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The protective role of Hepcidin against thalassemia

Afaf Farouk Mouloud *

Ministry of Education, Education Directorate, Diyala, Iraq.

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Abstract

Thalassemia: It is a defect resulting from Thalassemia is a hereditary condition where there is an abnormal balance of the globin chains found in hemoglobin. In healthy individuals, each alpha and beta chain is produced at approximately the same rate. In thalassemia, there is reduced production of one of the globin chains compared to the other; as a result, the two chains do not match and the overall percentage of hemoglobin in the bloos is decreased. The primary cause of thalassemia is the formation of ineffective erythrocytes that have a high rate of hemolysis and that cannot carry adequate amounts of oxygen to the tissues throughout the body. In summary, thalassemia is a diverse range of hereditary (genetic) diseases caused by reduced production rates of either of the two types of hemoglobin chains (alpha and beta). Hemoglobin transports oxygen to red blood cells; when there is an imbalance in the ratio between alpha and beta chains of hemoglobin, chronic hemolytic anaemia will result.

Iron homeostasis in the body is regulated by hepcidin (Hp) which promotes iron transport from intestinal absorption of iron-containing foods to blood circulation. Specifically, Hp stimulates iron absorption from intestinal epithelial cells (Enterocytes). Conversely, Hp has been shown to inhibit the function of iron-export protein ferroportin (Fpn), thereby preventing iron from being transported out of storage sites such as liver and bone marrow cells. The relationship between thalassemic individuals and hepcidin occurs primarily as a result of the relationship between blood transfusions, anemia, erythropoiesis (production of red blood cells) and inflammation. Furthermore, in thalassemics, blood transfusions are associated with increased hepcidin levels due to the increased production of erythrocytes as a result of increased haemoglobin concentrations within the blood. The role of hepcidin is now understood to provide a key and protective factor in regulating iron metabolism in those suffering from Mediterranean anaemia. (thalassemia).

Keywords: Thalassemia; Hepcidin; Iron; Mediterranean anemia

1. Introduction

1.1. Thalassemia

Thalassemia is an inherited blood disorder that affects a person's ability to produce hemoglobin in various parts of the body at normal levels, leading to anemia [1]. It is a defect resulting from one of the globin chains, i.e., one of the alpha and beta chains found in hemoglobin, which are produced equally under normal conditions. It is a genetic disorder in which the production rate of one of these two chains is slower than the other [2]. Thalassemia is caused by the production of defective red blood cell chains, which result in an altered percentage of hemoglobin in one's body. Thalassemia occurs when there is a decrease in the synthesis of the alpha or beta Hgb chain due to a genetic defect. The alpha/beta imbalance will cause a chronic hemolytic anemia, resulting from the inability of the affected cells to carry oxygen to body tissues. [3]. If one of these two chains is deficient enough, red blood cells cannot form properly and cannot carry enough oxygen. As a result of this deficiency, anemia will develop, which begins in early childhood and continues throughout life. Thalassemia has been described as a genetic disease, which means that at least one of the parents must

* Corresponding author: Afaf Farouk Mouloud

be a carrier of the disease, i.e. the cause of the disease is either a genetic mutation or the deletion of certain major genetic parts [4].

1.2. History of Thalassemia

The first to discover thalassemia was the Detroit pediatrician Thomas B. Cooley and Pearl Lee, while the inventor of the actual term thalassemia was the scientist George Whipple [5]. The term thalassemia is derived from the Greek words (Thalassa) meaning sea and (Heam) meaning blood, and this term refers to disorders associated with defective synthesis of the α-globin or β-globin subunits [6]. Thalassemia was diagnosed in cases of patients suffering from severe anemia and a group of symptoms such as bone deformities, fractures, yellowing of the skin, and the patient's eventual death. This disease was called Mediterranean anemia, and the word "sea" was coined by Whipple [7]. Thalassemia is a genetic disorder common worldwide and most prevalent in the Mediterranean region [8].

1.3. Classification of thalassemia based on the type of globulin chain

Thalassemia is classified based on the type of globulin chain into:

- Alpha (α-) thalassemia: Alpha thalassemia occurs when one or more of the four α-globin genes are damaged or altered.
- Beta (β-) thalassemia: Beta thalassemia occurs when the β-globin genes are damaged or altered (9).

All types of thalassemia are considered quantitative hemoglobin diseases, but alpha and beta thalassemia are common enough to be significant (10).

1.4. α-thalassemia

It is one of the disorders that occur in hemoglobin, which is caused by the deletion of alpha-globin genes [11, 12]. When free alpha-globin chains damage the red blood cell membrane, they produce an unstable state which allows for easy precipitation thus causing the death of red blood cell precursors (pronormoblasts). Alpha chain accumulation causes oxidative injury as alpha chains can easily lose iron (as is normal) from their structure and therefore free iron (from loss) and heme (from loss) will be the highest concentrations occurring on the membrane of red blood cells, providing maximum susceptibility to oxidative injury when compared to beta-thalassemia, particularly due to the fact that free iron is a very vulnerable site for oxidative damage (all measurable from red blood cells as well as large molecules such as DNA, lipid membrane proteins, etc.) and may lead to programmed cell death as well as reduce the life span of the thalassemic cell. [13].

The date of discovery of alpha thalassemia was in the mid-1950s and early sixties as a hypochromic anemia in the absence of iron deficiency [14], as alpha thalassemia usually results from deletion mutations and single nucleotide substitutions, and thus the link between insertion and deletion processes is less [15]. In addition, there are four genes responsible for the formation of the alpha globin chain in normal individuals, and any defect in these chains will lead to health problems depending on the number of genes [16]. Silent alpha thalassemia occurs as a result of the deletion of one or two alpha globin genes, leading to the formation of αo α+, and the patient does not show any symptoms other than simple anemia [17].

The other type is called Hemoglobin H disease, which is symbolized by Hb-H, and it occurs as a result of the deletion of three alpha globin genes, and thus an increase in beta globin occurs, which is unstable and precipitates in the form of β4. In this case, the person suffers from moderate anemia [16]. The last type of alpha thalassemia, called hydrops fetalis, occurs due to the deletion of all four alpha globin genes, and the gamma chain is dominant, so it is deposited in the form of (4γ). They found that alpha thalassemia is homozygous and common throughout the world and the resulting hemoglobin is known as Hb-Barts and thus leads to fetal death shortly after birth [18,19].

1.5. β-thalassemia

Beta-thalassemia is the inherited hemoglobinopathies due to different genetic defects within the promoter regions (13) of the beta-globin gene resulting in a decrease in the amount of hemoglobin produced by the cell. Many mutations exist that primarily affect the expression of the beta-globin genes which leads to beta-thalassemia. These mutations do not uniformly distribute across the body, as they have a specific geographical distribution, ethnic origin, and a small number of common mutations exist, while more uncommon and variable mutations are seen in alpha-thalassemia. [20].

Various mutations (including nucleotide substitution mutations and various mutations affecting the addition or removal of nucleotides) lead to the development of thalassemia in some patients, and these alterations were identified during

the cloning of the β-Globin gene, resulting in decreased production of the beta-Globin polypeptide and associated consequences from decreased beta-Globin production and additional damage. One of the possible disorders is caused by rapid accumulation of certain cell types (21). Various forms of β-thalassemia have also been recognized, including thalassemia-(°β), which is completely absent, and thalassemia-(+β), which has decreased or defective production of the beta-globin (22). There is another form of β-thalassemia, but it is present in very few forms, which is (β++), which is moderate and indicates a defect in the production of the beta-globin chain (23).

2. Classification of beta thalassemia according to severity:

2.1. Beta Thalassemia Major

Thalassemia major patients are usually diagnosed with lifelong anemia. Patients suffering from thalassemia major also have an early life defect in their production of red blood cells (17). Anemia, which is characterized by low levels of red blood cells, is by far the most serious disease complication that affects an individual diagnosed with thalassemia major because there are mutations in both of the individual's beta globin genes resulting in impaired beta globin chain synthesis (24). Three mutations/genes that affect thalassemia major phenotype are β⁰/β⁰, β⁰/β+, and possibly +β/+β (25). In addition, unpaired excess alpha globin chains in thalassemia major produce antibodies that negatively impact red blood cell membranes. Because of the lack of paired alpha globin chains, excess alpha globin chains enter into circulation throughout the body. An excessive amount of chains will damage the membranes of red blood cells that result in intravascular hemolysis (26). The more serious form usually presents early in life for patients with β-thalassemia major and requires frequent blood transfusions (27).

Individuals with thalassemia major usually present with severe anemia or chronic anemia (17). Due to hemolysis, the majority of red blood cells created do not live the normal lifespan of red blood cells (approximately 120 days). This leads to a reduced amount of hemoglobin, which in turn results in the individual suffering from dangerously low levels of hemoglobin. To counteract the rapid destruction of red blood cells, the body attempts to create more red blood cells but this typically results in the enlargement of the splenic, hepatic, and medullary sources of blood (28). Additionally, there is significant damage to and destruction of red blood cell precursors, leading to the production of ineffective red blood cells, and hence, there is a danger posed by the inability to supply adequate oxygen to the body's tissues (29).

Thalassemia patients may exhibit additional symptoms including poor feeding, diarrhea, irritability, recurrent fevers, and abdominal swelling. Thalassemia major patients will typically present with slow growth, pallor, jaundice, general weakness, enlarged liver, leg ulcers, and skeletal deformities associated with expansion of the bone marrow. Typical skeletal abnormalities associated with thalassemia major are those of the long bones of the legs, and those of the skull and face (an increased size of the skull, a flat nasal bridge, a downward slant of the eyes, and an enlarged/bulbous maxilla, which can cause significant protrusion of the upper jaw). teeth) (30,31).

2.2. Thalassemia intermedia

Thalassemia intermedia has milder forms of anemia so patients with that diagnosis often do not require blood transfusions at all or at most infrequently (32). The most common form of this type of thalassemia is β+/β+ (33). Patients with thalassemia intermedia usually experience moderate to mild anemic conditions which typically means that they do not receive blood transfusions (34) yet have milder forms of thalassemia than patients with major forms of the disorder due to inheriting a mutation in the β-globin gene, resulting in decreased production of the β-globin chain (35).

Thalassemia intermedia off a variety of rare beta-globin phenotype variants, including splenomegaly (36). The rare variant, "silent beta-thalassemia," has also been identified, where there is a small defect in the globin chain synthesis that results in a decreased Beta-globin synthesis resulting in thalassemia intermedia. The clinical phenotype of thalassemia intermedia is about halfway between that found in thalassemia major and thalassemia minor, and the most common clinical manifestations and complications associated with thalassemia intermedia are splenomegaly due to trapping of damaged red blood cells, with an associated risk of iron overload with subsequent increased intestinal absorption (37). The clinical manifestations of this form of thalassemia may include characteristic facial deformities, osteoporosis with long-bone pathological fractures, and clumped red blood cells found primarily in the spleen, liver, lymph nodes, chest, and spine. The enlargement of the spleen results from its primary function of removing damaged red blood cells from the blood.

Patients who have thalassemia intermedia generally have a higher incidence of developing gallstones than those diagnosed with thalassemia major. The presence of gallstones in this population may be related to neurological

complications caused by the lack of sufficient red blood cells being produced in the bone marrow, which can sometimes cause compression of the spinal column leading to hemiplegia. [38].

2.3. Beta Thalassemia Minor

Individuals with this type of thalassemia often suffer from mild anemia, and their hemoglobin levels range between 9-11 g/dL. This type differs from other types, as the patient has normal hemoglobin [39,40]. Note that these patients were detected through routine blood tests. Microcytosis has been detected in patients with thalassemia minor because there is a potential risk that these symptoms may develop into thalassemia major in the event of a blood transfusion if the person donating blood has thalassemia [41].

2.4. Presence and prevalence of thalassemia patients

Thalassemia is very common across a large geographic area, from the Mediterranean to the Middle East to the Indian subcontinent, parts of Africa, Southeast Asia, and the Pacific (42). Alpha thalassemia is found more frequently among African/Asian populations than beta thalassemia, while beta thalassemia predominates within Mediterranean countries but is also common among Southeast Asian countries and Africa (13).

It has been estimated that annually over 100,000 cases of thalassaemia are discovered at birth, however, the chance of thalassaemia being diagnosed are higher for people of Greek, Italian, East Asian, South Asian and African descent. Thalassaemia is prevalent in countries bordering the Mediterranean Sea (especially Southern Europe and Africa) the Caucasus region and India, The Maldives (19% carrier frequency) and Cyprus (15% carrier frequency) have the highest prevalence of thalassaemia carriers, the next highest being Sardinia (11% carrier frequency), whereas the lowest is found in Southeast Asia (3-5% carrier frequency). A likely explanation for these location differences is a result of malaria Plasmodium selective pressure (44). The burden of managing and taking care of Thalassemia has increased due to increased migration, and is now being recognised as a major concern for healthcare systems globally (45). As of 2018, it is estimated that approximately 5.2% of individuals across the globe carry thalassaemia and that 1.1% of couples are at risk of having a child who has a disorder due to abnormal haemoglobin (46).

Thalassemia is common in Iraq; from 2010 to 2015, the prevalence rose from 33.5 per 100,000 to 37.1 per 100,000 people (47). The average age of the patients was 13 years old, ranging from 1 to 35 years, and there were 1.2 patients for every male patient (48). Shells of thalassemia can be found throughout Iraq, but much more so in the northern regions of the country, as they are situated near Turkey and Iran, both of which have high rates of overall thalassemia. As of December 2015, there were 8,346 patients treated across 16 thalassemia treatment centers in Iraq, which means that the prevalence rate for thalassemia patients in Iraq as of December 2015 was 27.4 per 100,000 of the total population and this is a very high rate of prevalence. The cause of the continued increase in patients with thalassemia in Iraq is due to the lack of thalassemia prevention programs and because consanguineous marriages have been a significant contributing factor to the high number of thalassemia patients in Iraq (49). Thalassemia infections occur at a high rate due primarily to consanguinity in marriages. Every year, the greatest number of infants born with thalassemia occurs in Pakistan. [50].

3. Causes of thalassemia

The cause of thalassemia is linked to one of the parents being a carrier of thalassemia. The child may become a carrier of this disease despite the child not showing any symptoms. The child may also be afflicted with what is called minor thalassemia, in which case he may show mild symptoms [51]. Also, marriage should not be done to relatives who are infected with thalassemia, because if both parties are carriers of the disease, this will result in the birth of infected children at a rate of (25%) and children who are carriers of the disease at a rate of (50%). The infection rate decreases if one of the parents is a carrier of the disease and the other is healthy [52].

4. Symptoms

The primary signs of thalassemia are:

- Severe anemia, such that the patient becomes dependent on a blood transfusion to survive, and the affected infant is unable to gain weight normally (53).
- Anemia, paleness, diarrhea, and recurrent bouts of fever and malnutrition.
- Gradual abdominal enlargement due to enlargement of the liver and spleen. Over time, signs of anemia become apparent, and growth is slow.

- A type of mental retardation appears (54). In addition, the mucous membranes become pale, most notably in the lining of the mouth and conjunctiva.
- Skin pigmentation and ulcers appear in the lower extremities.
- Bone deformities, especially in the skull, facial bones, and long bones (55), which increases the risk of bone fracture, due to extramedullary hematopoiesis (56).

5. Treatment

Treatment for thalassemia depends on the type and severity of the disease. If the disease is mild thalassemia (Hb: 6 to 10 g/dl), signs and symptoms are usually mild and require little treatment. Sometimes, patients may require a blood transfusion, especially after surgery, after childbirth, or to help manage thalassemia complications. If the disease is moderate to severe thalassemia, the following is followed:

- Frequent blood transfusions: The more severe symptoms of thalassemia require regular and continuous blood transfusions, perhaps every two weeks. The goal of this regular process is to maintain the hemoglobin level at approximately 9 to 10 mg/dL to give patients a sense of well-being and complete recovery.
- Chelation therapy: Iron begins to accumulate in various organs due to repeated blood transfusions. Iron chelators (deferasirox, deferoxamine, deferiprone) are administered simultaneously to remove excess iron from the body.
- Stem cell transplant (bone marrow transplant): Bone marrow transplantation is the optimal option in specific cases, such as children born with severe thalassemia.
- Splenectomy: Splenectomy is the usual recommendation of the doctor for people who require extensive blood transfusions because the spleen controls the spread of blood formation outside the marrow. Sepsis can occur after splenectomy in children, so this procedure is postponed until the age of 6 to 7 years, and then penicillin is given as a preventative measure until they reach a certain age [57].
- Folic acid: The increased need for blood formation leads to an increased need for folic acid, as a deficiency in folic acid and vitamin B12 has been observed in cases of thalassemia. Folic acid is given at a dose of about (5 mg) daily in the event of a deficiency [58].

6. Hepcidin

Hepcidin belongs to the peptide hormone class and is produced by liver cells [59]. The number of amino acids that make up this hormone is 25 amino acids. It is the primary hormone that controls iron balance when iron levels exceed the normal level [60]. This hormone has the ability to regulate iron by a group of genetic signals based on the body's need for iron, as the main regulator of the hepcidin hormone level is iron and inflammation, as high iron levels stimulate the gene expression of the hepcidin hormone, while low iron prevents this gene expression as if it works by a feedback mechanism to maintain normal iron levels in the body [61,62]. As in Figure (1), the mechanism of hepcidin hormone regulation of iron [63].

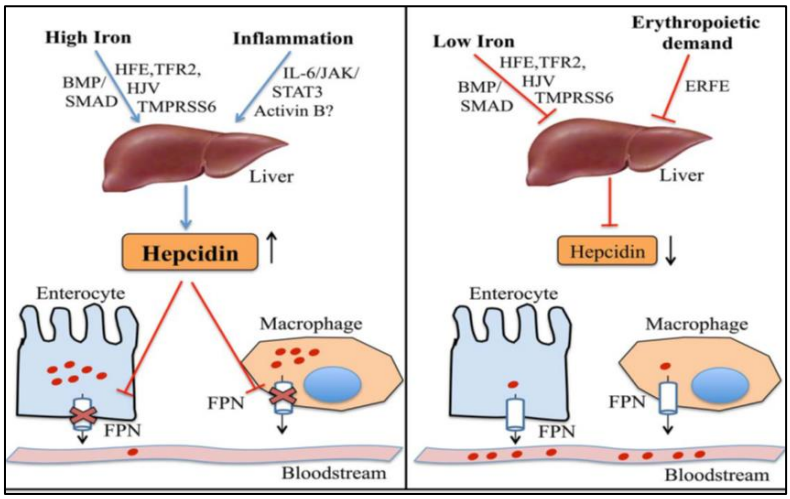

Figure 1 The mechanism of hepcidin hormone regulation of iron [63]

6.1. Discovery and synthesis of the hepcidin

Krause and his team were the first to identify the hepcidin hormone back in 2000 AD when they isolated this peptide from plasma and then found it in human urine and blood (64,65). Since it's synthesized in the liver and has an inherent capacity to kill bacteria, it was initially referred to as LEAP-1 (liver-expressed antimicrobial peptide-1). Hepcidin is a liver protein that has antimicrobial activity (66). After Park and his group isolated the hepcidin hormone from urine and found that it was related to inflammation, they re-named it hepcidin. They found that hepcidin is produced in the liver but only small amounts are available in other tissues such as adipose tissue (67,68). The hepcidin peptide. Its structure is fulfilled through a β-sheet structure (64%). There are also three disulfide bridges connecting each pair of the three loops together (as shown in figure (2)) and provide overall shape stability to the peptide. Hepcidin's structure was determined using nuclear magnetic resonance.

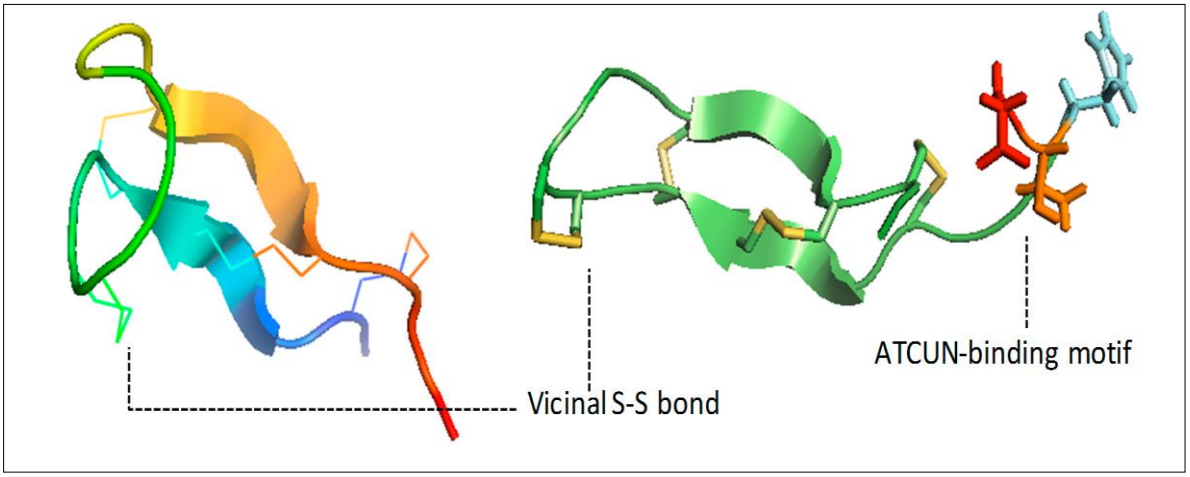

Figure 2 Structure of the hormone hepcidin [69]

One study showed a strong similarity between the cysteine-rich cytoplasmic tail of the COVID-19 virus protein and the hepcidin hormone protein found in both humans and the vertebrates from which it was isolated [70].

6.2. Regulating Factors fo Hepcidi Levels

There are several factors that affect hepcidin production in the body, including:

- Iron load: Low iron levels affect the amount of hepcidin produced in the liver because these low levels have the potential to increase hepcidin production, while high iron levels reduce hepcidin production [74].
- Inflammation: Inflammation has an important role in the production of hepcidin hormone because it increases its levels in the body and thus leads to the closure of the endothelial network and the iron supply in it becomes ineffective or stopped, and it can lead to a state of iron overload [75], including interleukin IL-6, which leads to stimulating or activating the production of hepcidin by binding the transcription activator to the hepcidin promoter [76].
- Effectiveness of red blood cell formation: Red blood cells have a protective role. When their production increases, it will lead to a decrease in the production of the hepcidin hormone, and thus lead to an increase in iron metabolism in the body [77].

6.3. The relationship between hepcidin and Mediterranean anemia (thalassemia)

The primary relationship between hepcidin and Mediterranean anemia (thalassemia) is blood transfusion, as blood transfusions lead to elevated hepcidin levels in the body. Blood transfusions mediate red blood cell hyperplasia, which in turn increases hepcidin production [78]. Therefore, the discovery of hepcidin helped regulate the role of iron in patients with thalassemia and other iron-deficient anemias [79]. In addition, hepcidin has the ability to regulate multiple dynamic factors, as when its level in the body increases, it controls its production process through opposing effects through the formation of red blood cells, anemia, and iron overload. It is regulated by increased iron levels in the body, infection and inflammation, and is also regulated by many factors such as anemia, hypoxia, iron deficiency, and ineffective red blood cell formation [80]. In addition to the anti-stimulation of repeated blood transfusions in thalassemia patients [81]. As in Figure (3), which shows the relationship between anemia and the hormone hepcidin [82].

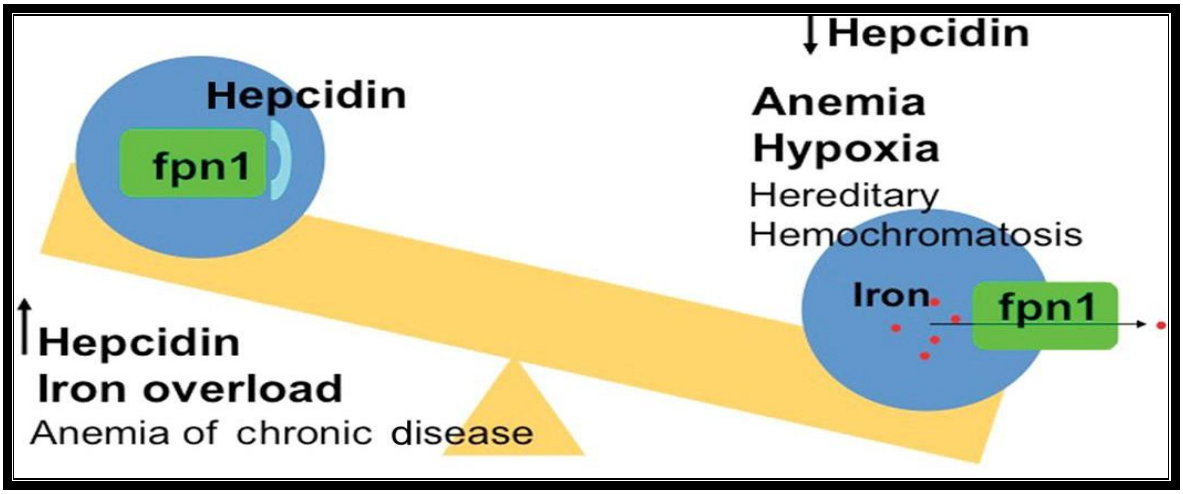

Figure 3 The relationship between anemia and the hormone hepcidin [82].

Multiple causes result in an increase in Hepcidin Levels, one main cause is from pro-inflammatory cytokines, which lead to destruction of ferroportin which leads to lower serum iron levels to deprive both quickly dividing cells and invading microbes in addition to the fact that there was already a decrease in 1) Red Blood Cell proliferation, 2) Expression of Erythropoietin, 3) Erythropoietin signaling, 4) Phagocytosis of erythrocytes. The end result of hyperhepcidinemia is likely exacerbated by a lack of renal clearance which results in Anemia of Chronic Disease (usually starting as mild-moderate with the potential of developing to microcytic and hypochromic) which has associated symptoms (fever, pallor, fatigue). Because the Iron tests shows a significant reduction in serum iron due to the increase in Ferritin due to Iron retention inside the cells, treating this is important to avoid the potential for worsening Inflammation in the future due to having it. [83,84].

7. Conclusions

Hepcidin plays a key role in regulating iron metabolism. Recent advances have provided the opportunity to regulate iron and hepcidin metabolism to control red blood cell formation. because hepcidin levels are responsible for iron deficiency and iron overload anemia, iron, along with erythropoietin, works to mature red blood cells. Conditions that lead to anemia may be associated with both high and low hepcidin levels , because hepcidin dysregulation may improve anemia control in preclinical models, future research is expected to reveal new hepcidin-related therapies for the treatment of anemia caused by it.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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