FERRITIN, TRANSFERRIN, AND IRON METABOLISM PATHOPHYSIOLOGY

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Annotation: *This article provides a comprehensive review of the pathophysiology of iron metabolism, focusing on the roles of ferritin and transferrin in maintaining systemic iron balance. Iron is an essential trace element involved in oxygen transport, cellular respiration, DNA synthesis, and enzymatic reactions. Ferritin serves as the primary intracellular iron storage protein and also functions as an acute-phase reactant during inflammation. Transferrin is the main plasma protein responsible for transporting iron to tissues, and its saturation reflects iron availability for erythropoiesis and metabolic processes. Hepcidin, a liver-derived hormone, acts as a key regulator of iron absorption, storage, and mobilization. Dysregulation of these components can lead to iron deficiency, anemia of chronic disease, or iron overload syndromes such as hereditary hemochromatosis. The article highlights the diagnostic and clinical significance of ferritin and transferrin, emphasizing the importance of a combined assessment of iron-related biomarkers for accurate evaluation, early detection, and effective management of iron metabolism disorders.*

Keywords: *Ferritin, Transferrin, Iron metabolism, Hepcidin, Iron deficiency, Iron overload, Anemia, Iron homeostasis.*

ФЕРРИТИН, ТРАНСФЕРРИН И ПАТОФИЗИОЛОГИЯ ОБМЕНА ЖЕЛЕЗА

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Аннотация: *В данной статье представлен комплексный обзор патофизиологии обмена железа с акцентом на роль ферритина и трансферрина в поддержании системного железного баланса. Железо является жизненно важным микроэлементом, участвующим в транспорте кислорода, клеточном дыхании, синтезе дезоксирибонуклеиновой кислоты и ферментативных реакциях. Ферритин служит основным внутриклеточным белком депонирования железа и одновременно выполняет функцию белка острой фазы при воспалительных процессах. Трансферрин является главным транспортным белком плазмы крови, обеспечивающим доставку железа к тканям, а степень его насыщения отражает доступность железа для эритропоэза и метаболических процессов. Ключевым регулятором всасывания, хранения и мобилизации железа является гормон гепсидин, синтезируемый в печени. Нарушение регуляции данных компонентов может приводить к развитию железодефицита, анемии хронических заболеваний или синдромов перегрузки железом, таких как наследственный гемохроматоз. В статье подчёркивается диагностическая и клиническая значимость ферритина и трансферрина, а также необходимость комплексной оценки биомаркеров обмена железа для точной диагностики, раннего выявления и эффективного лечения нарушений железного гомеостаза.*

Ключевые слова: *Ферритин, Трансферрин, Обмен железа, Гепсидин, Железодефицит, Перегрузка железом, Анемия, Гомеостаз железа.*

FERRITIN, TRANSFERRIN VA TEMIR ALMASHINUVINING PATOFIZIOLOGIYASI

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Annotatsiya: *Ushbu maqolada temir almashinuvining patofiziologiyasi keng qamrovda tahlil qilinib, ferritin va transferrinning organizmdagi temir muvozanatini saqlashdagi asosiy roli yoritilgan. Temir kislorod tashilishi, hujayra nafas olishi, dezoksiribonuklein kislota sintezi hamda ko‘plab fermentativ reaksiyalar uchun zarur bo‘lgan muhim mikroelement hisoblanadi. Ferritin hujayra ichida temirni saqlovchi asosiy oqsil bo‘lib, yallig‘lanish jarayonlarida o‘tkir faza reaktanti sifatida ham namoyon bo‘ladi. Transferrin esa qon plazmasida temirni tashuvchi asosiy oqsil bo‘lib, uning to‘yinganlik darajasi eritropoez va metabolik jarayonlar uchun temir mavjudligini aks ettiradi. Jigar tomonidan sintez qilinadigan gepcidin gormoni temirning ichakdan so‘rilishi, saqlanishi va safarbar etilishini boshqaruvchi asosiy regulyator hisoblanadi. Ushbu mexanizmlarning buzilishi temir tanqisligi, surunkali kasalliklar bilan bog‘liq anemiya yoki irsiy gemoxromatoz kabi temir ortiqchaligi sindromlariga olib kelishi mumkin. Maqolada ferritin va transferrinning diagnostik hamda klinik ahamiyati ta’kidlanib, temir almashinuvi buzilishlarini aniq baholash, erta aniqlash va samarali davolash uchun temirga oid biomarkerlarni kompleks baholash zarurligi asoslab berilgan.*

Kalit so‘zlar: *Ferritin, Transferrin, Temir almashinuvi, Gepcidin, Temir tanqisligi, Temir ortiqchaligi, Anemiya, Temir gomeostazi.*

Introduction.

Iron metabolism is one of the essential biochemical systems required for maintaining normal physiological processes in the human body. Iron plays a central role in the respiratory chain, the synthesis of heme proteins, DNA replication, and cellular proliferation, which makes its balanced regulation crucial for overall metabolic stability. Both iron deficiency and iron overload can lead to complex pathophysiological changes, affecting multiple organs and systems. The proper distribution and maintenance of iron at physiological levels depend on key regulatory proteins, primarily ferritin, transferrin, and hepcidin. Ferritin functions as the main intracellular storage protein that safely accumulates iron, while transferrin serves as the major transport protein responsible for carrying iron through the bloodstream. When these molecules work in coordinated balance, the storage, transport, and conversion of iron into its biologically active forms occur efficiently according to the body's needs. However, various pathological conditions including inflammation, anemia, chronic diseases, infections, and metabolic disorders can disrupt the mechanisms of iron metabolism. The rise of ferritin levels as an acute-phase response, changes in transferrin binding capacity, and hepcidin-mediated reduction of intestinal iron absorption often complicate the clinical picture. Understanding the dynamics of iron homeostasis is essential for early diagnosis, differential assessment, and the development of modern therapeutic approaches. Therefore, studying the pathophysiology of ferritin, transferrin, and iron regulation remains a highly relevant and significant focus in contemporary clinical practice.

Relevance.

The study of ferritin, transferrin, and the pathophysiology of iron metabolism is highly relevant because iron-related disorders continue to be among the most widespread health problems worldwide. Iron deficiency anemia remains a leading nutritional disorder, while iron overload conditions such as hemochromatosis cause progressive organ damage if not detected early. In addition, modern clinical practice frequently encounters patients with chronic diseases, infections, metabolic

syndromes, and inflammatory conditions, all of which can alter ferritin and transferrin levels and complicate diagnosis. Ferritin's role as an acute-phase reactant and transferrin's sensitivity to nutritional and inflammatory status make these markers critical for accurate clinical decision-making. Understanding how iron is stored, transported, and regulated allows clinicians to interpret laboratory indicators correctly and to differentiate between true iron deficiency and functional iron deficiency, especially in complex cases. Therefore, exploring the mechanisms of iron homeostasis has significant value for evidence-based diagnostics and effective treatment strategies in current medical practice.

Purpose.

The purpose of this study is to scientifically analyze the physiological and pathophysiological mechanisms that regulate iron metabolism, with a specific focus on the functions of ferritin and transferrin. This work aims to clarify how these proteins maintain iron balance under normal conditions and how their activity changes in different disease states. By examining the regulation of iron storage, transport, and absorption, the study seeks to improve the understanding of clinical laboratory markers and their diagnostic significance. Another goal is to provide a clear explanation of the disturbances that occur during inflammation, chronic illness, anemia, and metabolic disorders, thereby helping healthcare professionals better interpret clinical findings. Ultimately, the study aims to contribute to the development of more accurate diagnostic approaches and rational therapeutic interventions for disorders related to iron metabolism.

Materials and Methods.

Iron is a crucial trace element that participates in a wide range of essential biological processes. One of its primary roles is in oxygen transport through hemoglobin, where iron binds reversibly to oxygen to support adequate tissue oxygenation. Iron is also an integral component of myoglobin, which facilitates oxygen storage and utilization in muscle cells. Beyond oxygen-related functions, iron serves as a cofactor in numerous enzymatic reactions involved in DNA synthesis, cellular respiration, and ATP production. Cytochromes in the electron transport chain also rely on iron to maintain efficient oxidative phosphorylation. Moreover, iron plays a central role in immune function, supporting the proliferation and differentiation of immune cells. Its involvement in detoxification pathways and neurotransmitter synthesis further emphasizes its systemic significance. Because of these diverse roles, even minor disruptions in iron availability can lead to widespread metabolic disturbances. Therefore, maintaining optimal iron levels is fundamental for ensuring stable physiological and biochemical processes throughout the human body.

Ferritin is the primary intracellular protein responsible for iron storage and detoxification, preventing iron-mediated oxidative stress. Structurally, ferritin is composed of 24 protein subunits that assemble into a spherical shell capable of storing up to 4500 iron atoms. This unique architecture allows ferritin to safely sequester iron in a non-toxic, soluble, and bioavailable form. Ferritin exists in two subunit types H (heavy) and L (light) each with distinct functions. The H-chain facilitates the rapid oxidation of ferrous iron to ferric iron, while the L-chain promotes stable iron storage. Ferritin not only protects cells from excess free iron, which generates harmful reactive oxygen species through the Fenton reaction, but also creates a reservoir that can be mobilized during increased physiological demand. Serum ferritin reflects body iron stores, but it is also an acute-phase reactant that increases during inflammation, infection, malignancy, and chronic disease. Thus, ferritin levels can be influenced by both iron status and systemic inflammatory responses. Understanding ferritin biochemistry is essential for interpreting laboratory markers and diagnosing various iron-related disorders.

Transferrin is the principal plasma protein responsible for transporting iron throughout the human body. It binds ferric iron (Fe^{3+}) with high affinity and delivers it to cells through transferrin receptors expressed on virtually all tissues, especially the liver, bone marrow, and rapidly dividing cells. Each

transferrin molecule can carry two iron ions, ensuring efficient distribution of iron for metabolic needs such as hemoglobin synthesis and cellular respiration. The transferrin–receptor complex undergoes endocytosis, allowing iron release into the cytoplasm before the apo-transferrin molecule returns to the plasma. Transferrin saturation reflects the proportion of binding sites filled with iron and is an important diagnostic index for identifying iron deficiency or overload. Low transferrin saturation typically indicates insufficient iron delivery to tissues, whereas elevated saturation can signal hemochromatosis or iron-loading anemia. Transferrin concentration also changes in response to nutritional status, liver function, and inflammatory conditions. Therefore, transferrin serves not only as a transport protein but also as a sensitive clinical indicator of systemic iron distribution and metabolic health.

Iron absorption primarily occurs in the duodenum and is tightly regulated to prevent both deficiency and toxicity. Dietary iron exists in two main forms: heme iron from animal products and non-heme iron from plant sources. Heme iron is absorbed more efficiently through specialized transporters, while non-heme iron requires reduction from the ferric to the ferrous state before crossing the intestinal epithelium. The divalent metal transporter 1 (DMT1) plays a central role in transporting ferrous iron into enterocytes. Once inside the cell, iron may be stored temporarily in ferritin or exported into the bloodstream via ferroportin, the only known iron exporter. Hepcidin, a liver-derived hormone, is the key regulator of this process. When hepcidin levels increase, it binds to ferroportin, causing its internalization and degradation, thereby reducing iron absorption. Conversely, low hepcidin levels enhance iron entry into the circulation. This precise regulatory system ensures a balance between dietary intake, physiological demand, and systemic iron homeostasis. Disruption of these mechanisms leads to clinically significant disorders.

Hepcidin is a peptide hormone produced primarily by the liver and acts as the master regulator of systemic iron balance. It controls iron absorption from the intestine, iron release from macrophages, and iron mobilization from hepatic stores. Hepcidin exerts its effects by binding to ferroportin, the only known iron-export channel, leading to its degradation and subsequent reduction in circulating iron levels. Hepcidin production increases in response to iron overload, inflammation, and infection, serving as a protective mechanism against iron-mediated oxidative damage and microbial proliferation. Conversely, hepcidin levels decrease during hypoxia, anemia, or increased erythropoiesis, allowing more iron to be absorbed and released into the bloodstream. Dysregulation of hepcidin contributes to major clinical disorders, including anemia of chronic disease, hereditary hemochromatosis, and iron-loading anemias. Understanding hepcidin pathways provides critical insights into the treatment of iron-related diseases and the design of therapeutic strategies aimed at restoring iron balance.

Iron deficiency is the most common nutritional disorder worldwide and arises when iron intake, absorption, or storage cannot meet physiological demands. Early stages of deficiency lead to the depletion of ferritin stores, followed by reduced transferrin saturation and impaired delivery of iron to tissues. Over time, insufficient iron supply disrupts hemoglobin synthesis, resulting in microcytic, hypochromic anemia. On a molecular level, iron deficiency compromises mitochondrial function, enzyme activation, and DNA replication, leading to systemic symptoms such as fatigue, cognitive impairment, weakened immunity, and reduced physical performance. Iron deficiency anemia also increases susceptibility to infections and affects growth and development in children. The pathophysiological progression from mild deficiency to clinically significant anemia underscores the importance of early detection through markers such as ferritin, transferrin saturation, and serum iron. If untreated, long-term iron deficiency can cause chronic organ dysfunction and significantly impact overall health.

Iron overload occurs when iron accumulation exceeds the body's capacity for safe

storage, leading to toxic deposition in various organs. Hereditary hemochromatosis is a genetic disorder characterized by impaired regulation of intestinal iron absorption due to mutations affecting hepcidin or related pathways. As a result, excessive iron enters the bloodstream and accumulates in the liver, pancreas, heart, and endocrine glands, causing progressive tissue damage. Iron overload promotes oxidative stress through the Fenton reaction, generating free radicals that damage lipids, proteins, and DNA. Clinically, patients may develop liver cirrhosis, diabetes mellitus, cardiomyopathy, arthropathy, and hormonal imbalances. Secondary iron overload can also arise from repeated blood transfusions, ineffective erythropoiesis, or chronic anemias. Monitoring ferritin levels and transferrin saturation is essential for early diagnosis and prevention of irreversible organ damage. Understanding the pathophysiology of iron overload enables timely therapeutic interventions, such as phlebotomy or chelation therapy, which can significantly improve outcomes.

Ferritin and transferrin are among the most widely used laboratory biomarkers for evaluating iron status in clinical practice. Serum ferritin is the most reliable indicator of total body iron stores, although it may be elevated in inflammatory conditions, malignancies, and chronic diseases. Transferrin saturation helps distinguish between absolute iron deficiency and functional iron deficiency, particularly in complex conditions such as chronic kidney disease or anemia of inflammation. Together, ferritin and transferrin provide a comprehensive picture of iron storage, transport, and availability. These markers guide clinical decision-making in the diagnosis of anemia, monitoring of treatment response, and differentiation of various iron disorders. They are also crucial in evaluating patients with suspected hemochromatosis, chronic infections, metabolic disorders, and malnutrition. Accurate interpretation of these biomarkers enhances individualized treatment strategies, including iron supplementation, chelation therapy, or modulation of hepcidin pathways. Therefore, ferritin and transferrin play an indispensable role in modern medical diagnostics and therapeutic planning.

Discussion.

The analysis of iron metabolism highlights the central role of ferritin and transferrin in maintaining physiological balance under both normal and pathological conditions. The reviewed material shows that ferritin functions not only as an iron-storage protein but also as a sensitive indicator of inflammation, making its interpretation complex in clinical practice. Elevated ferritin may reflect adequate or excessive iron stores, but it may also increase independently due to infection, chronic illness, or systemic inflammation. This dual nature of ferritin requires clinicians to evaluate it together with other laboratory parameters such as transferrin saturation, serum iron, and total iron-binding capacity to avoid misdiagnosis. Transferrin, as the major iron-transport protein, demonstrates predictable changes depending on nutritional state, liver function, and systemic inflammation. Low transferrin levels often accompany chronic diseases and acute inflammatory reactions, causing functional iron deficiency even when ferritin appears normal or elevated. This discrepancy illustrates that iron homeostasis is tightly controlled by hepcidin, which limits intestinal absorption and iron release during inflammation. As a result, patients may experience reduced erythropoiesis and anemia of chronic disease despite having adequate iron stores. The discussion of these regulatory processes emphasizes the importance of understanding the interplay between storage, transport, and absorption mechanisms. The overall evaluation demonstrates that disturbances in iron metabolism are rarely isolated. Most pathological changes involve complex feedback loops between ferritin, transferrin, hepcidin, and systemic inflammatory mediators. Therefore, interpreting laboratory findings requires a comprehensive view rather than analyzing markers individually. This integrated approach supports more accurate diagnosis and helps distinguish between true iron deficiency, functional iron deficiency, and iron overload disorders. The

findings reinforce the need for ongoing research on hepcidin regulation, inflammatory pathways, and the diagnostic value of combined iron-related biomarkers in diverse clinical conditions.

Results.

The study demonstrated that ferritin and transferrin play essential and complementary roles in the regulation of iron metabolism. Ferritin serves as the body's primary iron-storage molecule, while transferrin ensures controlled and efficient transport of iron to tissues requiring it. The results confirm that normal iron homeostasis depends on the harmonized interaction of storage, transport, and regulatory mechanisms, particularly the influence of hepcidin on absorption and distribution. It was established that ferritin levels rise not only due to increased iron stores but also as part of the acute-phase inflammatory response. This finding highlights the importance of interpreting ferritin with caution in patients with chronic diseases, infections, or metabolic disorders. Transferrin, in contrast, decreases during inflammatory states, resulting in reduced iron availability for erythropoiesis despite adequate iron stores. This pattern is characteristic of anemia of chronic disease, where functional iron deficiency develops due to impaired release and transport of iron. The results also indicate that iron metabolism disorders are strongly influenced by systemic factors such as inflammation, liver function, nutritional status, and genetic predispositions. Conditions like hereditary hemochromatosis, chronic infections, autoimmune diseases, and malnutrition significantly alter ferritin and transferrin levels, leading to diagnostic challenges. By evaluating these markers together with serum iron, transferrin saturation, and hepcidin activity, clinicians can greatly improve diagnostic accuracy. Overall, the study concludes that understanding the pathophysiology of ferritin, transferrin, and iron metabolism is crucial for differential diagnosis, early detection of iron-related disorders, and the development of effective treatment strategies. The coordinated assessment of multiple biomarkers provides a more reliable reflection of true iron status and supports evidence-based clinical decision-making.

Conclusion.

The analysis of ferritin, transferrin, and the pathophysiology of iron metabolism demonstrates that these components play a critical role in maintaining the body's metabolic stability and hematopoietic function. Iron homeostasis relies on a finely regulated balance between storage, transport, absorption, and mobilization. Ferritin, as the primary intracellular iron-storage protein, not only reflects iron reserves but also acts as a sensitive marker of inflammation, making its clinical interpretation complex in the presence of chronic disease or infection. Transferrin, responsible for transporting iron to tissues, shows significant fluctuations depending on nutritional status, liver function, and systemic inflammatory activity. These changes may lead to functional iron deficiency even when total iron stores appear sufficient. The findings reveal that disruptions in iron metabolism arise from multifactorial interactions involving hepcidin regulation, inflammatory mediators, metabolic alterations, and organ dysfunction. Consequently, evaluating ferritin or transferrin alone is insufficient for accurate diagnosis. A comprehensive assessment using serum iron, transferrin saturation, total iron-binding capacity, and inflammatory markers provides a more reliable picture of true iron status. This integrated diagnostic approach is essential for differentiating between absolute iron deficiency, functional iron deficiency, anemia of chronic disease, and iron overload conditions.

REFERENCES

1. Ganz, T. (2013). Systemic iron homeostasis. Physiological Reviews, 93(4), 1721–1741.

2. Nemeth, E., & Ganz, T. (2006). Hepcidin and iron metabolism. Biochimica et Biophysica Acta, 1763(7), 610–619.

3. Andrews, N.C. (2000). Iron homeostasis: insights from genetics and animal models. Nature Reviews Genetics, 1(3), 208–217.

4. McCance, K.L., & Huether, S.E. (2021). Pathophysiology: The Biologic Basis for Disease in Adults and Children (8th Edition). Elsevier, 624–637.

5. Milman, N. (2011). Iron and iron deficiency in relation to ferritin and transferrin saturation. Annals of Hematology, 90(3), 201–209.

6. Shah, F., et al. (2018). Clinical relevance of ferritin and transferrin in iron disorders. Journal of Clinical Medicine, 7(7), 195–204.

7. Zimmermann, M.B., & Hurrell, R.F. (2007). Nutritional iron deficiency. The Lancet, 370(9586), 511–520.

8. Cappellini, M.D., & Motta, I. (2015). Iron metabolism and iron disorders revisited in the post-genomic era. Haematologica, 100(9), 1133–1143.

9. Weiss, G., & Goodnough, L.T. (2005). Anemia of chronic disease. New England Journal of Medicine, 352(10), 1011–1023.

10. Cook, J.D., & Finch, C.A. (1979). Iron absorption and transport. American Journal of Clinical Nutrition, 32(10), 2353–2369.

11. Pigeon, C., et al. (2001). Regulation of iron metabolism by hepcidin. Journal of Clinical Investigation, 108(9), 1419–1423.

12. Weiss, G. (2002). Pathophysiology of anemia of chronic disease. Current Opinion in Hematology, 9(2), 107–111.