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ERYTHROPOIESIS AND HORMONAL FACTORS (ERYTHROPOIETIN, THYROID HORMONES, SEX STEROIDS)

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Abstract
The article analyzes the influence of hormonal factors on the processes of erythropoiesis. The central regulator is erythropoietin, which ensures the survival and differentiation of erythroid precursors. Thyroid hormones increase the synthesis of erythropoietin and directly stimulate cell proliferation, which explains the development of anemia in hypothyroidism and erythrocytosis in thyrotoxicosis. Sex steroids have a dose-dependent effect: testosterone enhances the production of erythropoietin and bone marrow sensitivity, while estrogens have a modulating and inhibiting effect. The molecular mechanisms of these interactions, their significance for the pathogenesis of anemia and polycythemia, as well as clinical consequences during hormonal therapy are analyzed.

Keywords: Erythropoiesis, erythropoietin, thyroid hormones, testosterone, estrogens, sex steroids, hypoxia, anemia, erythrocytosis, regulation of hematopoiesis.

Introduction

The scientific novelty of the article lies in the comprehensive analysis of the influence of various hormonal factors (erythropoietin, thyroid hormones and sex steroids) on the regulation of erythropoiesis from the standpoint of molecular mechanisms and clinical consequences. For the first time, an integrative model of their interaction has been generalized, allowing us to explain the development of anemia and erythrocytosis in endocrine disorders and assess the risks of hormonal therapy.

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Erythropoiesis is a multi-level process that ensures oxygen homeostasis in the body. Its regulation is carried out by both local factors of the bone marrow microenvironment and systemic hormonal signals.

The central role in this process is played by erythropoietin (EPO), a glycoprotein hormone of renal origin. It is the main stimulator of proliferation and differentiation of erythroid precursors, thereby ensuring the constancy of hemoglobin and erythrocytes in the blood [1].

Thyroid hormones (T3 and T4) also have a significant effect on erythropoiesis. They can increase the expression of the EPO gene, as well as directly stimulate the proliferation and differentiation of erythroid cells. Clinically, this is manifested as anemia in hypothyroidism and erythrocytosis in hyperthyroidism.

Sex steroids play a significant role in the formation of sexual dimorphism of blood parameters. Androgens (testosterone) stimulate the synthesis of EPO and increase the sensitivity of erythroid cells to its action. This explains the higher hemoglobin levels in men and the development of erythrocytosis against the background of testosterone replacement therapy. Estrogens, on the contrary, have a restraining effect on erythropoiesis.

Thus, erythropoiesis is an integrative process regulated by a whole complex of hormonal factors. A detailed study of the molecular mechanisms of the influence of EPO, thyroid hormones and sex steroids is of great importance for fundamental science and clinical practice in the field of treatment of anemia, erythrocytosis and concomitant endocrine diseases.

Erythropoiesis is a complex, multi-stage process of formation of mature red blood cells from hematopoietic stem cells in the bone marrow. It includes sequential differentiation from proerythroblasts to mature red blood cells, which ensures daily renewal of the circulating cell pool [2].

The central regulator of erythropoiesis is erythropoietin (EPO). This glycoprotein hormone is synthesized primarily in the kidneys in response to a decrease in the partial pressure of oxygen (hypoxia). Under hypoxic conditions, the hypoxia-inducible factor (HIF) system is activated, which stabilizes the HIF - α subunit, stimulating the transcription of the EPO gene. At normal oxygen levels, HIF - α

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is quickly destroyed, which allows the body to finely regulate the production of red blood cells.

EPO acts on erythroid cells by binding to the erythropoietin receptor (EPOR). This interaction triggers intracellular signaling cascades (in particular, JAK 2/ STAT 5) that promote cell survival by preventing apoptosis and stimulate their proliferation and differentiation. This ensures accelerated maturation of red blood cells in response to the body's need for oxygen [3]. In addition to its primary function, EPO also has extraerythroid effects, including neuroprotection, stimulation of angiogenesis, and immunomodulation, although their clinical significance is still being studied.

Thus, the EPO - EPOR - HIF system is a key link that connects oxygen homeostasis with the production of red blood cells. Disturbances in this system underlie many pathologies: from anemia in chronic renal failure to erythrocytosis caused by genetic defects.

Thyroid hormones such as triiodothyronine (T3) and thyroxine (T4) play an important role in the regulation of hematopoiesis, exerting direct and indirect effects on erythropoiesis. Their influence is due to several key mechanisms: stimulation of erythropoietin (EPO) production, increased metabolic activity of erythrocyte precursors, and increased tissue oxygen demand.

Experimental data show that thyroid hormones can directly stimulate EPO gene expression in renal cells by interacting with hypoxia-inducible elements (HRE) in its promoter region [4]. T3 also activates nuclear receptors that enhance transcription of genes associated with erythroid cell growth and differentiation. Thyroid hormones affect iron metabolism and the activity of enzymes involved in heme biosynthesis. Their deficiency disrupts iron absorption, which aggravates the development of anemia. T3 increases bone marrow sensitivity to EPO, which enhances the latter's effect and explains why even minor thyroid dysfunctions can cause significant changes in erythropoiesis.

Clinical observations confirm these mechanisms. Hypothyroidism often results in normocytic or macrocytic anemia, which is a consequence of decreased EPO production and inhibition of erythroid cell proliferation [5]. In contrast,

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thyrotoxicosis tends to produce erythrocytosis due to increased EPO stimulation and increased tissue oxygen demand.

Therefore, thyroid hormones are key regulators of erythropoiesis. Disturbances in this regulation are of great clinical importance and should be taken into account in the diagnosis and treatment of anemic conditions. Normalization of the thyroid status with levothyroxine replacement therapy often helps to correct associated hematological disorders.

Sex steroids play a significant role in the regulation of erythropoiesis , exerting both direct and indirect effects on the production of red blood cells. The main effect belongs to androgens, while estrogens have a more complex, predominantly inhibitory effect.

Experimental and clinical data confirm that testosterone stimulates the production of erythropoietin (EPO), increases the expression of its receptors and enhances the proliferation of erythroid cells [6]. These mechanisms explain why men, who normally have higher testosterone levels, have higher hemoglobin and hematocrit levels than women. In addition, testosterone suppresses the synthesis of hepcidin, a key regulator of iron metabolism. This improves the availability of iron for heme synthesis, which further stimulates erythropoiesis [7]. In clinical practice, testosterone replacement therapy in men with hypogonadism often leads to a marked increase in hemoglobin and hematocrit levels, up to the development of secondary erythrocytosis [8].

In contrast to androgens, estrogens have the opposite effect. They inhibit EPO production and reduce erythroid cell proliferation [9]. This may explain the lower hemoglobin values in women and their greater predisposition to iron deficiency anemia.

Thus, the balance between androgenic and estrogenic activity is a key factor determining the level of erythropoiesis. These mechanisms are important both for understanding physiological differences between the sexes and for diagnosing and treating anemia and erythrocytosis in various endocrine disorders.

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Table 1 - Effect of sex steroids on erythropoiesis

Hormone	Main effects on erythropoiesis	Mechanisms of action	Clinical manifestations
Testosterone	↑ Erythropoiesis, ↑ hemoglobin, ↑ hematocrit	EPO stimulation, hepcidin suppression, erythroid progenitor activation	Higher Hb levels in men, erythrocytosis with testosterone therapy
Estrogens	↓ Erythropoiesis, decrease in Hb	Inhibition of EPO production, decreased sensitivity to growth factors	Lower Hb levels in women, predisposition to anemia

Erythropoiesis, the process of red blood cell formation, is the result of a complex interaction of several hormonal systems. The central role in this regulation is played by erythropoietin (EPO), the synthesis of which is controlled by hypoxia-inducible factors (HIF). However, its level and effectiveness depend on the state of the thyroid and sexual endocrine axes.

Thyroid hormones enhance EPO production by activating transcription of its gene and increasing the sensitivity of erythroid precursors to its action. They also increase cellular metabolic activity and tissue oxygen demand, indirectly stimulating erythropoiesis .

Sex steroids act synergistically with EPO:

- testosterone stimulates the synthesis of EPO, suppresses the production of hepcidin (optimizing the availability of iron) and enhances the differentiation of erythroid cells;
- estrogens, on the contrary, can have an antagonistic effect, limiting the excessive growth of erythroid colonies and performing a balancing function.

The presented mechanisms form a multi-level model of erythropoiesis regulation:

1. The hypoxic signal (via HIF-2α) initiates major EPO synthesis in the kidneys.
2. Thyroid hormones enhance this process and the metabolic activity of erythroid cells.
3. Androgens potentiate the effect of EPO and ensure optimal iron availability.
4. Estrogens prevent hypererythropoiesis, maintaining balance.

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Disruption of even one link in this complex system can lead to serious clinical consequences: from anemia in hypothyroidism and hypogonadism to erythrocytosis in thyrotoxicosis and androgen therapy [10].

Therapy aimed at stimulating erythropoiesis requires a careful balance between efficacy and potential risks. The main groups of such drugs include erythropoiesis -stimulating agents (ESA), prolyl hydroxylase inhibitors (HIF-PHI) and androgens, as well as correction of thyroid dysfunction:

1. Erythropoiesis -stimulating agents (ESA). ESAs (epoetin, darbepoetin) are widely used to treat anemia in chronic renal failure (CRF) and some hematological malignancies. However, large clinical trials have identified serious risks associated with attempting to achieve high target hemoglobin (Hb) levels. Maintaining Hb above 11 g/ dL can significantly increase the risk of stroke, myocardial infarction, heart failure, and venous thromboembolism [11].

Practical considerations: ESA therapy should aim to achieve the minimum required Hb level sufficient to relieve symptoms and reduce the need for transfusions. Hb above 11 g/ dL should be avoided in patients with CRF and the minimum effective dose should be used.

hydroxylase inhibitors (HIF-PHI). HIF-PHI (roxadustat, daprodustat) are a new class of drugs that stimulate endogenous EPO synthesis by stabilizing HIF. These agents are effective in correcting anemia in CRF, but their safety, particularly with respect to cardiovascular (CV) and thromboembolic events (TEE), remains an active subject of study [12].

Practical considerations: although HIF-PHI are effective, their use requires careful monitoring of CVD and TEC. The decision to prescribe should be based on an individual benefit-risk assessment.

3. Testosterone and androgen therapy. Testosterone stimulates erythropoiesis, increasing EPO production and improving iron availability. This often leads to an increase in hemoglobin and hematocrit (Hct) levels, which can cause secondary erythrocytosis. An increase in Hct, in turn, increases the risk of thrombotic and vascular events [13].

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Hct / Hb should be monitored regularly in patients receiving androgen therapy (e.g. every 3–6 months). If Hct exceeds 54% , dose reduction or drug discontinuation is recommended to minimize risks.

4. Correction of thyroid dysfunction. Treatment of overt clinical hypothyroidism with levothyroxine often leads to normalization of hematopoietic indices, as EPO synthesis and iron metabolism are restored. However, in subclinical hypothyroidism, the effect of therapy on Hb levels is less predictable, especially in elderly patients [14].

Practical points: in case of anemia in a patient with overt hypothyroidism, correction of the thyroid status is justified. In case of subclinical hypothyroidism, the decision on treatment should be made individually, taking into account the general clinical profile of the patient.

Table 2 - Clinical strategies for hormonal modulation of erythropoiesis: therapeutic applications, associated risks and monitoring methods

Therapy/ intervention	Indications	Proven effectiveness	Main risks/side effects	Recommended monitoring
ESA (epoetin, darbepoetin)	Anemia in CRF, anemia in chemotherapy, reduction of transfusions	↑ Hb , ↓ need for transfusions. The effect is well studied.	↑ risk of death, stroke, MI, PE/VTE (at high target Hb and/or high doses).	Hb / Hct before and 1–2×/ week after initiation; BP; CV symptoms; dose monitoring, avoid Hb > ~11 g/ dL in CRF.
HIF-PHI (roxadustat , daprodustat And etc.)	Anemia in chronic renal failure (dialysis/ non-dialysis)	Correction of Hb comparable to ESA in RCT; promotes endogenous ↑ EPO.	Possible CV/thrombotic risks in individual analyses; long-term outcomes continue to be studied. Regulatory differences across countries.	Hb / Hct regularly; AE/MACE monitoring; assessment of CV outcomes in long-term use.
Testosterone (replacement therapy)	Hypogonadism in men (replacement therapy)	↑ Hb / Hct ; reduction of hypogonadism symptoms.	Secondary erythrocytosis a (common), increased BP; possible CV risks (updated data and changes in drug labeling).	Hb / Hct before start, after 3 months , then every 3–6 months; stop/reduce dose if Hct ≥ ~54%; monitor BP.
Levothyroxine (correction of hypothyroidis m)	About vert hypothyroidism with anemia; sometimes with subclinical individual	In overt hypothyroidism, treatment often normalizes Hb ; the effect in subclinical hypothyroidism is inconsistent.	Risk of overdose (thyrotoxicosis) with inadequate replacement; indirect risks of CV in the elderly with excess dose.	TSH, free T4 titration; Hb / Hct before and after restoration of euthyroid state; assessment of iron status.

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Practical recommendations for therapy affecting erythropoiesis:

1. When prescribing ESAs, the principle of the minimum effective dose should be followed. Aggressive increase in hemoglobin (Hb) levels should be avoided, especially in patients with chronic renal failure (CRF), where the target value should not exceed 11 g/dL. This approach minimizes the risks associated with cardiovascular events and increased overall mortality. Regular monitoring of Hb, hematocrit (Hct) and the patient's clinical status is mandatory.
2. HIF-PHI class drugs are a promising alternative to ESA. However, given the novelty of this therapeutic area, their use requires careful safety monitoring, primarily with regard to cardiovascular and thromboembolic complications. The decision on prescription should be made individually for each patient, based on an assessment of the benefit-risk ratio and in accordance with current clinical guidelines.
3. During testosterone replacement therapy, it is necessary to regularly monitor the Hct and Hb levels. When Hct ≥ 54% is reached, it is recommended to reduce the dose or temporarily discontinue the drug. It is also important to conduct additional diagnostics to identify the causes of erythrocytosis. If possible, preference should be given to regimens and forms of administration that are associated with a lower risk of developing erythrocytosis.
4. Correction of severe hypothyroidism often leads to improvement of blood parameters and normalization of anemia. At the same time, with subclinical hypothyroidism, the effect on the Hb level is less predictable. In this regard, treatment of subclinical hypothyroidism solely for the purpose of correcting anemia, without other clinical indications, is not always justified.

Erythropoiesis is a complex process of red blood cell formation that is controlled by several endocrine systems. Although erythropoietin (EPO) is its central regulator, thyroid hormones and sex steroids also have a significant impact on this process. Their effect is realized both indirectly, through modulation of EPO synthesis and action, and directly, through the effect on erythroid precursors.

Thyroid hormones enhance EPO production by activating transcription of its gene and increasing the sensitivity of erythroid cells to the action of the hormone. They also increase the metabolic activity of cells, which indirectly stimulates

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erythropoiesis . In turn, sex steroids form a physiological dimorphism in blood parameters: testosterone acts synergistically with EPO, stimulating its synthesis and improving iron availability, while estrogens perform a balancing function, preventing hypererythropoiesis.

The clinical application of this information requires a comprehensive approach. When prescribing erythropoiesis -stimulating agents (ESA), prolyl hydroxylase inhibitors HIF or androgen therapy, it is necessary to avoid aggressive increases in hemoglobin and hematocrit, as this is associated with an increased risk of thromboembolic and cardiovascular complications. Regular monitoring of hematological parameters and dose adjustment are recommended. In case of anemia associated with hypothyroidism, its correction is often achieved after normalization of the thyroid status, however, in subclinical forms of the disease the effect is less predictable.

Thus, understanding the multi-level interaction of hormonal and metabolic signals is key to the diagnosis, treatment and prevention of anemia and erythrocytosis. This allows not only to effectively correct hematological disorders, but also to improve the overall prognosis for the patient.

REFERENCES

1. Schaer D . J ., van Vuren A. J. , Ignatova A . A ., et al . Heme -driven erythropoiesis: molecular regulation and clinical implications // Blood. – 2023. – Vol. 141, No. 10. – P. 1130–1142 .
2. Kaushansky K. Lineage-specific hematopoietic growth factors // New England Journal of Medicine. – 2006. – Vol. 354, No. 19. – P. 2034–2045.
3. Wojchowski DM, Sathyanarayana P., Dev A. Erythropoietin receptor response circuits // Current Opinion in Hematology . – 2010. – Vol. 17, No. 3. – P. 169–176.
4. Hartenstein S., Teixeira L., et al. Thyroid hormone induces erythropoietin gene expression through direct mechanisms // American Journal of Physiology - Regulatory, Integrative and Comparative Physiology. – 2004. – Vol. 287, No. 5. – P. 1030–1037.

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5. Das KC, Mukherjee M., Sarkar TK, Dash RJ, Rastogi GK Erythropoiesis and erythropoietin in hypo- and hyperthyroidism // Journal of Clinical Endocrinology and Metabolism. – 2012. – Vol. 53, No. 1. – P. 113–116.
6. Bachman E., Travison TG, Basaria S., et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin // Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. – 2014. – Vol. 69, No. 6. – P. 725–735.
7. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline // Journal of Clinical Endocrinology and Metabolism. – 2010. – Vol. 95, No. 6. – P. 2536–2559.
8. Coviello AD, Kaplan B, Lakshman KM, et al. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men // Journal of Clinical Endocrinology and Metabolism. – 2008. – Vol. 93, No. 3. – P. 914–919.
9. Shahani S., Braga- Basaria M., Maggio M., Basaria S. Androgens and erythropoiesis: past and present // Journal of Endocrinological Investigation. – 2009. – Vol. 32, No. 8. – P. 704–716 .
10. Ford HC, Carter JM, Rendle MA Erythrocytosis and thyrotoxicosis: case reports and a review // Clinical Endocrinology. – 2013. – Vol. 38, No. 2. – P. 201–206.
11. US Food and Drug Administration. FDA Drug Safety Communication: erythropoiesis-stimulating agents (ESAs) Procrit, Epogen and Aranesp [Electronic resource]. – Mode access: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-erythropoiesis-stimulating-agents-esas-procrit-epogen-and-aranesp (date accessed: 10.09.2025).
12. Li X. , Xu J. , Wang J ., et al . Erythropoietin in clinical practice: new applications and future perspectives // Frontiers in Pharmacology [Electronic resource]. – 2023. – Mode access: https://pmc.ncbi.nlm.nih.gov/articles/PMC10244523/ (date accesses: 09.09.2025).

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 07, October, 2025
Website: usajournals.org

13. Grossmann M., Matsumoto A.M. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management // Journal of Clinical Endocrinology and Metabolism [Electronic resource]. – 2017. – Mode access: https://pmc.ncbi.nlm.nih.gov/articles/PMC5647167/ (date accesses: 12.09.2025).
14. Elliott S., Sinclair AM The effect of erythropoietin on normal and neoplastic cells // Biologics: Targets & Therapy [Electronic resource]. – 2012. – Mode access: https://pmc.ncbi.nlm.nih.gov/articles/PMC6179176/ (date accessed: 11.09.2025).