Pediatr Pol 2025; 100 (3): 260-270
DOI: HTTPS://DOI.ORG/10.5114/POLP.2025.154704
Submitted: 23.05.2025, Accepted: 04.08.2025, Published: 24.09.2025

PEDIATRIA Polska
PISMO POLSKIEGO TOWARZYSTWA PEDIATRYCZNEGO
Polish Journal of PAEDIATRICS
OFFICIAL JOURNAL OF POLISH SOCIETY OF PAEDIATRICS

REVIEW PAPER

The role of hepcidin in iron metabolism

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ABSTRACT

Iron is an essential mineral component of the human body, and its deficiency leads to impaired function of many important systems. One of the elements controlling the bioavailability of dietary iron is the concentration of hepcidin in blood serum. Hepcidin is an acute phase protein produced mainly by hepatocytes. Its production is regulated by proinflammatory cytokines and by the activation of cellular pathways by the soluble transferrin receptor (TtF) in response to increased iron concentration. The basic role of hepcidin is reducing the absorption of dietary iron in enterocytes by changing the conformation of ferroportin and influencing its ubiquitination. Ferroportin plays a role in the release of iron ions by macrophages. Due to the important role of the hepcidin-ferroportin axis in the development of anemia in patients with chronic inflammatory diseases, it has been the focus of numerous studies seeking new therapeutic strategies for patients with chronic anemia.

KEY WORDS:
iron, anemia, hepcidin.

INTRODUCTION

Iron is an essential mineral component of the human body. This element is characterized by high reactivity. As a component of many proteins, it plays a significant role in maintaining the homeostasis of the body. For example, it participates in the process of oxygen exchange as one of the building particles of hemoglobin and myoglobin, and in iron-sulfur complexes it enables electron transport and the functioning of the respiratory chain in mitochondria, the citric acid cycle, and DNA synthesis [1]. Iron deficiency leads to anemia, which is a significant global health problem. According to the Global Burden of Disease Study report, in 2021 anemia affected over 1.9 billion patients worldwide [2]. Symptoms of iron deficiency include chronic fatigue and dizziness, hair, skin, and nail disorders, and tinnitus, in addition to delayed psychomotor development, difficulties with concentration and deterioration of learning performance, as well as changes in behavior in the pediatric population [3, 4].

Iron concentration in the blood depends on its dietary supply and several mechanisms influencing its metabolism in the body, such as regulation of intestinal absorption or intracellular metabolism and total iron reserves [5, 6]. In recent years, researchers focusing on iron metabolism have been paying particular attention to hepcidin and its importance in the regulation of iron homeostasis in the body.

PRODUCTION OF HEPCIDIN

Hepcidin, first described in 2001, is a 25-amino acid peptide produced primarily in the liver, whose role was initially associated with the body's response to infections, particularly bacterial and fungal [7]. In the same year, the first studies on animal models linking hepcidin production with iron metabolism appeared [8]. Predominance of hepcidin mRNA expression in liver tissues was revealed using the Northern blot method [7]. The same study also demonstrated expression of the abovementioned mRNA in the heart tissue and spinal cord, but it was much lower

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than in hepatocytes [7]. Hepcidin production takes place mainly in hepatocytes, and its synthesis is regulated by two independent pathways: negative feedback related to the concentration of iron in the blood serum, and stimulation by inflammatory mediators [9]. Research conducted on animal models demonstrated a two-pronged mechanism of control of hepcidin production in hepatocytes in response to iron overload: mice with mutations in the gene encoding human homeostatic iron regulator protein (HFE protein) or soluble transferrin receptor (sTfR) showed no reduction in hepcidin synthesis in hepatocytes in response to short-term iron overload, but increased hepcidin levels were still observed as a result of chronic iron overload and increased hepatic iron accumulation [10]. The regulatory role of HFE and sTfR in response to a sudden increase in extracellular iron concentration involves the stimulation of hepcidin production in response to increased serum iron concentration by amplifying the signal of the bone morphogenetic protein (BMP) dependent pathway [10]. Until now, BMP-6 has been considered the main element of this signaling pathway, but studies have also shown the involvement of BMP-2, -4, and -9 in increasing hepcidin synthesis [11, 12]. In the case of chronic iron overload, intracellular iron concentration increases. This in turn constitutes a separate signal for activation of the BMP suppressor of mothers against decapentaplegic (BMP-SMAD) pathway [10]. Both mechanisms have a common point in the activation of the BMP receptor, which leads to the formation of an active complex participating in phosphorylation of the receptor-regulated SMAD (R-SMAD) complex, which in turn, in the presence of the common mediator SMAD (Co-SMAD), acts as a transcriptional co-modulator directly in the cell nuclei, increasing the transcription of hepcidin mRNA [13]. Hemojuvelin also plays an important role in the regulation of the BMP/R-SMAD pathway; its role as a BMP co-receptor has been demonstrated in in vivo studies [14]. A study published in 2024 demonstrated the role of another transcription factor, FOXO1, previously associated mainly with glucose metabolism, in the activation of the BMP/SMAD pathway. Mice lacking the gene encoding the aforementioned factor were characterized by a reduced response to iron overload: hepcidin production in hepatocytes decreased and the amount of available ferroportin on the cell membranes of enterocytes increased [15]. Mechanisms that inhibit hepcidin transcription in the liver in response to reduced iron stores or increased demand are also important for regulating the body's iron metabolism. This is achieved, among other mechanisms, through the action of martyptase-2 (MT2) – a serine protease that has the ability to inhibit the BMP/R-SMAD pathway in response to reduced serum iron concentration [16]. MT2 synthesis is activated by increased BMP6 concentration in blood serum [17]. Inhibition of hepcidin transcription occurs as a result of disconnection of the hemojuvelin and its appropriate receptor [18]. Until recently, it was believed that this was the only mechanism by which MT-2 regulates hepcidin synthesis, but recent reports shed new light on the complexity of the problem, suggesting that there may be more substrates involved in this process, and the whole issue requires further research [16].

The role of hypoxia in the regulation of hepcidin production should also be emphasized. Reduction of hepcidin production due to hypoxia is the result of the inhibitory effect of erythroferrone (ERFE) [19]. ERFE, produced in erythroblasts in response to increased levels of erythropoietin secreted by the kidneys, also acts directly on the membrane ligand-receptor junction, inhibiting activation of the BMP/R-SMAD pathway [19]. This mechanism allows removal of iron solution during the period of increased demand. The same result in response to hypoxia may be achieved through hypoxia-inducible factor-2α (HIF-2α). Reduction of oxygen in cells causes activation of the prolyl hydroxylase domain (PHD), which results in accumulation of HIF-2α in the nucleus. Enhanced expression of the gene encoding MT2 in hepatocytes, as a result of HIF-2α accumulation, leads to inhibition of hepcidin production in hepatocytes [20].

The second path of regulation of hepcidin synthesis in hepatocytes is the body's response to inflammation. As a result of hepcidin regulation, inhibiting the flow of iron into plasma, the concentration of iron not bound to transferrin in the blood serum is reduced [21]. This mechanism, which is an element of innate non-specific immunity, helps to limit the development of infection caused by pathogens sensitive to the concentration of free iron in the blood serum, such as *Yersinia enterocolitica* [21]. This is based on the stimulating effect of interleukins – especially IL-1 and IL-6 – on the production of hepcidin in the liver [22]. IL-6, produced in response to the presence of pathogens, by binding to a specific receptor activates the classic Janus kinase (JAK)-dependent signaling pathway, i.e. JAK-2/signal transducer and activator of transcription 3 (JAK-2/STAT3), which stimulates the expression of hepcidin mRNA in the cell nucleus [18]. As a result of phosphorylation, active STAT3 enters the cell nucleus, where it binds to the gene promoter, activating its expression [18]. Within a few hours of the generalized inflammatory response, the concentration of hepcidin in the blood serum increases, which leads to a reduction of available iron concentration – initially by inhibiting the release and absorption, but in the long term also as a consequence of the constant consumption of iron by tissue metabolism and erythropoiesis [21]. Studies on animal models have also shown that in response to selected bacterial antigens, hepcidin expression increases in body cells other than hepatocytes – in response to inflammation – to a much lower degree than in the liver. Hepcidin is also produced in macrophages, with particular emphasis on production in the spleen [23, 24]. Attention should also be paid to increased hepcidin production as a result of non-infectious diseases associated with an increased concentration

TABLE 1. Diseases associated with dysregulation of hepcidin [27–31]

Hepcidin in blood serum – increased	Hepcidin in blood serum – decreased
Chronic kidney disease	Hereditary hemochromatosis
Inflammatory bowel diseases	Juvenile hemochromatosis
Neoplastic diseases (e.g. renal cell carcinoma, breast cancer, prostate cancer, myeloma, ovarian cancer)	Chronic liver disease
Iron-refractory iron deficiency anemia	Polycystic ovary syndrome
Anemia of chronic disease	Acromegaly
Rheumatoid arthritis	Iron deficiency anemia
Myelofibrosis	
Inflammation (e.g. *Yersinia* spp.)	
Systemic lupus	
Tuberculosis	

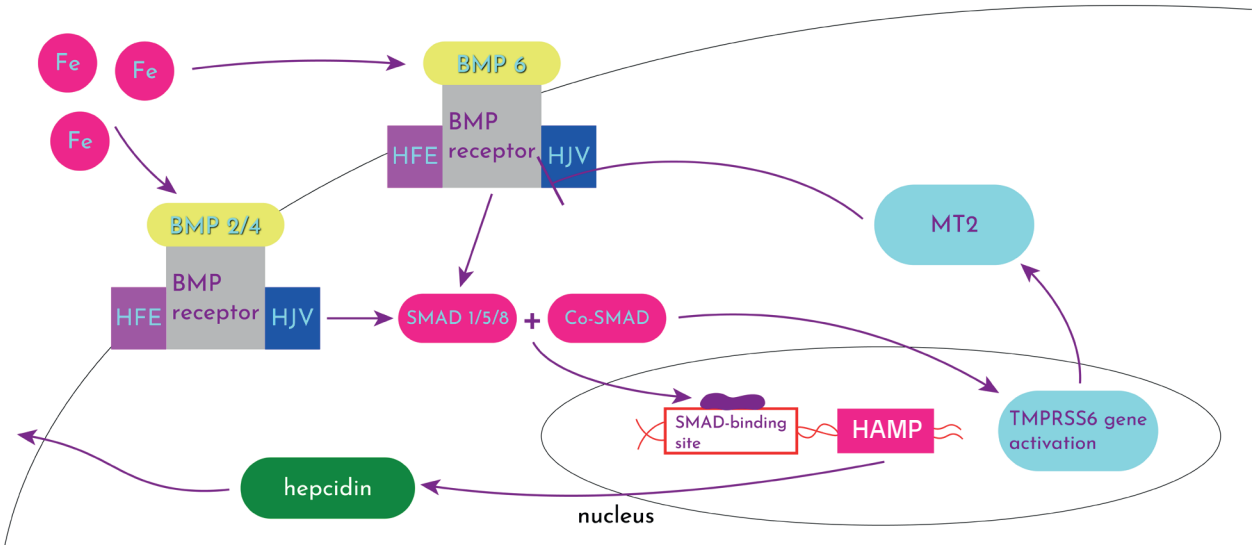

FIGURE 1. Hepcidin production – iron signaling

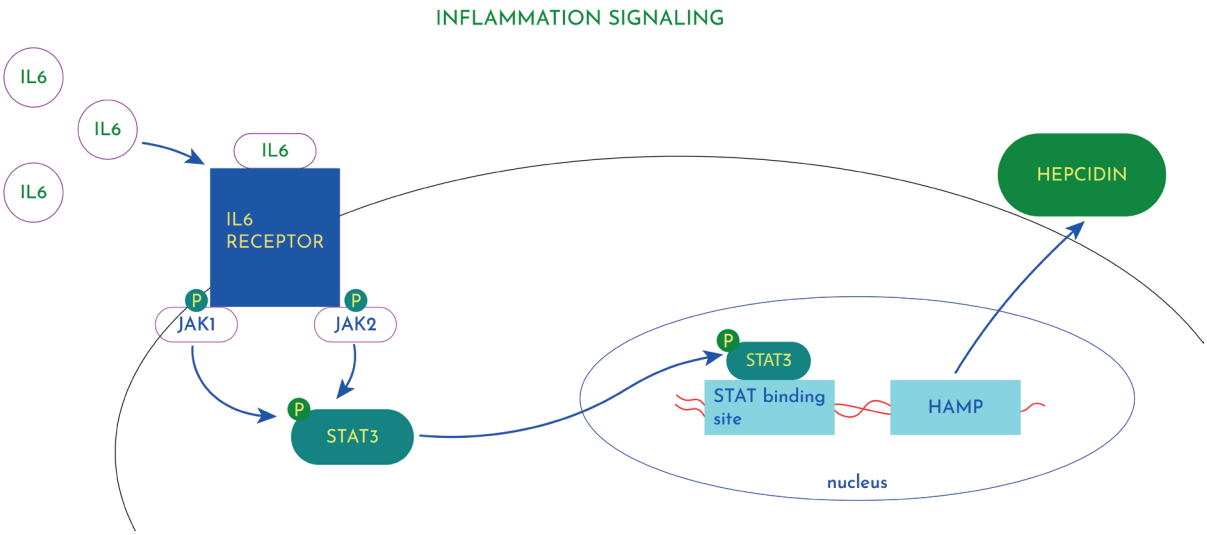

FIGURE 2. Hepcidin production – inflammation signaling

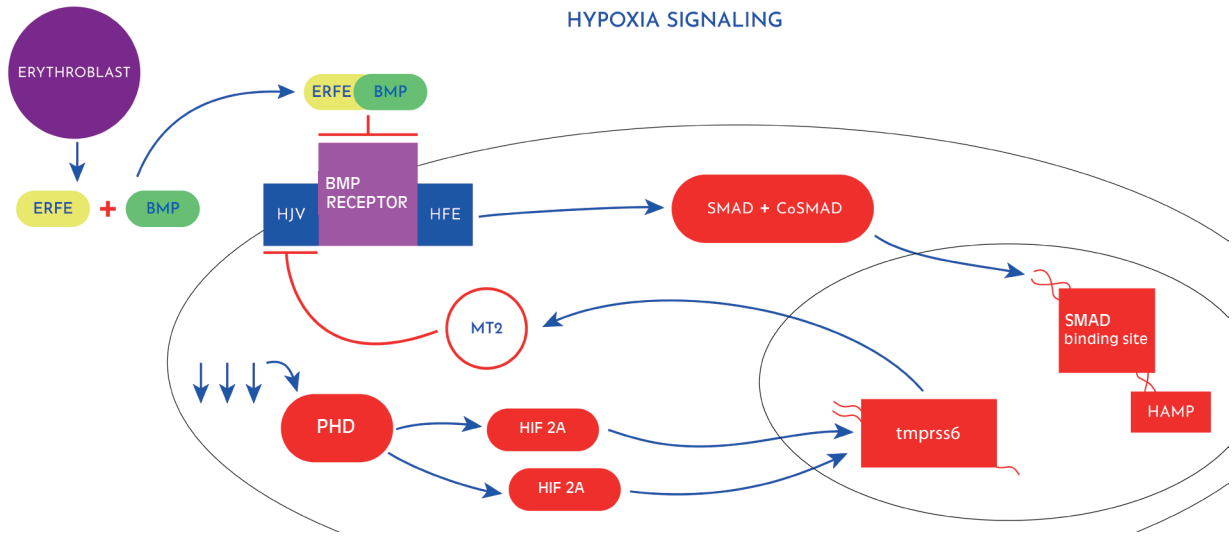

FIGURE 3. Hepcidin production – hypoxia signaling

of pro-inflammatory cytokines, e.g. in rheumatoid arthritis or chronic kidney disease [25, 26]. Examples of diseases connected to both increased and decreased hepcidin levels in blood serum are presented in Table 1. Mechanisms regulating hepcidin production are presented in Figures 1-3.

IRON ABSORPTION AND HEPCIDIN

The human body maintains a constant level of this element in tissues of about 3–4 g in the adult population; the daily loss of 1–2 mg is supplemented by the absorption of iron from food in the digestive tract [32]. Iron metabolism is slightly more dynamic in the pediatric population, and its regulation changes with age. Healthy, full-term newborns have tissue stores of iron after birth which enable them to function and develop properly despite the relatively low concentration of this element in mother's milk, and consequently low absorption from the digestive tract [33]. These reserves are depleted in the first six months of life, which is why, during the period of intensive growth and development, demand for this element increases significantly. During this time, the mechanisms of iron absorption control develop. This mechanism was investigated in a study showing a difference in iron absorption from food in two groups of children, 6 and 9 months old. In both groups, iron absorption from milk was monitored, both with and without additional supplementation. Patients from the younger age group did not show differences in absorption, whereas children aged 9 months who received supplementation showed lower absorption of iron from food compared to their peers without additional supplementation [33]. The differences in the recommended daily iron intake for children depending on age result from changes in the amount of iron stored and its absorption. The 2016 WHO guidelines suggest that the daily iron intake in children aged 6–23 months should be 10–12.5 mg, in the age group 24–59 months 30 mg, and from 5 years of age 30–60 mg [34].

Iron absorption from dietary sources takes place in the duodenum and proximal sections of the small intestine. Due to the presence of divalent metal ion transporter 1 (DMT-1) in enterocytes, iron ions previously reduced by duodenal cytochrome B (DcytB) are absorbed into the cells [35]. Further transport from the cytoplasm of enterocytes to the blood occurs thanks to the function of ferroportin – a transmembrane protein acting as an iron transporter in enterocytes, located in their basolateral wall [30]. To fully understand the mechanism by which hepcidin regulates iron absorption from the intestine by acting on ferroportin, it is also important to understand the structure of this carrier. Ferroportin is a protein composed of 571 amino acid residues with a complex three-dimensional structure [32]. It consists of 6 transmembrane spiral structures connected by a cytoplasmic loop, 2 of which form a cavity that is the point of iron transport from the cytoplasm to the blood [22, 32]. In the case of ferroportin dysfunction, iron is stored in the cytoplasm of intestinal epithelial cells, and with their death after 3–4 days and desquamation, iron loss increases [36].

Hepcidin regulates iron absorption from the gastrointestinal tract by two mechanisms. The first one involves the binding of the hepcidin molecule to the transmembrane coils that make up ferroportin. This leads to conformational changes in the ferroportin molecule, which inhibits its ability to transfer iron ions from the cytoplasm to the blood serum [37]. Studies show that the ability of hepcidin to bind to ferroportin is largely dependent on the initial saturation of the transport protein with iron ions. This mechanism allows hepcidin molecules to selectively block ion transport in enterocytes highly loaded with iron ions [38].

The second mechanism that inhibits iron absorption is the endocytosis and degradation of ferroportin in re-

sponse to binding to hepcidin molecules [39]. As a result of the above-mentioned connection, ferroportin is ubiquitinated – a process currently considered to be crucial for initiating the process of ferroportin endocytosis [40]. Further degradation of ferroportin occurs inside the cell in the presence of lysosomes [39].

THE IMPORTANCE OF MACROPHAGES IN IRON METABOLISM

Intestinal epithelial cells are not the only place where hepcidin affects iron metabolism in the human body. A separate target point is macrophages, whose role in regulating circulating iron concentration is based on phagocytosis and degradation of damaged and aging erythrocytes and subsequent recovery of heme iron contained in these cells [41]. This process involves the release of heme groups from hemoglobin molecules, which are then decomposed by heme oxygenase, releasing iron ions [32]. Free iron ions constitute a reserve that is released from phagocytic cells into the blood serum in the presence of ferroportin, the function of which is regulated by hepcidin in the mechanism described above. The impact of macrophage-released iron on bone marrow hematopoietic stem and progenitor cells was highlighted in a study published in 2025. Knock-out mice with targeted deletion of ferroportin in the myeloid lineage developed age-related anemia with microcythemia [42]. Deletion of ferroportin resulted in iron trapping in macrophages, leading to a number or irregularities, such as the aforementioned anemia, unbalanced erythropoiesis vs. megakaryopoiesis, tissue macrophage overload, and extramedullary hematopoiesis [42].

Differences in ferroportin expression were also observed in a study on circulating monocytes in patients with polycythemia vera (PV). It has been reported that monocytes play a role in heme degradation and externalization of residual iron after engulfment of erythrocytes. Moreover, in PV monocytes, ferroportin expression was reduced, which suggests its additional role in iron metabolism connected to this particular disease, as the iron may be maintained intracellularly in monocytes rather than being externalized [43].

HEPCIDIN AND ITS EFFECT ON ERYTHROPOIETIC CELLS

Ferroportin, an iron transporter, is also found on the cell membrane of erythroblasts[44]. It has been shown that by affecting the hepcidin-ferroportin axis, erythropoiesis is inhibited by the mechanism of limiting the availability of iron, which is a substrate for its production [44]. It is assumed that this mechanism is aimed at reducing the acquisition of iron by hematopoietic cells for erythropoiesis in situations when there is a deficiency of iron available to other tissues [44]. In contrast, when the systemic iron levels are high, hepcidin blocks ferroportin on erythroid cells, stopping the export of iron out of erythroid cells, leading to increased iron and red blood cell production [45].

A study on an animal model published in 2018 showed that ferroportin plays a significant role in erythropoietic cells, not only in the case of iron deficiency. Knock-out mice lacking ferroportin on the erythroblast membrane suffered mild hemolytic anemia, which was a result of erythrocytic iron overload and resulting oxidative injury [46]. Mice developed lower serum iron levels and ferroportin expression in spleen and liver was increased even though the hepcidin levels remained stable [46].

HEPCIDIN AND ITS ROLE IN ANEMIA

Anemia is defined as a decreased serum hemoglobin concentration, a reduced number of red blood cells, or a loss of function of red blood cells [2]. It is a significant health problem worldwide – in 2019 it affected 1.76 billion people – and the main cause is considered to be iron deficiency anemia [2]. Iron is necessary for hematopoiesis as a component of heme groups that enable hemoglobin to bind and transport oxygen. Beside the anemia resulting from an insufficient supply of iron in the diet, there is a completely different type of anemia also associated with a deficiency of functional iron in the body – anemia of chronic diseases, otherwise known as anemia associated with inflammation [47]. Diseases that increase the risk of anemia resulting from this mechanism include, among others, autoimmune diseases, cancer, chronic inflammatory diseases, obesity, and chronic kidney disease [47]. The process of developing anemia associated with chronic diseases is complex and is associated with reduced iron concentration in blood serum, impaired hematopoiesis, and shortened erythrocyte survival time [48]. The role of interleukins produced in chronic inflammation, their influence on hepcidin production, and, as a result, on the reduction of tissue iron availability – which is one of the above-mentioned mechanisms – has been described in detail above. Impaired hepcidin regulation leading to anemia may result not only from chronic inflammation, but also from genetic mutations leading to hepcidin overproduction. Patients with mutations of the Tmprss6 gene – whose product, martipase-2, as mentioned above, lowers hepcidin expression in liver – suffer from anemia with no or minimal response to oral supplementation. This phenotype, with congenital, lifelong moderate to severe microcytic hypochromic anemia and severe hypoferremia with very low transferrin saturation is known as iron-refractory iron deficiency anemia (IRIDA) [49]. IRIDA is typically considered an autosomal recessive disorder that needs iron IV therapy. However, heterozygous *TMPRSS6* variants have been reported, which respond better to oral supplementation [50].

The influence of hepcidin on the development of anemia, both hereditary and from chronic disease, has directed researchers' attention towards potential therapeutic pathways inhibiting its effect on iron metabolism.

The first target is reducing hepcidin production. The mechanism stimulating hepcidin production has been described above in relation to the concentration of hemojuvelin, acting as a BMP6 co-receptor. Research on mice showed that administration of antibodies directed against hemojuvelin resulted in suppression of hepcidin gene expression by inhibiting the BMP/SMAD pathway [51]. In March 2024, the results of the first clinical trial conducted on healthy volunteers were published. The study showed the efficacy of the molecule DISC-0974, a human antibody against hemojuvelin, in reducing the concentration of hepcidin in the serum of patients [52]. A similar effect based on the inhibition of SMAD 1/5/8 phosphorylation was obtained by administering LDN-193189 molecules to mice – in these mice the expression of the mRNA of the hepcidin antimicrobial peptide (Hamp) gene encoding hepcidin was inhibited [53]. However, it has been reported that LDN-193189 may affect other, non-SMAD pathways, resulting in "off target" results in human cells; further studies are important in this case [54]. Among the drugs that may potentially be used in the treatment of anemia of chronic diseases by inhibiting the production of hepcidin, one should also mention heparin, which, by binding to BMPs, inhibits the described signaling pathway [55]. This effect was confirmed in a study on healthy volunteers: reduction in serum hepcidin concentration was achieved after the use of sevuparin [56]. Reduction of the concentration of hepcidin in blood serum by inhibiting its production can also be achieved by inhibiting the pathway responsible for activation of mRNA expression in response to the inflammatory process; studies on animal models have shown the effectiveness of the AG 490 molecule – a tyrosine kinase inhibitor – in inhibiting the JAK2/STAT3 pathway [57, 58]. In patients with idiopathic primary myelofibrosis (MF), blood count parameters were improved by blocking the activin A receptor type 1 (ACVR1)/SMAD pathway, leading to increased transcription of genes encoding hepcidin. This effect was achieved by using momelotinib, a molecule blocking JAK tyrosine kinases responsible for activation of the BMP/SMAD pathway with the participation of AVCR1 [59]. In July 2024, the results of research on rocaglamide in an animal model were also published. It was found that by inhibiting the Il6/STAT3/hepcidin axis, iron metabolism parameters were improved in animals exposed to lipopolysaccharides, which in the process of chronic inflammation in the body have an activating effect on the production of IL6, leading to the development of anemia [60]. The MOMENTUM study assessed the efficacy of the treatment used in comparison with the previously recommended drug, danazol, demonstrating the superiority of the proposed new treatment [61]. The safety and efficacy of the proposed treatment were also confirmed in the randomized SIMPLIFY study, which compared momelotinib with ruxolitinib, previously used in the treatment of MF [62]. Similar effects were also reported for curcumin and the PpYLKTK peptide [63]. Tocilizumab, an antibody directed against IL-6, also plays a role in influencing this signaling pathway by inhibiting activation of the JAK2/STAT3 pathway [64]. A study conducted in monkeys showed beneficial effects in the treatment of anemia in individuals with chronic arthritis [64]. It should be mentioned, however, that JAK/STAT inhibition may have a dual effect on the human body: a positive one, improving iron levels in anemia of chronic disease, but on the other hand, this pathway plays a significant role in body defense mechanisms. This may result in lowering natural abilities to respond to potential infection, causing bacterial and viral disease having a more severe course. Such clinical implications are especially significant in the case of non-selective JAK inhibitors [65].

A separate therapeutic process in the treatment of anemia of chronic diseases resulting from excessive production of hepcidin involves not only blocking its production but also using substances that directly neutralize the molecules that have already been produced. One candidate for this function is PRS-080 # 022, a lipocalin-based molecule, whose action is based on direct antagonistic effects on hepcidin [66]. In 2019, the results of the first phase of research on the mentioned drug were published [66]. The results correspond to the results obtained in animal models but require further studies [66]. A method already known in clinical practice that allows inhibition of selected molecules is the use of specific antibodies directed against them. In 2017, the results of the first phase of clinical trials conducted in patients suffering from anemia in the course of oncological disease were published. The results of the studies showed good tolerance of the drug (LY2787106) and improvement in the scope of iron metabolism [67]. Hepcidin deactivation can also be achieved by using synthetic oligonucleotides – Spiegelmers – whose action allows binding and neutralization of selected molecules. In 2016, the results of research on a drug based on this method were published. The placebo-controlled study involved 64 healthy volunteers, and the results indicated a beneficial effect on the concentration of iron and ferritin in blood serum [68].

The effect of hepcidin on the body's iron metabolism can also be mitigated by blocking the hepcidin–ferroportin axis. In 2018, the results of clinical trials conducted on the monoclonal antibody LY2928057 blocking the binding of hepcidin to ferroportin were published [69]. Observations to date indicate a positive effect on iron concentration in blood serum, but the drug requires further research [69]. All of the aforementioned drugs are presented in Table 2.

The effect on the body's iron metabolism by modifying the concentration of hepcidin is also observed when

TABLE 2. Current therapeutic strategies targeting hepcidin – anemia treatment

Drug	Mechanism	Therapeutic implication	Potential side effects and additional information
Reduction of hepcidin blood serum concentration by suppressing production			
DISC-0974	Human antibody against hemojuvelin	Anemia associated with inflammation	Study on healthy volunteers – results published in March 2024 Safety and tolerability comparable to placebo
LDN-193189	Inhibition of Hamp expression leading to lowering hepcidin serum concentration	Anemia associated with inflammation	Studies on animal models May impact non-SMAD pathways, causing stress response signals [1]
Sevuparin	Heparin binds to BMPs, inhibiting the BMP-SMAD pathway	Anemia associated with inflammation	Study on healthy volunteers
AG 490	Tyrosine kinase inhibitor inhibiting the JAK2/STAT3 pathway	Anemia associated with inflammation	Studies on animal models JAK inhibition may impair host defense mechanisms, increasing susceptibility to certain bacterial and viral infections [2] JAK inhibitors may induce anemia through impaired hematopoiesis [3]
Momelotinib	Blocking JAK tyrosine kinases responsible for activation of the BMP/SMAD pathway, resulting in blocking the activin A receptor type 1 (ACVR1)/SMAD pathway	Idiopathic primary myelofibrosis Anemia associated with inflammation	Safety confirmed in SIMPLIFY study JAK inhibition may impair host defense mechanisms, increasing susceptibility to certain bacterial and viral infections [2] JAK inhibitors may induce anemia through impaired hematopoiesis [3]
Rocaglamide	Inhibition of the Il6/STAT3/hepcidin axis Reduction of hepcidin overproduction in response to inflammation	Anemia associated with inflammation	Study on animal models – July 2024 May present proapoptotic activity in leukemia cells by differential modulation of the activities of MAPKs [4]
Tocilizumab	Antibody directed against IL-6, inhibits activation of the JAK2/STAT3 pathway	Anemia associated with inflammation	
Molecules neutralizing hepcidin			
PRS-080 # 022	Lipocalin-derived molecule, directly antagonistic to hepcidin	Anemia associated with inflammation	Results of the first phase of research published in 2019
LY2787106	Antibody against hepcidin	Anemia associated with inflammation	Results of the first phase of clinical trials conducted in patients suffering from anemia in the course of oncological disease published in 2017
Spiegelmers	Binding and neutralization of hepcidin	Anemia associated with inflammation	Placebo-controlled study involving 64 healthy volunteers published in 2016
Hepcidin to ferroportin binding			
LY2928057	Antibody blocking binding hepcidin to ferroportin	Anemia associated with inflammation	Clinical trials published in 2018
Unknown mechanism			
Dapagliflozin	Improvement in iron metabolism parameters and decrease in serum hepcidin concentration in patients with type 2 diabetes treated with this SGLT2 inhibitor	Anemia associated with inflammation	

using drugs whose main mechanism of action on hepcidin expression has not yet been identified and which are used in other diseases. In 2020, a paper was published that reported an improvement in iron metabolism parameters and a decrease in serum hepcidin concentration in patients with type 2 diabetes treated with the SGLT2 inhibitor dapagliflozin [70].

All the above therapeutic pathways focused on inhibiting the hepcidin-ferroportin axis in a situation where iron resources are reduced. However, iron overload in the course of hematological diseases such as polycythemia vera is a separate clinical problem. In 2024 a revised classification of primary overload syndromes based on the hepcidin/ferroportin system was suggested [71]. In 2024 the results of the second phase of clinical trials of rusfertide – a peptide with mimetic activity to hepcidin – were published. In patients with polycythemia vera participating in the study, an improvement in hematocrit values as observed [72]. This drug has also completed the second phase of clinical trials for use in hereditary hemochromatosis; the results published in 2023 indicated a beneficial clinical effect [73]. In May 2024 the results of a study conducted on healthy volunteers were published, which assessed the pharmacokinetics, pharmacodynamics, and safety of this drug compared to placebo; the results supported the effectiveness and safety of the proposed therapy [74]. The study results were consistent with a randomized controlled trial examining the drug's pharmacokinetic properties and safety, the results of which were published in November 2024 [75]. Another proposed therapeutic approach for the treatment of iron overload in the course of polycythemia vera is the potential use of antisense nucleotides directed against transmembrane protease serine 6 (Tmprss6), leading to increased expression of genes responsible for the production of hepcidin [76]. One of them is sapablursen – currently in the second phase of clinical trials assessing its effect on reducing the need for therapeutic bloodletting in patients with polycythemia vera [77]. A similar potential target is small interfering RNA (siRNA)-based drugs causing a decrease in MT2 expression, and as a result an increase in serum hepcidin concentration and a decrease in iron overload. Such observations in animal models carry therapeutic opportunities for patients suffering from B-thalassemia using a substance designated as SLN124 [78]. All of the mentioned drugs are presented in Table 3 and Figures 4–6.

CONCLUSIONS

Hepcidin is an important element of the mechanisms regulating homeostasis by influencing iron metabolism. As an acute phase protein, it enables improvement of the body's defense mechanisms in the event of a threat from bacterial pathogens. The production of hepcidin dependent on inflammatory cytokines means that a significant increase in this protein is also noted in chronic inflammatory diseases. This is of particular importance in relation to the regulation of iron absorption and bioavailability in the human body. In patients suffering from chronic inflammatory diseases, anemia often occurs, which is not so much due to iron deficiency in the diet or its excessive loss, but rather to impaired absorption and reduced availability at the cellular level. This condition is caused by increased hepcidin production in response to the ongoing inflammatory process. For this reason, the mechanisms of iron metabolism control dependent on hepcidin have become of interest to research groups looking for therapeutic possibilities consisting in blocking

TABLE 3. Current therapeutic strategies targeting hepcidin – iron overload treatment

Drug	Mechanism	Treatment	Additional information and potential side effects
Rusfertide	Peptide mimicking hepcidin activity	Polycythemia vera Hereditary hemochromatosis	Results of 2nd phase of clinical trials in patients with polycythemia vera published in 2024 Results of 2nd phase of clinical trials for use in hereditary hemochromatosis published in 2023 Randomized controlled trial published in 2024
Sapablursen	Antisense nucleotides directed against MT2 Increased expression of genes responsible for production of hepcidin.	Polycythemia vera	Currently in second phase of clinical trials in polycythemia vera (2025)
SLN124	Small interfering RNA (siRNA)-based, causing a decrease in Tmprss6 expression Increased expression of genes responsible for the production of hepcidin	Polycythemia vera	Studies in animal models

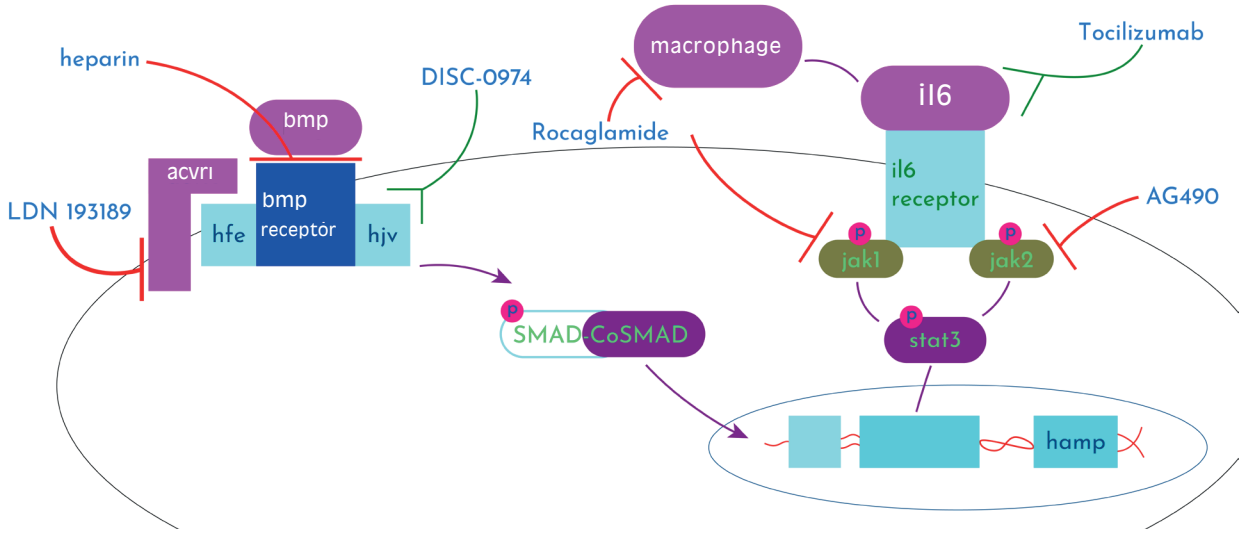

FIGURE 4. Treatment – hepcidin production

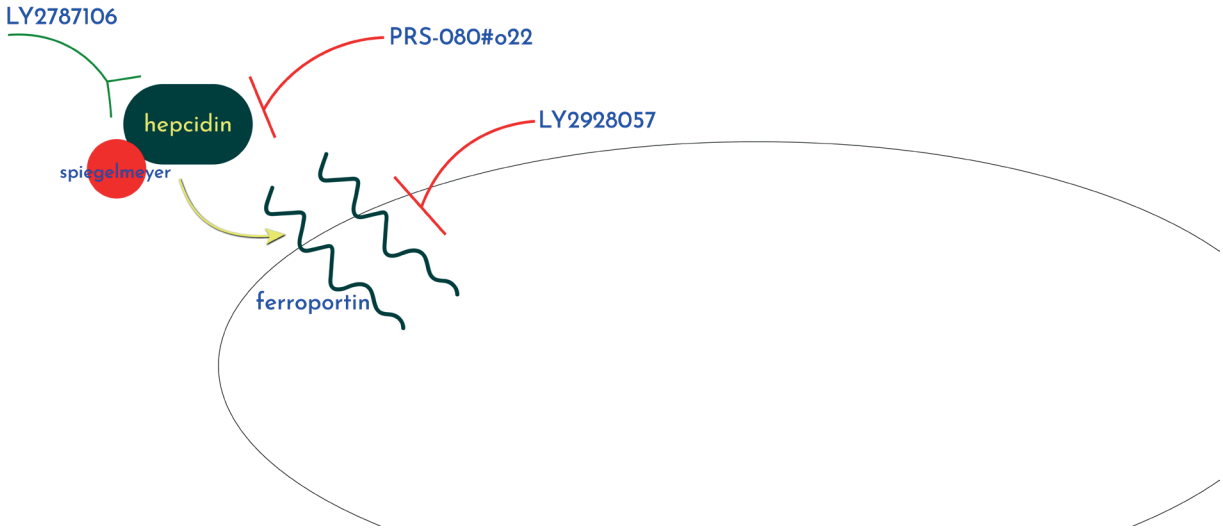

FIGURE 5. Treatment – hepcidin neutralizing

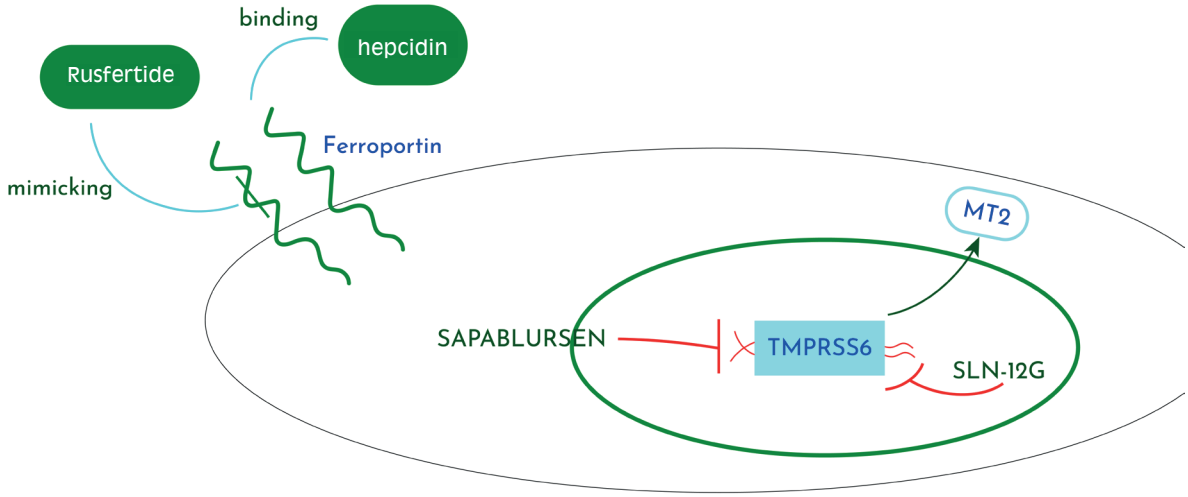

FIGURE 6. Treatment – iron overload

the function of this protein in reducing the bioavailability of dietary iron by blocking the hepcidin-ferroportin axis. The results of the studies indicate the possibility of developing this therapeutic pathway in the future, but they require in-depth clinical studies. A separate point of interest is attempts to treat hematological diseases associated with iron overload with drugs that perform a mimetic function to hepcidin. Also in this field, the results indicate the possibility of developing therapeutic directions.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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