Iron Deficiency Anemia, Anemia of Chronic Disease, Iron Overload: Use of Hepcidin as a Laboratory Marker in the Diagnosis Along With its Therapeutic Implications and Management of Iron Homeostasis

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***Abstract*- Purpose:** Iron deficiency is mostly affecting nutritional deficiency in low and middle-income countries. Infants, young children, adolescent females, young females with heavy bleeding during menstrual periods, women of childbearing age, and old people are at a significant risk of iron deficiency. Doctors usually prescribe iron therapy in treating iron deficiency. Along with iron deficiency, iron overload is a serious complication when there is an excess of iron storage in the human body. Hemochromatosis, a hereditary genetic defect where an excess of iron absorption happens, caused primary iron overload. Iron overload also develops secondary to multiple transfusions in transfusion-dependent anemic patients (thalassemia, Myelodysplastic syndromes, etc.). Iron overload can damage organs, including the heart and liver, leading to serious complications if it is inadequate or lacks iron chelation therapy. Cytokines and acute phase proteins play a significant role in the etiology of anemia of chronic disease, which is also known as anaemia of inflammation. Hepcidin a peptide hormone regulates iron efflux from plasma-absorbing enterocytes, iron-recycling macrophages, and iron-storing hepatocytes. Hepcidin binds to its receptor ferroportin, a cellular iron exporter, and regulates the membrane content of ferroportin and ferroportin-mediated iron transfer to blood plasma. In iron deficiency, hepcidin reduces iron efflux into the plasma and promotes iron-dependent erythropoiesis. Inflammatory stimuli promote the production of hepcidin, which reduces iron intake in inflammatory anaemia. Hepcidin deficiency results in iron overload in hereditary hemochromatosis, whereas excess hepcidin is associated with inflammatory anaemia, chronic renal disease and iron-refractory anaemia, leading to iron deficiency anemia. The mechanism of hemochromatosis is because of impaired synthesis of hepcidin or impaired hepcidin binding to ferroportin. Hematology parameters and iron studies have limits in diagnosing iron deficiency anaemia , anaemia caused by chronic disorders, according to several studies, as both conditions can produce similar laboratory results. This paper reviews the importance of hepcidin in making a thorough diagnosis of anemia, before starting the treatment, along with serum hepcidin as a prognostic tool for the early detection of early response to oral iron therapy and iron overload (hemochromatosis). Current therapeutic options are limited to control iron levels by regulating the hepcidin/ferroportin axis. This literature review includes reviewing a summary of some of the research in advanced clinical studies on various aspects of hepcidin tuning**,** understanding the mechanism of hepcidin and its pathological components which may lead to advanced therapies, and alternative therapies, along with the importance of new treatment options, including modulation and inhibition of hepcidin activity and its future use in clinical trials and implementing the latest treatment options.

Methodology: The information was collected from secondary sources published in various scholarly journals selected from google scholar. The research articles systematically reviewed and identified hepcidin's role in iron homeostasis, therapeutic and diagnostic advances, and research gaps in the research field.

Results/Findings: Based on a systematic review, the current status of the management of iron homeostasis and its limitations are identified. Hepcidin's role in the diagnostic and therapeutic field is explained. Future advances and research gaps in the management of iron homeostasis are explained in the literature review.

***Index Terms*-** Hepcidin, Iron deficiency, Iron overload, Anemia, Ferroportin

I. INTRODUCTION

Around two billion individuals worldwide, especially in developing and under-developed nations, suffer from iron deficiency anemia. IDA is more common in babies after six months of age, young women with heavy menstrual bleeding, women of childbearing age, and older people. Iron therapy is the primary treatment for iron deficiency. [1]. Common iron deficiency anemia

symptoms include tachycardia, tachypnea, headache, palpitations, rash, glossitis, restless leg syndrome, irritability, and fatigue. According to Sonia Bouri et al.2018 [2], determining the cause of anemia is important because patients with iron deficiency deserve prompt investigation, as eight to fifteen percentage of these patients diagnosed with gastrointestinal cancer. If there is no iron deficiency, the research may be directed elsewhere. If iron deficiency is suspected, the following laboratory tests are performed.
Laboratory features of iron deficiency include:

Hematology:
Hemoglobin, RBC count
Low red cell indices, including MCV, MCH, and MCHC.
High RDW
Low reticulocyte hemoglobin content (CHr)
Biochemistry:
Low serum iron
Low ferritin
Increased serum ferritin
Low transferrin saturation
Increased iron zinc protoporphyrin
Increased soluble transferrin receptors
Low serum hepcidin
*MCV: Mean cell volume
*MCH: Mean cell hemoglobin
*MCHC: Mean cell hemoglobin concentration
*RDW: Red cell distribution width

In iron-refractory anemia bone marrow does not respond to oral iron therapy and the hemoglobin level rises >=1g/dl after4 -6 weeks. Persistent anemia is usually associated with gastrointestinal diseases. In pathological conditions, where the content of hepcidin increases, the absorption of iron weakens, reducing the content of plasma iron in blood circulation. Margherita et al. [2021] summarized underlying conditions, gastrointestinal diseases, hepcidin dysfunction, and therapeutic and diagnostic approaches in refractory anemia. Refractory anemia shows a genetic disease caused by a mutation in TMPRSS6. The gene that encodes the serine 6 transmembrane protease, also known as matriptase-2. To prevent the progression of iron deficiency anaemia, the responsiveness to iron therapy in refractory anaemia needs particular care and treatment. [3].

Anemia of inflammation (AI), also known as anaemia of chronic disease, includes chronic lung disease, kidney failure, congestive heart failure, etc. AI is the most prevalent anaemia in hospitalised and chronically ill individuals. owing to inflammation, cytokines (e.g., interleukin-6) increase hepcidin synthesis causes reticuloendothelial cells to retain iron, inhibit iron absorption in the intestine and results in shortened red blood cells' half-life [4]. Proinflammatory cytokines, including interleukin-1, interleukin-6, interleukin-10, and gamma interferon or alpha tumour necrosis factor, produced during anemia of chronic disease (anemia of inflammation), increase the expression of hepcidin, which inhibits absorbing iron and releases iron into the blood, causing iron-depleted erythropoiesis. Anemia of chronic disease also leads to a decrease in erythropoietin as chronic kidney disease progresses, especially because of the coexistence of other diseases such as diabetes, which causes nephropathy and reduces erythropoietin production in the kidneys, which also causes anemia [5]. Patients suffering from chronic diseases may have a poor appetite and insufficient dietary iron, as well as increased cytokines and interleukins, which cause an increase in hepcidin, which reduces iron absorption. Iron absorption, transport, and storage are tightly regulated in the body, and ferritin plays a crucial role [6].

Iron overload disorders represent a range of medical conditions that cause an increase in the body's iron stores and subsequent organ damage [7] β-Thalassemia's are inherited disease of hemoglobin production characterized by deficient hemoglobin synthesis leading to shortened erythrocyte (RBC) survival because of hemolysis and ineffective erythropoiesis in the bone marrow. In order to prevent heart failure and other iron related problems, iron chelation therapy is essential. Despite the availability of potentially affordable oral iron chelation therapy, many patients experience the adverse outcome of iron overload and eventually die each year as a result of inadequate or inadequate iron chelation therapy [12].

Hepcidin binds to ferroportin and regulates iron homeostasis. Hepcidin is produced in response to increased body iron stores to prevent iron absorption and prevent iron overload.BMP/SMAD signaling pathway, which triggers hepcidin induction of transcription. Inactivating mutations in components of this pathway lead to hepcidin deficiency and increased absorption into the bloodstream, leading to a genetically heterogeneous autosomal recessive disease of iron metabolism, known as hereditary hemochromatosis (HH),. The dominant form of HH is associated with mutations in the HFE gene and represents the most common genetic disease among Caucasians. Other variants caused by inactivating mutations in hemojuvelin (HJV), HAMP (hepcidin), or TFR2 (transferrin receptor 2). SLC0A1 (ferroportin) mutations that confer HH's metabolic phenotype is recapitulated by hepcidin resistance. However, ferroportin-associated

hemochromatosis happens in an autosomal dominant manner. Loss-of-function ferroportin mutations cause ferroportin disease, characterized by macrophage iron overload and low transferrin desaturation. Aceruloplasminemia and atransferrinemia are also inherites iron overload disorders resulting from the absence of ceruloplasmin or transferrin, plasma iron oxidase, and iron carrier, respectively [8].

Table 1: Hemochromatosis (iron overload)

DISEASE CONDITION	GENE	LOCUS	TRANSMISSION	PATHOLOGY HAPPENING	LABORATORY FEATURES	MAIN CLINICAL MANIFESTATION
HFE hereditary hemochromatosis	HFE	6p21.3	Recessive	Hepatocyte iron loading	↑ serum ferritin & transferrin saturation	Hepatic
HJV juvenile hemochromatosis	HJV	1q21	Recessive	Hepatocyte iron loading	↑↑ serum ferritin & transferrin saturation	Cardiac and endocrine
HAMP juvenile hemochromatosis	HAMP	19q13	Recessive	Hepatocyte iron loading	↑↑ serum ferritin & transferrin saturation	Cardiac and endocrine
TfR2 hereditary hemochromatosis	TFR2	7q22	Recessive	Hepatocyte iron loading	↑ serum ferritin & transferrin saturation	Hepatic
Ferroportin hemochromatosis	SLC40A1	2q32	Dominant	Hepatocyte iron loading	↑↑ serum ferritin & transferrin saturation	Hepatic
Ferroportin disease	SLC40A1	2q32	Dominant	Mainly Kupffer cell iron loading	↑↑ serum ferritin, normal/low transferrin saturation	Hepatic
Congenital aceruloplasminemia	CP	3q23-q24	Recessive	Mainly Kupffer cell iron loading, CNS iron loading	↑ serum ferritin & normal to low transferrin saturation	Neurologic
Congenital atransferrinemia	TF	3q22.1	Recessive	iron hepatocyte loading	↑ serum ferritin & transferrin saturation	Hepatic and hematologic

Hepcidin binding to its receptor ferroportin (a cellular iron exporter) and regulates the membrane content of ferroportin and ferroportin mediated iron transfer into the blood plasma. Ferroportin is a part of the solute carrier family. Through a conformational flip-flop mechanism that alters iron access from the intracellular and extracellular surfaces of the transformer, ferroportin promotes iron transport. Hepcidin regulates the activity of ferroportin by:

1. Ferroportin endocytosis and proteolysis induced by hepcidin
2. Hepcidin binds to the ferroportin's central cavity to seal it during iron transport to achieve high ferroportin occupancy.

Besides hormonal modulation of hepcidin-hepcidin-ferroportin, other systems, like hypoxia-inducible factors (HIFs) prolyl hydroxylases, are involved in the controlling systemic iron sensitive to iron concentration and hypoxia [9].

Alteration of hepcidin is a compensatory mechanism to regulate iron homeostasis under physiological conditions, including pregnancy. In pathophysiological conditions such as beta-thalassemia, myelodysplastic syndrome, inflammatory anemia, and hereditary hemochromatosis, the role of hepcidin is significant [10]. Understanding the underlying pathophysiology of iron metabolism can help improve the evaluation of iron deficiency and overload. Future therapy options could include targeted pharmacological manipulation of the hepcidin regulatory system besides iron supplementation and iron chelation. [11]. Understanding the role of hepcidin in iron

overload, iron deficiency and, a systematic review of current therapy in the management of iron homeostasis, advanced therapeutic options to control iron homeostasis by upregulating or downregulating hepcidin and the use of hepcidin as a diagnostic and prognostic tool in the early identification of iron excess and deficiency along with research gaps included in this paper.

II. OBJECTIVES :

A few targeted questions were and research objectives developed to understand hepcidin's role in iron deficiency anemia, iron overload, anemia of inflammation

1. Current diagnostic methods, and their limitations in early diagnosis of iron overload and iron deficiency
2. Role of hepcidin in making a thorough diagnosis of anemia
3. Role of hepcidin as a prognostic tool for the early detection of early response to oral iron therapy and iron overload.
4. Current therapeutic options for controlling iron homeostasis and its limitations
5. Understanding the role of hepcidin in new therapies, alternative therapies, the importance of hepcidin tuning and its implication in iron therapy, and its future use in clinical trials and implementing the latest therapeutic options.
6. To find out the research gap and research agenda which supports the physicians to change the treatment of physiological and pathophysiological conditions based on hepcidin treatment.

III. METHODOLOGY :

The literature review was based on a reviewing latest information collected from various secondary sources, including published literature from various scholarly journals. Relevant articles were selected using a computerized search using google scholar. In order to understand the current status of hepcidin in the laboratory diagnosis and its therapeutic implications, recent secondary sources were only used for literature evaluation.

IV. IRON HOMEOSTASIS.

4.1 Understanding Hepcidin's role in iron homeostasis.

Hepcidin is a small (25 amino acid) peptide hormone that is mainly responsible for regulating iron homeostasis in the body. Hepcidin is mainly produced by hepatocytes and, after entering the circulation, hepcidin can interact with the membrane-active cellular iron exporter ferroportin, causing its endocytosis, preventing iron efflux and promoting cellular iron retention. Together, hepcidin and ferroportin are currently the only known regulators of cellular iron export. Ferroportin is mainly expressed in cells involved in dietary iron assimilation and homeostasis in duodenal enterocytes, macrophages, and hepatocytes. Hepcidin expression is controlled by plasma iron levels and storage; this transcriptional control is made possible by the SMAD signalling pathway connected to the bone morphogenetic protein receptor. Hepcidin production is also increased by infection and inflammation, and this is associated with IL-6-induced JAK/STAT pathway activation. [13][14][15].

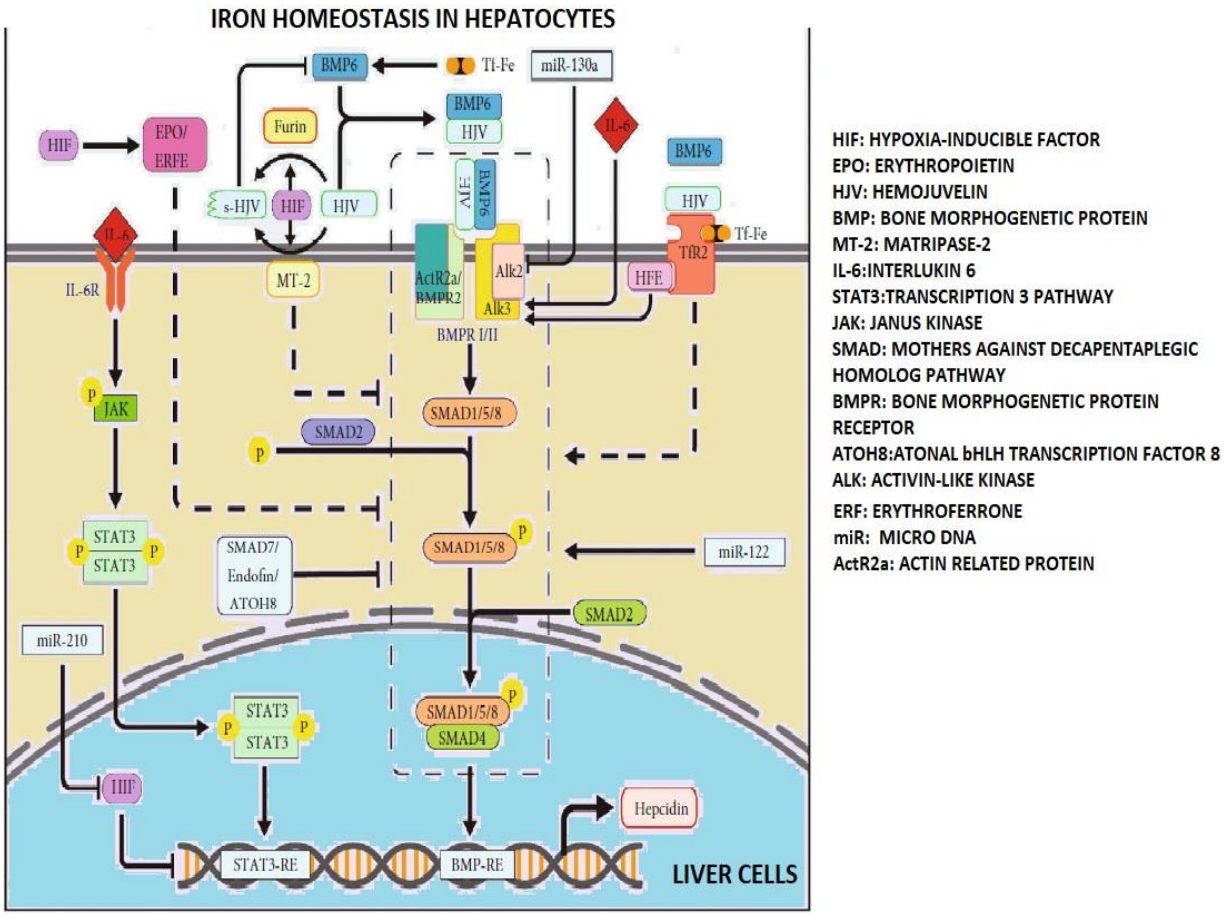

Fig. 1: Mechanism of iron homeostasis

4.2 Role of Hypoxia Inducible factors (HIFs)

Hypoxia-inducible factors (HIF'S) a transcription regulate how the body reacts to hypoxia (HIFs). HIFs bind hypoxia response elements to control erythropoiesis-related genes (e.g., Epo), angiogenesis, and metabolism. Normally, a hypoxic environment and increased HIF2α in the small intestine caused iron absorption on the apical side of enterocytes and iron absorption on the basolateral side, and iron limitation increases sensitivity to hypoxia [16].

4.3 Iron homeostasis in polycythemia vera

The most frequent JAK2 driver mutation is JAK2 V617F, which causes constitutive Epo-independent JAK-STAT activation and the overexpression of genes involved in the JAK-STAT pathway in polycythemia vera. Even before starting therapeutic phlebotomy, the cornerstone of therapy and subsequent phlebotomies, which frequently worse iron shortage, most patients with polycythemia are anemic at diagnosis. [16].

4.4 Acquired and genetic disorders in Iron homeostasis

Acquired and genetic disorders in iron homeostasis led to iron deficiency and iron overload [17]

Table 2: Acquired and genetic disorders in iron homeostasis led to iron deficiency and iron overload

DISORDER	INHERITANCE	GENE	PHENOTYPE
GENETIC IRON OVERLOAD WITHOUT ANEMIA			
HH type 1	AR	HFE	Inappropriate low hepcidin
HH type 2	AR	HJV	Low hepcidin
HH type 3	AR	TFR2	Low hepcidin
HH type 4	AD	SCL40A1	Hepcidin resistance

DISORDER	INHERITANCE	GENE	PHENOTYPE
GENETIC IRON OVERLOAD WITHOUT ANEMIA			
Ferroportin disease loss-of-function FPN mutations	AD	SCL40A1	Macrophage iron overload

DISORDER	INHERITANCE	GENE	PHENOTYPE
IRON LOADING GENETIC ANEMIAS			
ALPHA THALASSEMIA	AR	HBA	Iron overload, Microcytic anemia
BETA THALASSEMIA	AR	HBB	Iron overload, Microcytic anemia
CONGENITAL IRON SIDEROBLASTIC ANEMIA	X linked AR	TFR2	Iron overload, Microcytic anemia, Ring sideroblasts
SA and ataxia	X-linked	ABCB7	SA and ataxia
SIFD	AR	TRNT1	SA, immunodeficiency, and development delay
Type 1	AR	CDAN1	Anemia, splenomegaly, jaundice, erythroblasts
Type 2, HEMPAS	AR	SEC23B	
Type 3	AR	KIF23	
Hypotransferrinemia	AR	TF	Microcytic anemia, iron overload
DMT1 mutations	AR	SLC11A1	Microcytic anemia, iron overload
IRIDA	AR	TMPRSS6	Iron-deficiency anemia
Hyperferritinemia-cataract syndrome	AD	FTL promoter (IRE)	High serum ferritin in the absence of iron excess
Ferritinopathy	AD	FTL	Accumulation of iron in the Brain

DISORDER	INHERITANCE	GENE	PHENOTYPE
GENETIC IRON DEFICIENCY			
IRIDA	AR	TMPRSS6	Iron refractory anemia, Iron deficiency anemia

DISORDER	INHERITANCE	GENE	PHENOTYPE
GENETIC REGIONAL IRON FERRITIN ACCUMULATION			
Hyperferritinemia-cataract syndrome	AD	FTL promoter (IRE)	Increased ferritin in absence of iron overload, congenital cataract because of ferritin deposition in the eye
Ferritinopathy	AD AR	FTL FRDA	Iron accumulation in the brain, cardiac brain overload, neurodegenerative changes

DISORDER	INHERITANCE	GENE	PHENOTYPE
ACQUIRED IRON OVERLOAD			
Chronic blood Transfusion			Iron overload

DISORDER	INHERITANCE	GENE	PHENOTYPE
ACQUIRED IRON OVERLOAD			
Chronic blood Transfusion			Iron overload

DISORDER	INHERITANCE	GENE	PHENOTYPE
ACQUIRED IRON-LOADING ANEMIA			
RS MDS	Clonal disorder with somatic mutations	SF3B1	Iron overload, Macrocytic anemia, Ring sideroblasts

DISORDER	INHERITANCE	GENE	PHENOTYPE
ACQUIRED ABSOLUTE IRON DEFICIENCY			
Iron deficiency			Microcytic anemia with low iron

DISORDER	INHERITANCE	GENE	PHENOTYPE
ACQUIRED FUNCTIONAL IRON DEFICIENCY			
Anemia of Inflammation			Microcytic anemia with low iron

* AR= Autosomal recessive, AD= Autosomal disease, IRIDA= Iron refractory anemia, RS MDS =Myelodysplastic syndrome with ring sideroblasts

4.4 Published research work on the current and future advances in the treatment and diagnostics of iron disorders
De Amicis et al. [3] presented the current therapy used for iron deficiency anemia. Intravenous iron therapy is preferred for patients who don't respond to oral iron therapy, which is the most popular treatment technique used by clinicians worldwide.

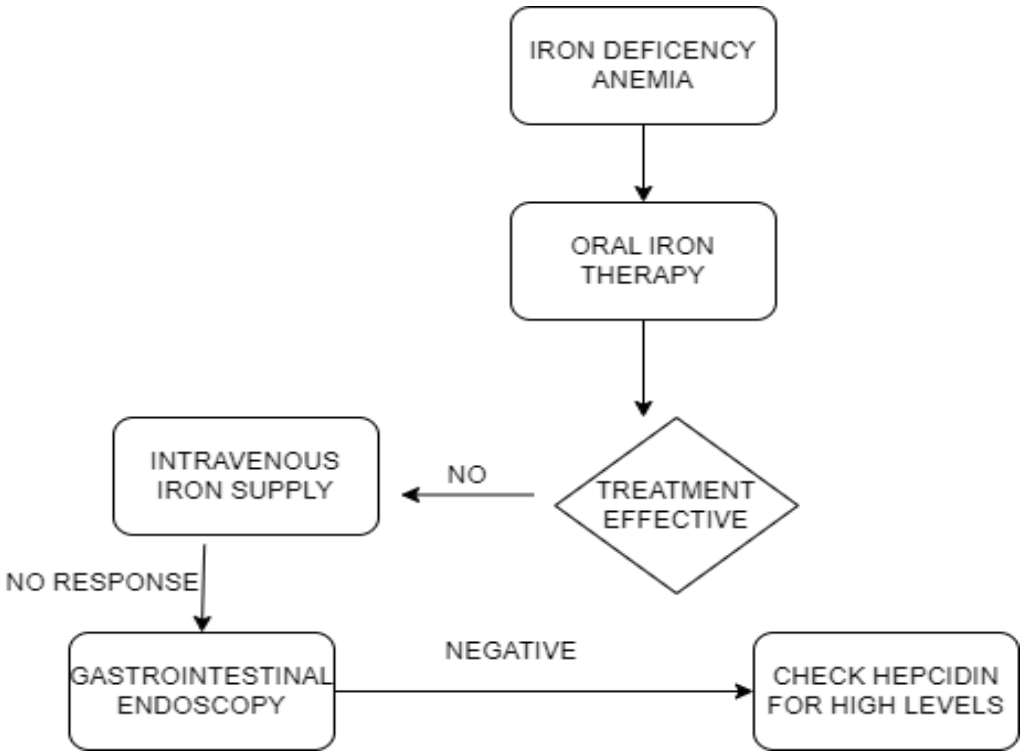

Fig. 2: Current Iron therapy

4.5 Related scholarly work in therapeutic advances, current trials of hepcidin in treated disorders in iron homeostasis

Table 3: Therapeutic advances in clinical trials in iron homeostasis disorders

SL.NO	Research Area	Outcomes and Findings	References
1	Inflammation impact on ferritin, hepcidin, in the management of iron deficiency anaemia in chronic renal failure.	Iron absorption in macrophages, a shortening in erythrocyte half-life, and cytokine-mediated malfunction of erythropoietin and erythroid progenitor cell development are all results of altered iron metabolism in macrophages in inflammatory anaemia. A reduction in iron content and a rise in the acute phase reactants ferritin and hepcidin are characteristics of inflammatory anemia .Effective treatments for inflammatory anaemia include managing the underlying condition, iron therapy, erythropoietin-stimulating agents, and blood transfusion in severe anemia cases. The paper highlights the significance of new therapy alternatives, such as hepcidin activity modulators or prolyl hydroxylase (hypoxia-inducible factor) inhibitors, and their usage in further clinical studies and the application of the latest treatment options.	L.Lanser et al. [2021] [18]
2	The latest drugs that can counterattack hepcidin's impact on iron homeostasis and treat the underlying disease that causes inflammatory anemia with iron therapy and erythropoiesis-stimulating agents	Anemia of inflammation (AI), commonly referred to as anaemia of chronic disease, is the most prevalent anaemia in hospitalised and chronically ill patients. Inflammation causes cytokines (like interleukin-6) to enhance the production of hepcidin, which therefore inhibits intestinal iron absorption and causes iron to be retained in reticuloendothelial cells and reduced red cell half-life. In addition to treating the underlying condition that causes inflammatory anaemia with iron therapy and erythropoiesis-stimulating medications, the study emphasises the importance of developing new drugs that can block hepcidin's effects, which include the redistribution of intestinal iron absorption and iron retention in reticuloendothelial cells. It was challenging to diagnose concurrent iron deficiency in the trial due to the fact that usual low iron deficiency and high ferritin also supported AI.	Weiss et al. [2019] [4]
3	Hepcidin's role in inflammation and neuronal iron overload	Recently, the role of hepcidin in neuronal iron overload and inflammation has been explained. Iron overload and inflammation often lead to neurodegeneration. Hepcidin crosses the blood-brain barrier, and when neurons are stimulated by a high dose of an inflammatory cytokine, the result is an increase in hepcidin levels, which causes the efflux of iron from the plasma to the brain, causing nerve cell damage. In addition, the manipulative function of hepcidin to restore neuronal degeneration and damage has been used in recent studies in animal models and cell cultures. Understanding hepcidin's dual role in iron overload and inflammation in brain cells will help open a new door to the treatment of neuronal damage in neurodegenerative diseases. Driton Vela [2018] found in his observational studies that the suppression of hepcidin occurs in inflammation, which leads to the flow of iron into the	Driton Vela et al. [2018] [19]

		brain, causing damage to neurons. Pre-treatment with hepcidin prevents brain neuronal iron overload in and protects cells against oxidative stress and inflammation-induced biochemical changes in neurons. However, the therapeutic significance of hepcidin pre-treatment in neurodegenerative diseases has not been thoroughly studied. Based on the importance of hepcidin in brain physiology, future studies of hepcidin in Alzheimer's and Parkinson's disease are warranted.	
4	Role of hepcidin and erythroferrone in the Pathogenesis of Beta Thalassemia and its key development of new strategies in its treatment	Iron overload (hemochromatosis) is common in patients with transfusion-dependent thalassemia major because of ineffective erythropoiesis and multiple transfusions. Tsz Yuen Au et al. [2022] summarized current clinical trials and research on the clinical implications of HAMP gene single nucleotide polymorphisms and new treatments for thalassemia and the role of hepcidin and erythroferrone. The review suggested the importance of including serum hepcidin and erythroferrone as prognostic tools for the early detection of hemochromatosis in beta-thalassemia because low hepcidin and high erythroferrone are important in the early diagnosis of iron overload. Mini hepcidins (hepcidin-like compounds) can restore iron in thalassemia, e.g.: LJPC-401, PTG-300, etc., it prevents the expression of TMPRSS6, or erythroferrone, which is effective in restoring in preliminary. studies iron homeostasis. In addition, research shows that the use of astragalus polysaccharide and icariin has recently been recognized as an inducer of hepcidin expression. The article sheds light on studying iron metabolism regulators and gene polymorphisms affecting iron homeostasis in the treatment of iron overload and beta-thalassemia.	T Y Au et al. [2022] [20]
5	Hepcidin's role in advanced treatment of thalassemia	Gene therapy and erythropoiesis regulation are two important advancements in thalassemia treatment that are currently in rapid development. Hepcidin levels are markedly decreased in thalassemia, and hepcidin therapeutic correction has a positive effect on erythropoiesis and iron metabolism. Synthetic hepcidin and hepcidin mimetic created for the clinical trial phase did not have an acceptable efficacy/safety profile, according to Filomena Long et al. [2022]. According to the paper, the best course of action is to specifically target erythroferrone, the major factor preventing hepcidin expression. Altering TMPRSS6, TfR1, TfR2, or ferroportin, a hepcidin target, are other strategies to enhance hepcidin function.	Filomena Long et al. [2022] [21]
6	Managing iron overload in Beta thalassemia patients	In this clinical case review, they focused on their experience treating such patients and addressed certain issues related to the management of iron overload in patients with beta-thalassemia syndrome. In a case series study, the pathophysiology of hemochromatosis and several techniques to assess, measure, and monitor it were looked at.. They also discussed chelation techniques that can be used with	V.M Pinto et al. [2020] [22]

		currently available chelating agents. They balanced the need to maintain minimal (zero) non-transferrin-bound iron levels 24 hours/7 days a week with the risk of over-chelation. The onset of endocrinopathy, osteoporosis, cirrhosis, renal failure, and malignant changes is linked to long-term exposure to iron toxicity. The study highlights that chelation therapy's main objective is to prevent 24 hour exposure to toxic iron and to keep the body's iron levels within normal ranges, preventing any chelation-related damage. The article states that secondary hepcidin suppression and increased intestinal absorption result in the primary portal and subsequent hepatocyte iron load and relatively lower serum ferritin levels compared to transfused patients. However, the study emphasized the importance of chelation therapy rather than therapeutic hepcidin reconstitution in the managing iron overload. In relation to chelation therapy in thalassemia patients, studies on regulating iron homeostasis by hepcidin rearrangement are necessary.	
7	Auranofin may increase hepcidin expression, reduces systemic iron overload and induce ferroptosis.	Lei Yang et al. [2020] identified iron modulators by functionally screening hepcidin agonists using a library of 60 FDA-approved drugs in human liver Huh7 cells. They also confirmed the results in C57BL/6J mice and a mouse model of hemochromatosis (Hfe-/- mice). The results of research recommended that the rheumatoid arthritis medication auranofin (AUR) may increase hepcidin expression. AUR at high doses (25mg/kg) produces ferroptosis and causes lipid peroxidation by decreasing the activity of thioredoxin reductase (TXNRD). The study provides evidence that thioredoxin reductase is a significant regulator of ferroptosis and that the drug auranofin is a novel hepcidin activator, suggesting a promising strategy to the treatment of hemochromatosis and hepcidin-deficient diseases.	Lei Yang et al [2020] [23]
8	Potential of dapagliflozin (a drug used to treat type 2 diabetes) in suppressing hepcidin and increased erythropoiesis	Husam Ghanim et al. [2022] investigated the potential of dapagliflozin (a drug used to treat type II diabetes) in a prospective, randomized, placebo-controlled trial. Type II diabetes is a pro-inflammatory condition in which hepcidin levels are increased because of inflammation, which inhibits erythropoiesis. They included 52 obese patients with type 2 diabetes who were randomized (1:1) to receive dapagliflozin (10 mg/day) or a placebo for 12 weeks. After dapagliflozin treatment, HbA1c significantly decreased, and concentration of hemoglobin and hematocrit significantly increased. Dapagliflozin treatment significantly decreased circulating hepcidin and ferritin concentrations, while the hepcidin inhibitor erythroferrone significantly increased plasma transferrin level and transient erythropoietin concentration. Transferrin receptors 1 and 2 in mononuclear cells were increased by a hypoxia-induced reduction in factor-1α expression in mononuclear cells (MNC), while it increased the expression of its inhibitor, prolyl hydroxylase-2.	Husham Ghanim et al. [2022] [24]

		MNCs harvested from lymphocyte media, and the expression of iron regulatory mediators was measured in MNCs by RT-PCR. HbA1c, and iron studies complete blood count, were calculated by established clinical tests and determination of hepcidin, erythroferrone, and ferritin by ELISA. They were not important. Changes in these indices in the placebo group. In summary, the study found a small but significant increase in hematocrit after treatment with dapagliflozin. Plasma hepcidin concentration was significantly decreased, and plasma transferrin concentration and transferrin receptor expression were increased. The significant reduction of hepcidin causes increased uptake of iron, resulting in increased erythropoiesis followed by increased hematocrit.	
9	Hepcidin, Iron and death in patients with acute renal failure	The study looked at the results of the Acute Renal Failure Research Network trial, which assessed the association of plasma catalytic iron, transferrin, ferritin, hepcidin, free hemoglobin, and total iron with 60-day mortality. Patients who are critically ill with acute kidney disease were included in the study. Of the 807 patients enrolled in the study, 51% (409) died before the 60th day. Both lower levels of hepcidin and higher levels of plasma catalytic iron were substantially related with an increased risk of mortality. The risk of death was 4.06 times higher for patients with catalytic iron levels in the highest quartile compared to the lowest quintile, and 3.87 times higher for patients with hepcidin levels in the lowest quintile compared to the highest quintile. The study's findings were consistent, and while other iron markers were also connected to mortality, catalytic iron and hepcidin had the strongest links. Patients requiring renal replacement therapy because of kidney illness are independently related to higher plasma levels of catalytic iron and lower levels of hepcidin. The study results suggest that hepcidin and catalytic iron can serve as effective prognostic indicators for patients with acute kidney injury and suggest that further studies needed to determine hepcidin and catalytic iron administration strategies that possibly useful in patients with renal failure.	DE Leaf et al. [2019] [25]
10	Hepcidin a key regulator of iron homeostasis	Recent evidence has shown that mutations in the human hemochromatosis gene (HFE) cause hepcidin deficiency, which leads to iron overload and contributes to hemochromatosis. Figuring out the mechanism of hepcidin and its pathological components in blood and iron disorders may lead to new therapeutic advances. Hepatic bactericidal protein (Hepcidin) is an iron-regulating hormone designed primarily for iron homeostasis. It is a cysteine-rich small cationic peptide produced by liver cells. Hepcidin has recently been extracted from human urine and plasma by ultrafiltration. The hepcidin antimicrobial peptide (HAMP) gene, also known as HFE, for high iron Fe, human hepcidin is	Saneela s et al. [2019] [26]

		located on chromosome 19q13,2637 base pairs long, consisting of two introns and three exons. The HAMP 19q13 gene is expressed in several locations, including the brain, liver, spinal cord, lung, heart, skeletal muscle, intestine, stomach, pancreas, testes, adipocytes, and macrophages. The post-translational process of hepcidin is mediated by the liver prohormone-converted furin. Hepcidin is initially produced as a larger precursor protein that undergoes two cleavages and is quickly secreted from the cell. Using the chemical inhibitor decanoyl-Arg-Val-Lys-Arg-chloromethyl ketone (dec-RVKR-cmk) to block furin protein convertase or block furin synthesis with small interfering ribonucleic acid (siRNA) results in the inhibition of the second cleavage of hepcidin precursor. However, its release from the cell is not blocked, which means that furin is the main enzyme involved in the maturation of hepcidin.	
11	Effect of treating iron deficiency diagnosed by hepcidin quantification on outcomes after a longer period of intensive care compared with conventional care	A controlled, single-blind, multicenter trial were conducted in seriously ill patients discharged from the ICU who were admitted for over 5 days awaiting intervention with either a hepcidin treatment protocol or a control. Hepcidin levels were evaluated to determine whether hepcidin levels provide an accurate guide to the management of iron deficiency in critically anemic patients after prolonged intensive care. Out Of the 399 analyzed patients, 220 (55%) had iron deficiency at discharge, with a hepcidin level of <41 µg/l. The prolonged stay was not reduced but significantly reduced 90-day mortality and improved 1-year survival in critically ill patients discharged home after a long stay. Patients were treated with intravenous iron (1 g ferric carboxymaltose) when hepcidin was < 20 µg/l and with intravenous iron and erythropoietin when hepcidin ≤20 and <41 µg/l.	Lasocki S et al. [2021] [27]
12	The renal hepcidin/ferroportin axis controls iron absorption and determines the extent of renal and systemic iron overload.	A new mice model with an inducible renal tubule-specific fpnC326Y knock-in encoding a hepcidin-resistant ferroportin called FPNC326Y. Under conditions of normal iron availability, female mice carrying this allele had a persistent decrease in renal iron content, but a transient increase in the systemic iron index. Under circumstances of excess iron availability, male and female mice carrying this allele had milder renal iron overload but greater systemic iron overload compared with controls. Despite comparable systemic iron overload, renal iron overload developed in wild-type mice fed an iron-rich diet, but not in hemochromatosis mice with a systemic fpnC326Y knock-out. The research demonstrates that, under physiological circumstances, endogenous hepcidin regulates ferroportin-mediated tubular iron absorption. It also demonstrates how crucial such regulation is for maintaining renal and systemic iron homeostasis in cases of iron overload.	Mohamad, G et al. [2021] [28]
13	Hepatic heparan sulfate is a master regulator of hepcidin expression	Hepcidin expression is regulated by the bone morphogenetic protein (BMP6)/SMAD1/5/8 pathway and the pro-inflammatory cytokine	M Pauli et al. [2019] [29]

		interleukin 6 (IL6). Heparin found to suppress hepcidin expression and BMP6 activity in the liver, and modulation of endogenous heparan sulfates alters hepcidin and thus iron homeostasis. Enzymatic removal of the heparan sulfate-protein interaction with sodium chlorate or surfen reduces hepcidin expression. The study also shows that inactivation of the biosynthetic genes N-deacetylase and N-sulfotransferase 1 in mouse hepatocytes reduces the expression of hepatic hepcidin, leading to iron accumulation in the liver and serum of mice. Heparan sulfate manipulation inhibits IL-6 and IL-6-dependent iron redistribution and stimulates iron redistribution. Therefore, the study showed that inactivation or manipulation of heparan sulfate results in hepcidin-dependent iron homeostasis regulation.	
14	Polychlorinated biphenylquinone induces hepatocyte iron overload by upregulating hepcidin expression	polychlorinated biphenyls (PCBs), an industrial by-product, have adverse impact on human health, especially the liver. A surrogate for PCB-induced lipid peroxidation and iron overload (PCB29-Qp) studied in vivo and in vitro and found that iron overload resulting from reactive oxygen species (ROS)-hepcidin disruption in hepatocytes and hepcidin elevation is regulated by nuclear factor erythroid. 2-related factor 2 (Nrf2), which binds directly to the hepcidin promoter to promote hepcidin transcription.	J Liu et al. [2020] [30]
15	Better treatment of anemia of chronic disorders (anemia of inflammation)	Before starting the treatment of anemia, it is important to make a thorough diagnosis of the root cause of anemia and prescribe a specific treatment, along with the old practice of treating anemia using iron, folate, and vitamin B12 supplements. According to Michali et al. [2020] concluded that besides traditional anemia treatment, including dietary supplements, the administration of drugs targeting specific proteins, including hepcidin, should be considered in the treatment of anemia of chronic disease. The article highlights the prophylactic administration of heparin to cancer patients significantly reduces hepcidin levels in the blood because bone morphogenetic protein 6 (BMP6) binds to heparin. The study also found a reduction in hepcidin levels in rheumatoid arthritis patients who received anti-α tumour necrosis factor antibodies and in lung cancer patients who received anti-interleukin-6 antibodies. The article found that recent therapies such as HIF-2α stabilizers and prolyl hydroxylase (PHD) enzyme inhibitors such as roxadustat, molidustat, vadadustat, and desidustat, which stabilize hypoxia-inducible factor (HIF), resulting in positive erythropoiesis are in the late phase of clinical trials.	Michali et al. [2020] [5]
16	Hepcidin, ferritin, and the treatment of iron deficiency anaemia in chronic kidney disease are all impacted by inflammation.	Iron deficiency is common in chronic kidney disease. Inflammation in CKD increases the acute phase reactants ferritin and hepcidin independently of iron status, leading to iron deficiency. Intravenous iron therapy is more effective than oral iron therapy in CKD patients compared to non-CKD patients.	N Ueda et al. [2018] [31]

		However, inflammation lowers the predictive value of ferritin and hepcidin for iron content and response to iron therapy. The review article suggests that treatment of iron deficiency should be different in patients with CKD compared to patients without inflammation because ferritin levels are low in iron deficiency anemia without inflammation compared to iron deficiency in CKD. Thus, they suggest that further studies needed to assess the effect of inflammation on ferritin and hepcidin and the therapeutic strategy of IDA in CKD.	
17	Hepatic hepcidin regulates intestinal HIF-2α in iron deficiency, anemia, and iron overload	The most frequent diseases worldwide are iron related diseases. Systemic iron homeostasis depends on hepcidin, a hormone produced by the liver that regulates iron mobilisation through its molecular target ferroportin (FPN), the sole known mammalian iron exporter. Diseases that result in iron excess disrupt this pathway. Intestine HIF-2α (hypoxia-inducible factor) plays a crucial role in local absorption in both systemic iron deficit and iron overload. According to data, intestinal HIF-2α is controlled by hepatic hepcidin under conditions of iron overload, anaemia, and deficiency. The results of the study showed that FPN controls the activity of intestinal prolyl hydroxylase domain enzymes that depend on iron to control cell-independent iron efflux to stabilise and activate HIF-2α (in phase II clinical trials for clear-cell renal cell carcinoma) In a mouse model, HIF-2α successfully eased iron overload. These findings show a molecular link between hepatic hepcidin and intestinal HIF-2α, which regulates physiological iron absorption and causes iron overabsorption during iron overload, and the study results show that inducible deletion of hepatic hepcidin leads to intestinal HIF-2α activation and rapid iron accumulation.	Andrew J. Schwartz et al. [2019] [32]
18	Hepcidin ferroportin in health and disease	Transcription factors known as hypoxia-inducible factors (HIFs) regulate physiological responses to hypoxia. HIFs bind hypoxia response elements to regulate genes central to erythropoiesis (e.g., Epo), angiogenesis, and metabolism. HIFs are degraded in the proteasome because of HIF hydroxylation by propyl hydroxylases under normoxic conditions. Propyl hydroxylase activity requires iron, and inactivating mutations of propyl hydroxylases increase HIF and stimulate erythrocytosis, bypassing inflammation-related increases in hepcidin and resulting in suppression of hepcidin. Normally, a hypoxic environment and increased HIF2α in the small intestine caused iron absorption on the apical side of enterocytes and iron absorption on the basolateral side, and iron limitation increases sensitivity to hypoxia. Polycythemia vera: the most common JAK2 driver mutation is JAK2 V617F, leading to constitutive Epo-independent JAK-STAT signaling and upregulation of genes downstream of the JAK-STAT pathway. Most patients with polycythemia vera shows iron deficiency at	Y Z Ginzburg. et al. [2019] [33]

		diagnosis, even before starting therapeutic phlebotomy, the mainstay of therapy, and repeated phlebotomies, often worse iron deficiency.	
19	New insights into the relationship between hypoxia and iron homeostasis	Recently, the importance of the hepcidin-ferroportin axis in the modulation of intestinal HIF-2 in regulating iron absorption are emphasized. Recent advances also show that erythroferrone directly titrates bone morphogenetic proteins, contributing to hepatic hepcidin suppression and increasing iron availability. Hypoxia signaling links erythropoiesis to iron homeostasis. Using drugs that stabilize or inhibit HIF is a promising therapy for iron-related diseases.	Renassia, C et al. [2019] [34]
20	Treatment options for patients with secondary iron overload	Iron overload disorders represent a range of medical conditions that cause an increase in the body's iron stores and subsequent organ damage. Increased ferritin and transferrin iron saturation can usually be seen when evaluating for elevated liver enzymes. Confirmatory homeostatic iron regulator (HFE) genetic testing for C282Y and H63D, the most common mutations in hereditary hemochromatosis, should be pursued in the evaluation of hyperferritinemia. If necessary, magnetic resonance imaging should be used with a quantitative evaluation of iron content or liver biopsy (especially if the cause of the iron overload is liver disease). If the HFE gene test is negative for homozygous C282Y or C282Y/H63D heterozygous mutations, a secondary cause of iron overload should be considered. Hematologic disease, iatrogenic reasons, or chronic liver disease are among the differential diagnoses for secondary iron overload. Thalassemia syndromes, myelodysplastic syndrome, myelofibrosis, sideroblastic anemias, sickle cell anaemia, or pyruvate kinase deficiency are examples of common hematologic illnesses. Evaluation of the causes of hyperferritinemia should begin once iron overload has been ruled out. Chronic liver illness, cancer, infections, renal failure, and rheumatic diseases such as adult-onset Still's disease or hemophagocytic lymphohistiocytosis are among the factors that can lead to hyperferritinemia. In this review, they discussed the diagnostic procedures for people who may have hereditary hemochromatosis, the assessment of patients whose serum ferritin levels are elevated, the characteristics of secondary overload, and the therapy choices for people who have secondary iron overload.. In patients with elevated iron tests but negative for HFE genes C282Y or H63D, evaluation for CLD is warranted, and hematologic disorders such as thalassemia or MDS should be considered for anemia.	Christine C. Hsu et al. [2022] [7]

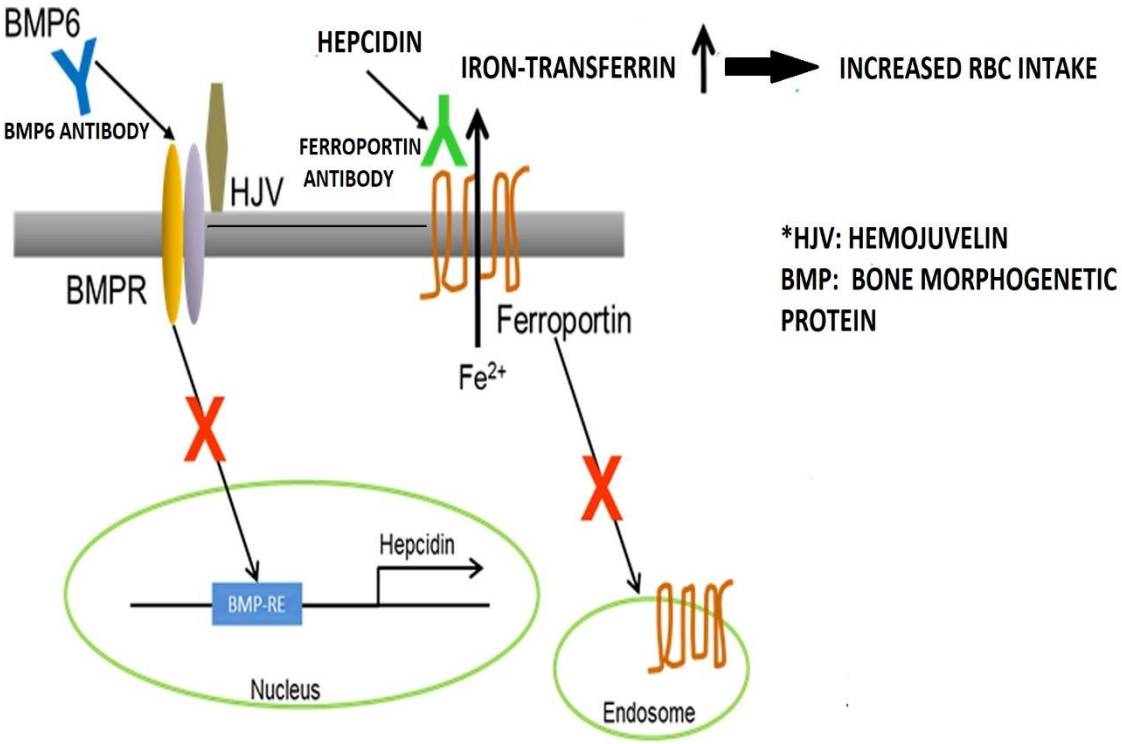

Fig 3: Monoclonal antibody therapy in the regulation of hepcidin ferroportin axis

Sheetz M et al. [2019] study shed light on the use of monoclonal antibodies as a new therapy for CKD anemia. The ferroportin antibody prevents the interaction of hepcidin with its receptor, thus reducing the internalization of ferroportin. BMP antibody prevents binding of the BMP6 to its receptor, reducing hepcidin mRNA transcription and hepcidin expression. Monoclonal antibodies LY3113593 and LY2928057 directed against BMP6 and ferroportin tested to investigate alternative therapies for erythropoietic-stimulants for individuals with chronic kidney dysfunction. Results include LY2928057 bound ferroportin and blocked interactions with hepcidin, allowing iron efflux, which increases serum iron, transferrin saturation levels and increases hepcidin levels in monkeys and humans. Whereas LY3113593 specifically blocked BMP6 binding to its receptor and increased iron and transferrin saturation and hepcidin pre-clinically and clinically. LY3113593 increased hemoglobin and decreased ferritin in CKD patients [35].

A review by Hawula et al [2019] explores the role of hepcidin and ferroportin agonists and antagonists in the induction and promotion of these proteins that regulate iron homeostasis. The hepcidin/ferroportin axis controls the regulation of systemic iron homeostasis, and multiple stimuli affect the axis. Factors such as plasma iron, inflammation, and erythropoietic demand. Long-term cytokine-dependent inflammation and genetic defects lead to dysregulation of the hepcidin/iron axis, leading to hemochromatosis and anemia. Currently, there are limited therapeutic options to control iron levels by regulating the hepcidin/ferroportin axis. The study examines the therapeutic use of hepcidin/ferroportin inducers and inhibitors in the regulation of the hepcidin/ferroportin axis and the treatment of hemochromatosis and iron deficiency anemia. [36].

Current Therapeutic Treatments for Hepcidin Deficiency

- Weekly phlebotomy
- Iron chelators, including deferoxamine, deferiprone

Current Therapeutic Treatments for Lowering Hepcidin
Direct Hepcidin inhibitors

- Anti-Hepcidin antibodies
- Short Interfering and Short Hairpin RNA
- Hepcidin-Binding molecules
- Hepcidin binding L RNA aptamers

Inhibitors of hepcidin production and synthesis

- Heparin-based targeting of the BMP/SMAD pathway
- Bone morphogenetic protein receptor (BMPR) inhibitors
- Hemojuvelin (HJV) and transferrin receptor 2 (TRF2) inhibitors
- Interleukin 6 targeting antibody

- AMP-activated protein kinase (AMPK
- Hypoxia-Inducible Factors (HIF) Stabilisers

Current Therapy for increasing Hepcidin
- Mini hepcidins
- Hepcidin Analogues
- Small molecule hepcidin analogues

Current therapeutics targeting ferroportin
- Ferroportin agonists (Fursultiamine-a thiamine derivative

Some drugs are in clinical trials and the emergence of these drugs may overcome the current limitations in the treatment of iron homeostasis.

Alessia Pagani et al. [2019] described hepcidin manipulations may be useful in all iron deficiency anemia, inflammatory anemia, and iron overload disorders. Compounds that antagonize hepcidin or its effects may be useful in inflammation and refractory iron deficiency anemia, while hepcidin agonists may improve ineffective erythropoiesis. In animal studies, restoring inefficient erythropoiesis decreases hepcidin inhibition, which improves iron homeostasis and anaemia. There are now certain focused strategies under clinical trials, which may result in new anaemia treatments. [37].

Table 4: Compounds that upregulate and downregulate hepcidin and ferroportin

Compounds that lowers hepcidin or enhance ferroportin function		
Class I	Reduction of the signaling pathway stimulating hepcidin	Anti IL6-R, anti-IL-6 Anti-BMP6 monoclonal antibody, BMPR inhibitors, Anti-HJV monoclonal antibody
Class II	Hepcidin binders	Non-anticoagulant heparins Anti-HAMP monoclonal antibody
Class III	Interfering with hepcidin-FPN interaction	Oligonucleotides aptamers Anti-FPN Moab, GDP
Compounds that increase hepcidin or decrease ferroportin function		
Class I	Hepcidin mimics	Hepcidin analogues
Class II	Activating hepcidin Blocking the hepcidin inhibitor Blocking the hepcidin receptor	Mini hepcidin, BMPs Anti-TMPRSS6, FPN Inhibitors
Class III	Others	Human transferrin infusions, Protoporphyrin IX (inhibition of heme oxygenase) Bone marrow TFR2 inactivation

4.6 Related scholarly work in the diagnostic and prognostic role of hepcidin in iron homeostasis disorders

Table 5: Diagnostic and prognostic role of hepcidin

SL.NO	**Research Area**	**Outcomes and Findings**	**References**
1	Oxidative stress and hepcidin expression in sickle cell anemia in children with iron overload	Patients with sickle cell disease who receive regular blood transfusions develop oxidative stress and iron hemochromatosis (iron overload). Eman A Elbostany et al. [2021] at the Egyptian National Research Centre investigates the relationship between oxidative stress, iron profile, hepcidin mRNA gene expression, iron overload and gene expression in sickle cell disease patients. 90 children, were divided into two groups (45 each). groups 1 (serum ferritin<938 ng/ml) and group 2 Serum	Eman A Elbostany et al. [2021] [38]

		ferritin >=938 ng/ml). 55 children took part as a control group. Malondialdehyde (MDA) and nitrite (to measure oxidative stress), s. iron, s. total iron-binding capacity (sTIBC), transferrin saturation percentage, ferritin, hepcidin, and hepcidin mRNA gene expression. The gene expression of hepcidin and s. hepcidin was significantly lower in the two patient groups than in the controls. TIBC, iron, ferritin, percent transferrin saturation, ferritin/hepcidin ratio, and MDA levels were higher in SCD patients than in controls. The study also showed that group 1 had a higher mean ratio of ferritin/hepcidin and MDA than group 2. Based on the research relationship of hepcidin, hepcidin gene expression and MDA can be used as biomarkers of oxidative stress and iron overload in patients with SCD.	
2	Role of serum hepcidin and reticulocyte hemoglobin concentration in predicting anemia in patients with ulcerative colitis.	A study by Amr Mohamed et al at Tanta University. [2022] had to evaluate the role of serum hepcidin and reticulocyte hemoglobin (CHr) concentration in anemia in patients with ulcerative colitis (UC). The study conducted on 80 UC patients and 30 healthy controls. 80 patients were divided into group I: 50 UC anemic patients and group II:30 non-anemic patients. CHr demonstrated a statistically highly significant reduction in anemic UC patients than in the other two groups. They observed a substantial negative correlation between CHr, serum hepcidin, and serum ferritin, and a positive correlation of hepcidin between CHr, hemoglobin level, MCV, ferritin, and transferrin. The study concluded that serum hepcidin had an excellent performance in predicting anemia of chronic disease and CHr for iron deficiency anemia of CHR and anemia of chronic disease.	Amr Mohamed et al. [2022] [39]
3	Urinary hepcidin concentration in the assessment of iron homeostasis in children	They conducted the study with 75 children with iron deficiency and 25 healthy control children. Receiver operating curve analysis assessed the diagnostic performance of urinary hepcidin. A diagnostic cut point with a high predictive value for iron deficiency was selected. Hepcidin levels were considerably lower compared to the control group at all stages of iron insufficiency. They confirmed significant positive correlations between urinary hepcidin levels and hemoglobin, mean tissue volume, serum iron, ferritin, and transferrin saturation. The study revealed that hepcidin levels were significantly lower in all phases of iron deficiency than in the control group. Urine hepcidin analysis offers a reliable non-invasive screening method for the diagnosis of iron deficiency in children.	Sonia G et al. [2019] [40]
4	Evaluation of serum hepcidin levels and iron content in anemic patients admitted to the intensive care unit	A prospective study was conducted on 80 patients admitted to the intensive care unit of Zagazig University Hospital to improve the prognosis of anemia in critically ill patients by evaluating serum hepcidin and iron levels in critically ill anemic patients to determine the association between hepcidin levels and outcomes in critically anemic patients. Significantly elevated serum hepcidin and	MM Yousif et al. [2022] [41]

		ferritin levels seen in critically ill anemic patients in the MICU. Serum hepcidin and ferritin levels are markedly elevated in critically anemic patients characterized by disease-induced inflammatory stress. The study showed that serum hepcidin levels, measured at the time of admission to the medical intensive care unit, did not affect the short-term outcome of the intensive care unit in terms of mortality or length of hospital stay.	
5	Hepcidin as a biomarker in the differentiation between iron deficiency anaemia and anaemia of chronic disease	Serum iron, total iron-binding capacity, transferrin saturation, serum ferritin, haemoglobin, and erythrocyte indices such as cellular haemoglobin (MCH), mean cellular haemoglobin concentration (MCHC), mean cell volume (MCV), and erythrocyte distribution width are typically assessed in the laboratory in diagnosing iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD) (RDW). These measures have some limitations in differentiating iron deficiency anaemia from anaemia caused by chronic diseases, according to several studies. RBC indices, which play minimal role in distinguishing IDA from ACD because these illnesses occasionally exhibit identical alterations in the RBC indices, are the mainstay of anaemia diagnosis. Here, it is necessary to consider the significance of hepcidin in the distinction between anaemia caused by chronic illness and iron deficiency anaemia.	Ephraim Chikwanda [2018] [42]
6	Threshold levels of ferritin and hepcidin show an early iron deficiency in young women due to increased iron absorption	The study aimed to determine the concentration of ferritin at which the body regulates the absorption of iron from food, and they interpreted that the physiological increase in iron absorption, the threshold of ferritin, is 50mg/L, which corresponds to the threshold hepcidin <3 nmol/l shows an incipient iron deficiency in young women. In addition, the study results include a linear increase in hepcidin, as ferritin increases throughout almost the entire range of ferritin values in healthy women without inflammation.	Valeria Galetti [2021] [43]
7	Hepcidin and iron deficiency in women one year after sleeve gastrectomy	The aim of the study was to investigate the effect of weight loss on the rescue of iron balance in patients who underwent sleeve gastrectomy (SG), which preserves the duodenum, the primary site of iron absorption. The cohort included 88 obese women; blood samples and duodenal biopsies collected from 35 patients before and one year after SG. Analysis of 35 patients included assessment of iron homeostasis, including hepcidin, expression of markers of erythroid iron deficiency (soluble transferrin receptor (sTfR) and erythrocyte protoporphyrin (PPIX)), duodenal iron transporters (DMT1 and ferroportin), and inflammatory markers. After surgery, sTfR and PPIX decreased. Serum hepcidin levels increased despite a significant reduction in inflammation (levels of the inflammatory markers AGP and IL-6 significantly decreased after surgery). DMT1 abundance is negatively correlated with higher serum hepcidin levels. Ferroportin numbers have not changed. This study provided fresh insight	Thibaud Lefebvre [2021] [44]

		into the ineffective iron recovery routes following SG, which include hepcidin's beneficial regulation of iron homeostasis, inflammatory inhibition, improved iron absorption, iron supply and erythropoiesis efficiency. In order to evaluate iron status, these new characteristics should be taken into account when making recommendations for iron supplements in patients after SG.	
8	Relation between obesity and iron deficiency anemia and the role of hepcidin	Iron deficiency is common in obese children, although the underlying mechanism is unclear. The study investigated the relationships between iron parameters, leptin, adiponectin, and hepcidin levels in obese children. Complete blood count, serum iron content, iron-binding capacity, ferritin level, leptin, hepcidin, and adiponectin concentrations studied in 237 children aged 5-18 years, of which 180 were with primary obesity and 57 healthy children and adolescents. White blood cells, platelets, binding of iron, high-sensitivity C-reactive protein, leptin, and hepcidin levels were all higher in the obese group than they were in the control group. However, the study concluded that hepcidin levels do not cause iron deficiency anemia in obese children. In addition, they recommended larger studies to clarify the relationship between iron and hepcidin in obese children compared with non-obese children.	E Sal [2018] [45]
9	Acute inflammation and iron deficiency anaemia have opposing effects on serum hepcidin and iron absorption in young women.	Their study involved a 45-day prospective follow-up of young women aged 18-49 years with and without iron deficiency anemia and compared iron and inflammatory markers, serum hepcidin, and erythrocyte iron incorporation from a 57Fe-labeled test meal, before and after 8, 2, and 36 hours after influenza. After DPT vaccination as an acute inflammatory stimulus. Iron studies and hemoglobin erythropoietin levels measured. C-reactive protein and alpha-1-acid glycoprotein were used to determine the degree of inflammation. In women with IDA, mild acute inflammation did not increase blood hepcidin levels, indicating that low iron levels and limited erythropoietic activity offset the inflammatory triggers that cause hepcidin expression. It is possible that iron-recycling macrophages are more sensitive than enterocytes to high serum hepcidin levels during inflammation because inflammation increased serum hepcidin levels and led to mild hypoferremia in non-anemic women but did not affect dietary iron absorption.	Nicole U. [2019] [46]
10	Association of serum erythropoietin, hepcidin and haptoglobin levels with disease severity and other biochemical values in patients with COVID-19 infection	Studies have shown that covid infection affects iron metabolism. The study was conducted in Sisli Hamidiye Etfal Research and Training Hospital in Turkey with 59 patients with covid infection, who were divided into groups with mild, severe, and critical severity of the disease, serum iron, and hepcidin levels decreased in COVID-19 patients along with erythropoietin. and haptoglobin levels were much lower in the patient groups who were critically ill and deceased.	Sema Yağcı [2021] [47]

11	Hepcidin as an early biomarker that predicts oral iron therapy in children	Tanya Singh et al. (2021) evaluated serum hepcidin levels in children aged 2–12 years with iron deficiency anemia. A prospective study was conducted to determine serum hepcidin levels on day 0 (pre-treatment) and days 1 and 14 of oral iron therapy to determine if there was a relationship between baseline or day 1 hepcidin levels and change in hemoglobin levels on day 14. A total of 64 children were recruited, excluding children with severe IDA (Hb<7 g/dl); suffering from fever/acute infectious disease; if they have taken oral iron in the last 3 months, or had a blood transfusion, or if they have oral iron intolerance. A complete blood count performed on day 0 to assess red blood cell indices, iron profile, serum ferritin, and serum hepcidin and was repeated on day 1 and day 14 The study found that baseline hepcidin on day 0 increased on day 1 and continued to increase on the 14th day. On day 14, a negative correlation (statistically insignificant) was observed between changes in hemoglobin and hepcidin. The study concluded that hepcidin appears to be a biomarker that predicts early response to oral iron therapy in children with IDA.	Tanya Singh et al [2021] [48]
12	Threshold levels of ferritin and hepcidin indicate an early iron deficiency in young women due to increased iron absorption	The goal of the study by Valeria Galet et al. [2021] was to determine the ferritin concentration at which the body regulates iron absorption from food. In addition, the study assumed that the threshold concentration of ferritin corresponds to the threshold concentration of hepcidin, where iron absorption increases. They performed a pooled analysis on healthy women aged 18-50 between 2006 and 2019 using an iron isotope. Iron absorption was measured by mass spectrometry of ELISA-labelled test meals containing physiological amounts of iron. Hepcidin and ferritin were analyzed by immunoassay. The result of the study suggests that, based on the physiological increase in absorption of iron, the threshold value of ferritin < 50 mg/l, which corresponds to the threshold value of hepcidin and <3 nmol/l shows a developing iron deficiency in women	Valeria Galet et al. [2021] [49]
13	Hepcidin as a biomarker	The clinical use of hepcidin as a biomarker is limited because of the lack of an appropriate diagnostic test. Recently, assays have been developed for the evaluation of serum and urinary hepcidin, which are likely to facilitate the use of hepcidin in research and institutional care soon. Current research into the mechanism of action and control mechanism of hepcidin has enabled new pathological associations and the development of new diagnostic tests and therapeutic options.	Arunava Kali et al. [2015] [50]
14	Hepcidin discriminates sepsis from other illness	The study was conducted on 16 adult patients admitted to the intensive care unit (ICU) within 2 hours of hospital admission. Hepcidin, heparin-binding protein (HBP), and standard biomarkers were measured in blood samples taken daily for seven days in a row. At inclusion, blood cultures were started. Daily clinical scores were evaluated, and death was noted at 28 and 180 days. Six patients did not meet the sepsis threshold, while 100 did.	Jon Olinder et al. [2022] [51]

		Septic patients had significantly higher hepcidin levels than non-septic patients. Hepcidin levels in septic individuals significantly dropped after two hours, then followed by a continuous decline. Hepcidin levels and SAPS 3 were found to be significantly inversely correlated in patients with sepsis. Hepcidin levels were considerably greater in septic patients with projected mortality and a 180-day survival rate at inclusion. Hepcidin levels in sepsis patients admitted to the critical care unit are shown in their data to have prognostic value for mortality..	
15	Hepcidin as a prognostic marker in prostate cancer	The results showed that high hepcidin expression levels and low ferroportin expression levels in pancreatic cancer tissues were significantly associated with poor prognosis in overall survival analysis. Thus, hepcidin and ferroportin expression may be new prognostic indicators of pancreatic cancer.	Toshiyamma et al. [2018] [52]

V. RESEARCH GAP :

Despite being the first country tointroduce the National Nutritional Anemia Prophylaxis Programme in 1970, treatment of iron deficiency continues to be a major problem in India. Besides present treatment options, the knowledge of physicians on the role of hepcidin in the diagnosis and treatment of iron homeostasis are limited. Many of drugs, including hepcidin modulators, are in the phase of clinical trials only. Development of these drugs may overcome current limitations in the treatment of iron homeostasis

5.1 Research Gap 1

The diagnosis of concomitant iron deficiency was difficult, as anemia of inflammation is also supported by typical low iron deficiency and elevated ferritin. Gene polymorphism affecting iron homeostasis needs to be studied. However, the technique is complex and costly. Current options for diagnosing iron deficiency and iron overload are cheaper. Advanced iron metabolism regulators, and biomarkers, including evaluation of hepcidin, are complex and expensive compared to traditional methods, which makes their implementation difficult. Under normal conditions, serum ferritin is a sensitive marker of iron status, but ferritin is an acute-phase reactant that increased as a result of inflammation, making diagnosis difficult. Hepcidin has less predictive value when iron deficiency anemia with anemia of inflammation coexists.

5.2 Research Gap 2

Iron chelation therapy increases the cost and standard of life and lowers its quality, which is considered a challenge when choosing chelation therapy. The price of chelation therapy comprises not only the cost of the treatment itself but also the costs of symptom management, treatment, follow-up, complications, quality of life, compliance, and the consequences of non-compliance. The number of research needed to determine the risks and benefits of iron supplements for others with a genetic predisposition to iron overload is limited. More research is needed. Despite the availability of potentially affordable oral iron chelation therapy, many patients experience the side effects of iron overload and pass away each year as a result of inadequate or lack of iron chelation therapy.

5.3 Research Gap 3

The lack of an adequate diagnostic test restricts the clinical application of hepcidin as a biomarker. The therapeutic significance of hepcidin, hypoxia-inducible factors, ferroportin, erythroferrone, and gene polymorphisms (refractory anemia, thalassemia) needs to be studied. Many of the therapeutic advances are still in the phase of clinical trials only. More detailed research works only will help in the implication of advanced therapeutic options in treating iron homeostasis along with current treatment options.

VI. FINDINGS BASED ON THE REVIEW :

(1) Currently, there are limitations in the treatment and early diagnosis of iron deficiency and iron overload.
(2) The mechanism of hemochromatosis is because of impaired synthesis of hepcidin or impaired binding of hepcidin to ferroportin.
(3) In pathophysiological conditions such as beta-thalassemia, myelodysplastic syndrome, inflammatory anemia, and hereditary hemochromatosis, the role of hepcidin is significant.
(4) Therapeutic hepcidin management in iron overload is important, along with iron chelation therapies.
(5) Hepcidin can be used as a prognostic marker in patients with acute kidney injury

(6) The use of drugs that stabilize or inhibit hypoxia-inducible factors can be promising in the treatment of iron homeostasis disorders
(7) Targeted pharmaceutical upregulation and downregulation of hepcidin will help in maintaining iron homeostasis.
(8) Most of the therapeutic advances are still in the phase of clinical trials, hence more detailed studies need to be carried out before implementing the new therapeutic advances.
(9) Hepcidin has an excellent role in predicting anemia.

VII. CONCLUSION :

This study analyzed the hepcidin's role in the management of iron homeostasis. Currently, there are limitations in the diagnosis and treatment of iron deficiency and iron overload. Understanding the role of hepcidin ferroportin, and hypoxia-inducible factors in iron homeostasis sheds light on advanced therapeutic options and the use of hepcidin as a diagnostic and prognostic biomarker. In this review paper, the importance of advanced clinical studies on various aspects of hepcidin that needs to be carried out in the diagnostic and therapeutic field is explained. The study highlighted various aspects of hepcidin tuning, understanding the mechanism of hepcidin and its pathological components, which may lead to advanced therapies and alternative therapies, and the importance of new therapeutic options, including modulation and inhibition of hepcidin activity, and its future use in clinical trials and introduction of the latest therapeutic options. However, more researches on a large number of subjects and clinical trials need to be carried out. Further education is needed for physicians, health professionals, and patients to understand the role of hepcidin and its diagnostic and therapeutic value, which may lead to new advances in the management of iron homeostasis.

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