volume, not hemoglobin concentration is related to VO2 max in endurance athletes. Med Sci Sports Exerc 1999: 31: S50.
83. Schmidt W, Prommer N. Effects of various training modalities on blood volume. Scand J Med Sci Sports. 2008 Aug;18 Suppl 1:57-69.
84. Schmidt-Kastner R et al. Hypoxia-Inducible Factor-1 (Hif-1) in Experimental Brain Ischemia. ScientificWorldJournal. 2002 Apr 9;2:123-124.
85. Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol. 1992 Dec;12(12):5447-54.
86. Shoemaker JK et al. Failure of prolonged exercise training to increase red cell mass in humans. Am J Physiol. 1996 Jan;270(1 Pt 2):H121-6.
87. Suresh S, Lee J, Noguchi CT. Effects of Erythropoietin in White Adipose Tissue and Bone Microenvironment. Front Cell Dev Biol. 2020 Nov 24;8:584696.
88. Tsiftsoglou AS. Erythropoietin (EPO) as a Key Regulator of Erythropoiesis, Bone Remodeling and Endothelial Transdifferentiation of Multipotent Mesenchymal Stem Cells (MSCs): Implications in Regenerative Medicine. Cells. 2021 Aug 20;10(8):2140.
89. Urrutia AA et al. Prolyl-4-hydroxylase 2 and 3 coregulate murine erythropoietin in brain pericytes. Blood. 2016 Nov 24;128(21):2550-2560.
90. Vernec AR. The Athlete Biological Passport: an integral element of innovative strategies in antidoping. Br J Sports Med. 2014 May;48(10):817-9.
91. Vizcardo-Galindo G, León-Velarde F, Villafuerte FC. High-Altitude Hypoxia Decreases Plasma Erythropoietin Soluble Receptor Concentration in Lowlanders. High Alt Med Biol. 2020 Mar;21(1):92-98.
92. Wan L et al. EPO promotes bone repair through enhanced cartilaginous callus formation and angiogenesis. PLoS One. 2014 Jul 8;9(7):e102010.
93. Wang L, Di L, Noguchi CT. Erythropoietin, a novel versatile player regulating energy metabolism beyond the erythroid system. Int J Biol Sci. 2014 Aug 23;10(8):921-39.
94. Warnecke C et al. (2004) Differentiating the functional role of hypoxia-inducible factor (HIF)-1α and HIF-2α (EPAS-1) by the use of RNA interference: erythropoietin is a HIF-2α target gene in Hep3B and Kelly cells. The FASEB journal, 18(12), 1462-1464.
95. Watson CJ et al. Performance-enhancing drugs and the Olympics. J Intern Med. 2022 Feb;291(2):181-196.
96. Watts, D et al. Hypoxia Pathway Proteins are Master Regulators of Erythropoiesis. Int. J. Mol. Sci. 2020, 21, 8131.
97. Weil JV et al. Hypoxic ventilatory drive in normal man. J Clin Invest. 1970 Jun;49(6):1061-72.
98. Wilber RL. Detection of DNA-recombinant human epoetin-alfa as a pharmacological ergogenic aid. Sports Med. 2002;32(2):125-42.
99. Wilber RL, Stray-Gundersen J, Levine BD. Effect of hypoxic "dose" on physiological responses and sea-level performance. Med Sci Sports Exerc. 2007 Sep;39(9): 1590-9.
100. Wu H et al. Generation of committed erythroid BFU-E and CFU-E progenitors does not require erythropoietin or the erythropoietin receptor. Cell. 1995 Oct 6;83(1):59-67.
101. Wu H et al. Inactivation of erythropoietin leads to defects in cardiac morphogenesis. Development. 1999 Aug;126(16):3597-605.
102. Yasuoka Y et al. Progress in the Detection of Erythropoietin in Blood, Urine, and Tissue. Molecules. 2023 May 30;28(11):4446.
103. Young AJ et al. Effects of erythrocyte infusion on VO2max at high altitude. J Appl Physiol (1985). 1996 Jul;81(1):252-9.
104. Zanjani ED et al. Studies on the liver to kidney switch of erythropoietin production. J Clin Invest. 1981 Apr;67(4):1183-8.