



An Overview of Iron Metabolism in Health and Disease

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i830888

Editor(s):

(1) Dr. Ashish Anand, GV Montgomery Veteran Affairs Medical Center, USA.

Reviewers:

(1) Kalinca da Silva Oliveira, Federal University of Health Sciences of Porto Alegre (UFCSPA), Brazil.
(2) Thomas Rolf Erdmann, Universidade Federal de Santa Catarina, Brazil.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/66724>

Review Article

Received 25 January 2021

Accepted 30 March 2021

Published 13 April 2021

ABSTRACT

Human iron metabolism is the set of chemical reactions that maintain human homeostasis of iron at the systemic and cellular level. Iron is both necessary to the body and potentially toxic. Controlling iron levels in the body is a critically important part of many aspects of human health and disease. Iron deficiency states are the reason for a decrease in working capacity, an increase in susceptibility to viral diseases, especially in children and cause growth and development retardation. Iron overload and poisoning lead to the activation of processes that can cause cell death. Timely diagnosis of disorders of iron metabolism and subsequent monitoring of treatment require knowledge of not only pathophysiological mechanisms, but also methodological capabilities and correct interpretation of clinical and biochemical parameters of iron metabolism.

Keywords: *Diagnosis; iron deficiency anemia; hemochromatosis; hepcidin; hemosiderin; transferrin; ferritin.*

1. INTRODUCTION

Iron is an essential metal for hemoglobin synthesis of erythrocytes, oxidation–reduction reactions, and cellular proliferation, whereas

excess iron accumulation causes organ dysfunction through the production of reactive oxygen species (ROS). The total amount of body iron is approximately 3–4 g, two-thirds of which is composed of red blood cell (RBC) iron and

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recycled iron by RBC destruction; the remainder is stored in ferritin/hemosiderin, while only 1–2 mg of iron are absorbed in the intestinal tract and circulated in the blood (Fig. 1) [1].

The key regulator of iron metabolism is the hepatic bactericidal protein (hepcidin), a hormone synthesized primarily in the liver. Hepcidin contains 25 amino acids, is rich in cysteine, with 4 disulfide bridges. Human hepcidin is derived from the portion of 84-amino acid precursor. The synthesis and secretion of hepcidin is controlled by three proteins:

HFE (hereditary hemochromatosis protein), hemojuvelin, transferrin receptor 2. Hepcidin is excreted in the urine, where it was first excreted. An excess of iron induces the synthesis of hepcidin by hepatocytes. Hepcidin inhibits intestinal absorption of iron, blocks the transport of iron everywhere, including internal epithelium, macrophages, placenta and other cell types, and the transfer of iron across the placenta [2].

Hepcidin induces the immersion of ferroportin into the cell cytoplasm, blocking the only pathway for iron transport from the cell (Fig. 2).

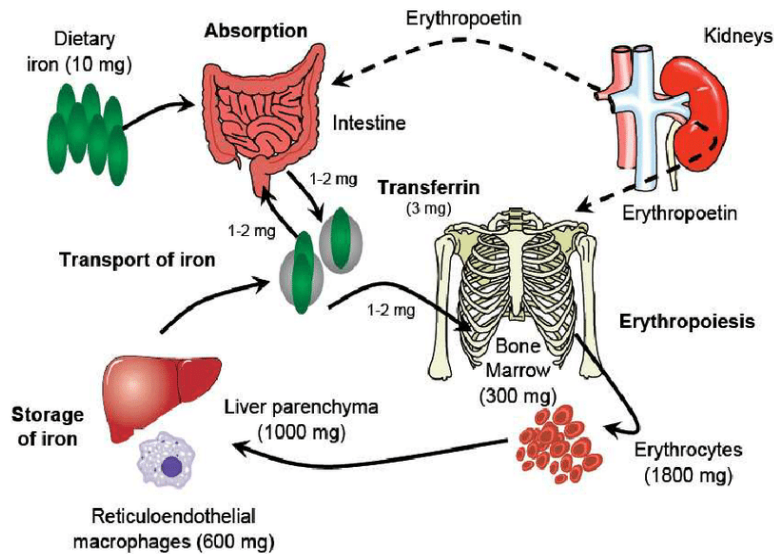


Fig. 1. The intestinal tract and circulated in the blood

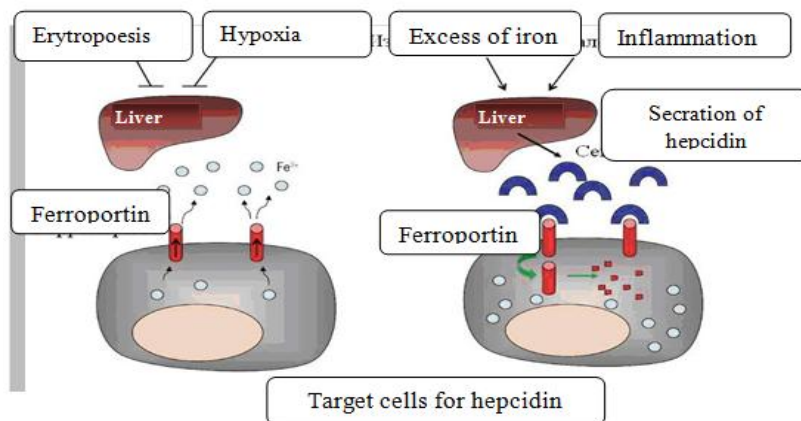


Fig. 2. Role of hepcidin in iron metabolism

Hepcidin is secreted by hepatocytes and Kupffer cells of the liver during iron overload and inflammation. Hepcidin causes the immersion of ferroportin into the cytoplasm of the cell, blocking the only pathway of iron transport from the cell

Hepcidin has antibacterial activity to gram-negative, gram-positive bacteria and antifungal activity. Like other antibacterial peptides, hepcidin is able to rupture the bacterial membrane, which is due to its structure: Hydrophilic (positively charged) and hydrophobic (negatively charged) [3].

Hepcidin is capable of destroying bacterial membranes, affecting the accumulation of iron by macrophages. In this case, microorganisms are deprived of the necessary component for the production of superoxide dismutase, which, in turn, protects them from the host's oxygen radicals. Decreased serum iron is an important defense mechanism to avoid inflammatory organ damage. In infections, this is also part of the immune strategy. Hepcidin inhibits the synthesis of IL-6 and TNF α in macrophages, and thus has an anti-inflammatory effect [4].

Bacteria and pathogen-specific macromolecules act on macrophages, including hepatic Kupffer cells, and induce increased production of IL-6. This cytokine, in turn, initiates the synthesis of hepcidin by hepatocytes through the induction of its mRNA. Simultaneously with increased expression of hepcidin, it increases serum ferritin and IL-6 levels. The same situation is observed with tumors: Anemia develops, hepcidin, ferritin and IL-6 levels increase [5].

The opposite situation occurs with anemia and hypoxia. The suppressive effect of hemolytic anemia on the production of hepcidin is observed even when the body is overloaded with iron, thus confirming that the requirements of erythropoiesis in the gland are a stronger stimulus than an excess of iron, which should cause hepcidin induction. This hierarchy of effects explains why hemosiderosis develops in hemolytic anemias. Since in such cases, a decrease in hepcidin production leads to an overload of the body with iron, only chelation therapy can prevent the increasing excess of iron [6].

People with hepcidin-producing adenomas develop iron deficiency anemia that is resistant to iron therapy. Mutations in the hepcidin gene are the cause of hemochromatosis. Overproduction of hepcidin during infection and inflammation may be responsible for anemia of inflammation or anemia of chronic disease. Inflammatory anemia is caused primarily by hepcidin-induced iron deposition in macrophages.

Transferrin is synthesized in liver cells and in small amounts in lymphoid tissue, mammary gland, testes and ovaries. It consists of one polypeptide chain and two hydrocarbon side regions. The normal serum concentration is about 2-4 g / L, which corresponds to about 4% of the total plasma protein. In addition to blood serum, under physiological conditions, transferrin is determined in lymph and tissue fluid, and under pathological conditions - in urine and effusion. Disorders of iron metabolism in patients can be associated with both its deficiency and overload. Iron deficiency is clinically manifested by iron deficiency anemia, overload - by hemochromatosis [7].

The main cause of iron deficiency in pathology is blood loss, usually from the gastrointestinal tract, urinary tract, especially in women, and relatively rarely - as a result of bleeding from the kidney or bladder. The clinical picture of latent or manifest iron deficiency resulting from blood loss can be easily identified from the patient's history or during a diagnostic examination. Men who donate blood 4 or more times and women who donate 2 or more times a year should be tested for ferritin once a year.

Iron deficiency can result from malabsorption in the intestine (after extensive resection of the small intestine, with chronic enteritis). Violation of the acid and enzyme-forming function of the stomach (atrophic gastritis) may be an additional cause of the development of iron deficiency. Iron deficiency in adolescents, especially girls, is aggravated by fasting. A limited diet often leads to the fact that only about half of the recommended amount of iron is consumed with food and this, naturally, when combined with the onset of menstruation, leads to iron deficiency. Endogenous iron deficiency can occur in chronic infections (tuberculosis), intoxications, hypovitaminosis (especially Chypovitaminosis) and malignant neoplasms [8].

Rarely, iron deficiency develops due to a lack of transferrin (hereditary atransferrinemia). Latent iron deficiency is typically found in long-distance swimmers. Occupational physical overload is, apparently, additional factors of hemolysis.

Most often, it becomes necessary to differentiate iron deficiency anemia from chronic anemias associated with tumors, infections, sideroblastic anemia, or thalassemia (Table 1).

Table 1. Laboratory indicators of primary and secondary iron deficiency

| | Iron | Trance ferrin | Saturation transferrin | Ferritin | Soluble transferrin receptors |
|--|-------------|----------------------|-------------------------------|-----------------|--------------------------------------|
| Primary iron deficiency in: - lack of food - impaired absorption - iron loss | Reduced | Increased | Reduced | Reduced | Increased |
| Secondary iron deficiency in: -infections -inflammation -tumors -continuous dialysis | Reduced | Normal or reduced | Reduced or normal | Increased | Normal |

The human body is not able to actively excrete iron. If the ability of these proteins to bind iron is exceeded, it begins to be deposited in the parenchymal organs. Iron poisoning, unlike iron deficiency, is relatively rare. This is a serious condition that can be life threatening. An increased ferritin content always accompanies iron overload. However, ferritin cannot be a differential diagnostic indicator of primary or secondary hemochromatosis. At the same time, the cause of the iron overload must be established, as it is necessary for informed treatment [9].

Primary hemochromatosis: Hereditary hemochromatosis is a serious disease with a genetically determined disorder of iron metabolism. The primary functional defect in hereditary hemochromatosis is an abnormality in the regulation of iron uptake by the cells of the gastrointestinal mucosa (there is no limitation of absorption), which leads to a massive intake of a trace element into the body, followed by the deposition of iron in various organs (liver, spleen, heart, pancreas, gonads, adrenal glands). A close relationship with the HLA-A locus was found. Primary hemochromatosis occurs about 10 times more often in men than in women. Usually clinical manifestations are observed at age 35 - 55 years old, there are liver dysfunctions up to cirrhosis, diabetes mellitus, pigmented dermatosis, cardiomyopathy and heart rhythm disturbances. The classic triad of primary hemochromatosis is melasma, liver cirrhosis, diabetes mellitus. Sometimes symptoms of secondary hypogonadism and adrenocortical insufficiency occur. Hepatocellular carcinoma develops in about 15% of cases.

Hereditary hemochromatosis is characterized by clinical polymorphism due to excessive iron load to one degree or another in all organs and tissues. Therefore, these stages of the disease are conditional. Dysfunction and the corresponding clinical manifestation occur with advanced morphological changes in organs, after decompensation occurs. Laboratory diagnostics of the disease should be early, in connection with which widespread introduction of screening tests is necessary (hemogram in combination with a complete study of iron metabolism). If hereditary hemochromatosis is suspected, HLA typing and liver biopsies should be performed. In order to remove excess iron from the body, patients are treated with desferal and regular bloodletting [10].

Secondary acquired hemochromatosis: Hemosiderosis (secondary hemochromatosis) is possible with hemolytic anemias, with ineffective erythropoiesis (including with sideroblastic and aplastic anemia, thalassemia), malaria, intoxication (lead, tin, etc.), alcoholic cirrhosis, chronic viral hepatitis, some types of porphyria , after repeated blood transfusions.

Therefore, only with prolonged chronic iron overload conditions arise for the development of diseases of iron accumulation with damage to organs [11].

The duration of chronic iron overload is a determining factor in organ pathology in secondary hemochromatosis.

Iron, which enters the body during blood transfusions, brings a significant addition to the iron that has already entered the intestine.

Serum ferritin concentration closely correlates with the corresponding degree of iron overload in the reticuloendothelial system.

Ineffective erythropoiesis:

Stages of heme synthesis:

1. Formation of 5-aminolevulinic acid: 5-Aminolevulinic acid synthase, the first enzyme on the heme biosynthesis pathway, catalyzes the condensation of glycine with succinyl coenzyme A to form 5-aminolevulinic acid. This enzyme is localized on the inner mitochondrial membrane; its cofactor is pyridoxal-5-phosphate. In the cells of the erythroid and non-erythroid series, synthase is encoded by different genes.
2. Formation of porphobilinogen: Under the action of aminolevulinic acid dehydratase (this enzyme is localized in the cytosol), two molecules of 5-aminolevulinic acid are converted into mono-pyrroloporphobilinogen with the release of two water molecules. Lead inhibits aminolevulinic acid dehydratase, displacing zinc, which is necessary for the enzyme to function. The most potent inhibitor is succinylacetone (a structural analogue of aminolevulinic acid), which is present in the urine and blood of patients with hereditary tyrosinemia.
3. Formation of hydroxymethylbilane: Porphobilinogen deaminase catalyzes the condensation of four porphobilinogen molecules to form a linear tetrapyrrole - hydroxymethylbilane. In the absence of the next enzyme, uroporphyrinogen III synthase, hydroxymethylbilane spontaneously cyclizes with the formation of the first tetrapyrrole, uroporphyrinogen I. There are two isoforms of porphobilinogen deaminase; one is present only in non-erythroid cells. These isozymes are encoded by different messenger RNAs, which are transcribed from the same gene, but in different ways and undergo different splicing.
4. The formation of uroporphyrinogen III from hydroxymethylbilane is catalyzed by uroporphyrinogen III-synthase. This stage consists in intramolecular rearrangement, affecting only the D ring of the porphyrin "large ring".
5. Formation of coproporphyrinogen: Cytosolic enzyme uroporphyrinogen decarboxylase catalyzes the sequential

removal of four carboxyl groups from the carboxymethyl side chains of uroporphyrinogen to form coproporphyrinogen.

6. Formation of protoporphyrinogen IX: The mitochondrial enzyme coproporphyrinogen oxidase catalyzes the removal of the carboxyl group and two hydrogen atoms from the propionic groups of the pyrrole rings A and B of coproporphyrinogen with the formation of vinyl groups at these positions.
7. Formation of protoporphyrin IX: The oxidation of protoporphyrinogen IX to protoporphyrin IX is catalyzed by protoporphyrinogen oxidase, which removes 6 hydrogen atoms from the porphyrinogen core.
8. The last stage of heme biosynthesis is reduced to the incorporation of iron into protoporphyrin IX. This reaction is catalyzed by the mitochondrial enzyme ferrochelatase.

The rate-limiting enzyme that determines the intensity of porphyrin synthesis in all organs is the enzyme 5-aminolevulinic acid synthase. Heme (as well as hematin) is able to inhibit the activity of 5-aminolevulinic acid synthase. Since heme is not a direct product of the reaction with the participation of 5-aminolevulinic acid synthase, the inhibition appears to be due to the steric effect [12].

Nevertheless, this effect is a negative feedback mechanism that controls the hemoglobin content in the circulation system. About 100 different drugs and metabolites are known that can affect the activity of 5-aminolevulinic acid synthase, in particular 3,5-dicarbethoxy-1,4-dihydrocollidine 40 times increases the activity of the enzyme in the experiment.

Porphyrin metabolism disorders manifest clinically as porphyrias. Porphyrias are hereditary and acquired anemias associated with impaired porphyrin synthesis, characterized by hypochromia, high serum iron, and organ hemosiderosis [13].

A form of the disease associated with a violation of the synthesis of 5-aminolevulinic acid is observed relatively more often. Violation of the formation of protoporphyrin causes the impossibility of binding iron and, as a result, its accumulation in the body. In young people, anemia in most cases is not expressed (80-90 g /

l), but hemoglobin gradually decreases to 50-60 g / l. The content of reticulocytes is normal or slightly reduced. Erythrocytes are hypochromic, there is anisocytosis, poikilocytosis, single target erythrocytes. In the bone marrow - a sharp irritation of the red sprout, increased basophilic polychromatophilic and decreased oxyphilic normoblasts, many sideroblasts. The content of iron in the blood serum is significantly increased (up to 5.5 mg / l), transferrin is saturated with iron by almost 100%. When examining the content of porphyrins in erythrocytes in some patients, a decrease in protoporphyrin to 3-9 $\mu\text{mol} / \text{l}$ (norm 18-90 $\mu\text{mol} / \text{l}$) and an increase in coproporphyrin to 60-75 $\mu\text{mol} / \text{l}$ (norm to 12 $\mu\text{mol} / \text{l}$) are found, in some cases decreases both protoporphyrin and coproporphyrin. The content of 5-aminolevulinic acid and coproporphyrin in the urine is normal. Acquired disorders of porphyrin synthesis are most often associated with lead poisoning or occur with a lack of vitamin B6. The patient's appearance is peculiar - an earthy pallor with a grayish tinge, associated with both anemia and vasospasm and deposition of porphyrins in the skin, there may be a purple border on the gums. The hemoglobin content gradually decreases to 40-60 g / l, the color index is sharply reduced, erythrocytes are sharply hypochromic, aniso-poikilocytosis is detected [14].

2. MATERIALS AND METHODS

The quantitative determination of transferrin in serum is carried out by immunochemical methods based on the antigen-antibody interaction reaction. The serum transferrin concentration is high enough that the first reaction between antigen and antibody may be an agglutination or precipitation reaction. The result could be measured directly, often a reaction to the eye.

Direct reactions can be quantified by methods turbidimetry, nephelometry, radial immunodiffusion, radioimmunoassay, etc.

In contrast to these direct specific immunochemical methods for the determination of individual proteins, conventional chemical methods allow an indirect and approximate determination of the concentration of transferrin by the total iron-binding capacity of serum (TIBC). TIBC is the amount of iron that can bind transferrin to about limit volume of serum.

In clinical diagnostic laboratories, due to the ease of implementation, TIBC is more often determined instead of transferrin. Modern methods for the determination of ferritin are based on immunological analysis. Ferritin is present in serum at very low concentrations ($0.2-7 \times 10^{-12} \text{ mol} / \text{L}$). Therefore, test kits of the first generation for the determination of ferritin were based on methods of indirect measurement - ELISA, RIA. In recent years, the sensitivity of direct methods (turbidimetry, nephelometry), therefore, turbidimetric latex agglutination test, ELISA-based ELISA kits, nephelometry, fluorescence analysis, luminescence immunoassay, RIA are used to determine ferritin. Physicochemical and immunological differences of isoferritins contribute to the fact that radioimmunological methods or enzyme-linked immunosorbent assay, depending on the type of antigens or antibodies used, can be accompanied by significant differences the results of measuring the concentration of ferritin in serum. International contacts on a single standard for ferritin were coordinated by the World Health Organization (WHO), the International Committee for Standardization in Hematology (ICSH), the International Federation of Clinical Chemistry (IFCC), and the Standardization Committee of the International Union of Immunological Societies (IUIS). A standardized sample of human liver ferritin is currently stored at the National Institute for Biological Standards and Control in London. The criteria for diagnostic kits for ferritin have been worked out, which, in particular, must meet the safety requirements (tested for the absence of HIV infection), sensitivity, specificity and accuracy, could be used on automatic machines, and be commercially available. Ferritin, like transferrin, does not have circadian rhythms. Based on the fact that the vertical position of the body affects the composition of high-molecular-weight proteins, it is recommended to take samples for ferritin with a standard position of the body from a vein. Preferably, the same blood sample is used for the determination of ferritin, transferrin and iron. Determining reference values for ferritin is always a challenge, as gender and age affect serum ferritin levels. For example, the ferritin content in newborns increases very sharply during the first month of life, since physiological hemolysis of erythrocytes takes place, then its concentration in serum decreases significantly, reaching minimum values by 6 months of age, and then gradually increases up to 15 years of age. In adult women before menopause, the amount of iron and

ferritin stores is significantly less than in men. In old age, the serum ferritin concentration is approximately the same in men and women. It is recommended to set the boundaries of "normal values" in the group of persons in whom latent iron deficiency can be suspected - these are permanent donors and young women. Naturally, people with a manifest form of iron deficiency and patients with infectious diseases should be excluded. An increased serum ferritin content, which does not correlate with the amount of deposited iron in the body, is often determined in Hodgkin's disease, acute leukemia, breast cancer, malignant gonadal tumors, melanoma and carcinoma of the gastrointestinal tract and liver [15]. An increase in ferritin concentration depends on the type and stage of the disease and can be caused by the following reasons: increased synthesis of ferritin by tumor cells, release of ferritin during their destruction, nonspecific increase in serum ferritin concentration. In patients with malignant tumors, an increase in ferritin is due to a high concentration of acidic isoferritins. Normal serum ferritin concentration does not exclude malignant neoplasm. Therefore, ferritin is not used as a screening indicator for early diagnosis of tumors. In selected patients, an elevated serum ferritin concentration may be a useful parameter for detecting metastasis and relapse and, in part, for monitoring the effectiveness of treatment.

3. RESULTS AND DISCUSSION

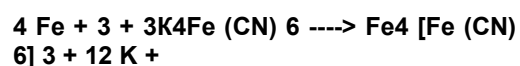
The value of ferritin determination in differential diagnosis causes of iron deficiency and anemia. Extremely important when differential diagnosis to distinguish iron deficiency anemia (primary) from other hypochromic anemias, since only with iron deficiency anemia is treatment with iron preparations indicated. Similar treatment for other hypochromic anemias can cause symptoms of secondary hemochromatosis.

The most important diagnostic finding is the amount of iron reserve, as measured by the serum ferritin concentration. All anemias, with the exception of iron deficiency, have normal or elevated ferritin levels. A combination of anemia of chronic diseases with iron deficiency anemia is possible. In cases of low ferritin content, treatment with iron preparations is indicated [16]. It should be emphasized that the diagnostic significance of individual indicators of iron metabolism under physiological conditions and most pathological processes does not allow

diagnosing the real cause of the violation of iron metabolism. To avoid an erroneous diagnosis, it is necessary to determine all clinical and biochemical parameters of iron metabolism and interpret them on the basis of (patho) physiological laws. The cost of a comprehensive examination is much less compared to the consequences of erroneous (incorrect) therapy. Normally, at the stage of the middle polychromatophilic normoblast, the Hb concentration reaches a critical value, which almost completely stops DNA synthesis and turns off the cell from the mitotic cycle. In this case, the rate of Hb synthesis also slows down. Further maturation of red cells occurs without division [17].

Cytochemical determination of iron: Sideroblasts and siderocytes Siderocytes are erythrocytes containing ferric iron, the reserves of which are not associated with hemoglobin. Sideroblasts are the corresponding nucleated cells of the erythrocyte series. Iron granules are detected in reaction with Prussian blue.

Principle: The interaction of iron ions (Fe^{+3}), unbound with hemoglobin, with iron-cyanide potassium in a HCl solution is called the reaction of Prussian blue.



4. CONCLUSION

Iron is necessary for redox reactions during energy production, peroxidation, oxygen transfer and other critical processes.

Both iron deficiency and excess cause severe disease. Functional dysfunctions at each of these stages can affect overall iron metabolism. Nevertheless, the multistage metabolism allows the body to compensate to a large extent for metabolic shifts. Therefore, clinically there are both latent and, to varying degrees, clinically expressed states of iron deficiency or excess in the body. Moreover, blocking the utilization of iron at the stages of its utilization may be accompanied by the development of a clinical picture of iron deficiency and laboratory indicators of its excess. Incorrect interpretation of the results will be accompanied by incorrect prescription of iron-containing drugs and an even greater deterioration in the patient's condition. Limited access of iron for infectious agents is one of the most effective mechanisms of infectious

tolerance. This pathway is actively expressed in chronic pathology and is manifested by anemia of chronic diseases [18].

Therefore, the comprehensive laboratory analysis outlined in this study guide, aimed at analyzing the pathophysiological mechanisms of iron metabolism and the formation on this basis of algorithms for laboratory diagnostics and monitoring of the effectiveness of treatment with iron preparations. The offered laboratory technologies provide for the analysis of biochemical, immunochemical, hematological, cytological, general clinical studies.

For adequate laboratory diagnostics, it is necessary to introduce into practice and laboratory research standards such significant indicators of iron metabolism as the determination of transferrin, ferritin, soluble transferrin receptors, hepcidin, cytochemical indicators for hemosiderosis. Modern therapeutic approaches are able to significantly correct and normalize iron metabolism, but for this it is necessary to carry out both screening studies in groups prone to pathology of iron metabolism, and personalized laboratory studies of patients with clinically expressed pathology [19].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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