THE IRON HOMEOSTASIS HORMONE HEPCIDIN AS AN IMPORTANT INDICATOR OF ANEMIA

Abstract

Anaemia may pose as a common hematological state where each tissue of the body cannot get sufficient oxygen for appropriate working. Customarily it is measured by haemoglobin concentration level less than 11g/dL in venous blood. Withinthe final decade, fast advance has been made on anaemia and its connection with peptide hormone Hepcidin. Still there is lack of information of this iron regulatory hormone and its work in our body. To demonstrate the cause of anaemia within the human body it is not adequate to measure the hemoglobin level .Level of hepcidin will also offer assistance to uncover many causes behind the failure of the body to take-up iron appropriately.

The display endeavor isto audit the existing literature concerning iron control and role of hepcidin in iron control, and its impact, pathways that offer assistance in hepcidin direction and measuring forms of hepcidin so that the significance of hepcidin estimation in iron deficiency can get focussed and come in hone. After understanding all these points it can be said it is not only a suitable modern iron biomarker like: hemoglobin, ferritin, transferrin etc, it will also help to state the iron accessibility within the body, Hepcidin is additionally a significant biomarker that reflects the entire iron storage, mandate of iron metabolism and the disparity of intracellular and extracellular iron level.

Keywords: anemia, hepcidin, iron metabolism,biomarker

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I. INTRODUCTION

Anemia is a hematological condition in which blood is not properly oxygenated to circulate throughout the body. Red blood cells are the main carriers of oxygen, and the main component that plays this role is hemoglobin (Hb). This hemoglobin level varies with age and sex, physiological condition, height, etc. The hemoglobin consists of heme iron and globular protein. There are two main types of anemia, resulting from either overload or iron deficiency, which results in insufficient hemoglobin and red blood cell formation. In iron deficiency anemia, the patient thrives with insufficient micronutrient iron in their diet, preventing RBCs from proper formation. On the other hand, in iron overload anemia, there is enough iron to meet all of the body's needs, but the body cannot use the iron. Both types of anemia involve a malfunction of the iron in the body [1].

Iron as a substance in diet has many functions.Besides formation of Hb, iron additionally iron stays in different forms like- haemoprotein in muscle, protein in liver, globulin in blood stream. Iron has many roles in cells , with an atomic number 8 like-chemical reactions within the body to come up with energy, biological process, DNA synthesis etc. In diet iron stays as protoheme iron and nonheme iron. Protoheme iron is additionally bioavailable and simply absorbed from the gut walls. Iron in the physiological state is the main regulator,which is responsible for deficiency inside the body[2].

In iron-homeostasis, Hepcidin is the main player to control the entry and circulation of iron intracellularly [3].

In the year 2000, Hepcidin was discovered as an internal secretion secreted from the liver. Once the invention was made, several scientific studies were done to grasp the performance of this amide in its internal secretion.Out of many others,the main target of this internal secretion was to play the prominent role in iron-homeostasis. In 2016, the importance of blood serum hepcidin activity was reviewed as a diagnostic variable of anemia [4]. This article is making an attempt to disclose the role of hepcidin and body iron relation so that anemia will be treated properly.

Two processes are necessary to control correct utilization of iron in homeostasis, they are- organic process and Ferroprotein expression. A biological process is additionally a crucial process to make Hb from iron which is a macromolecule. Ferroprotein expression is that the method wherever iron transport happens from intracellular pathway and by dynamic mechanism (Figure1).Hepcidin levels within the body trigger or hinder both these processes [5].

There are many applied analysis done to grasp the relation of hepcidin and haemoprotein level within the body in numerous physiological conditions such as gestation, puberty, biological time etc. Most of those studies found vital correlation between each level and this could be an honest parameter for knowing the particular reason for anemia [6].

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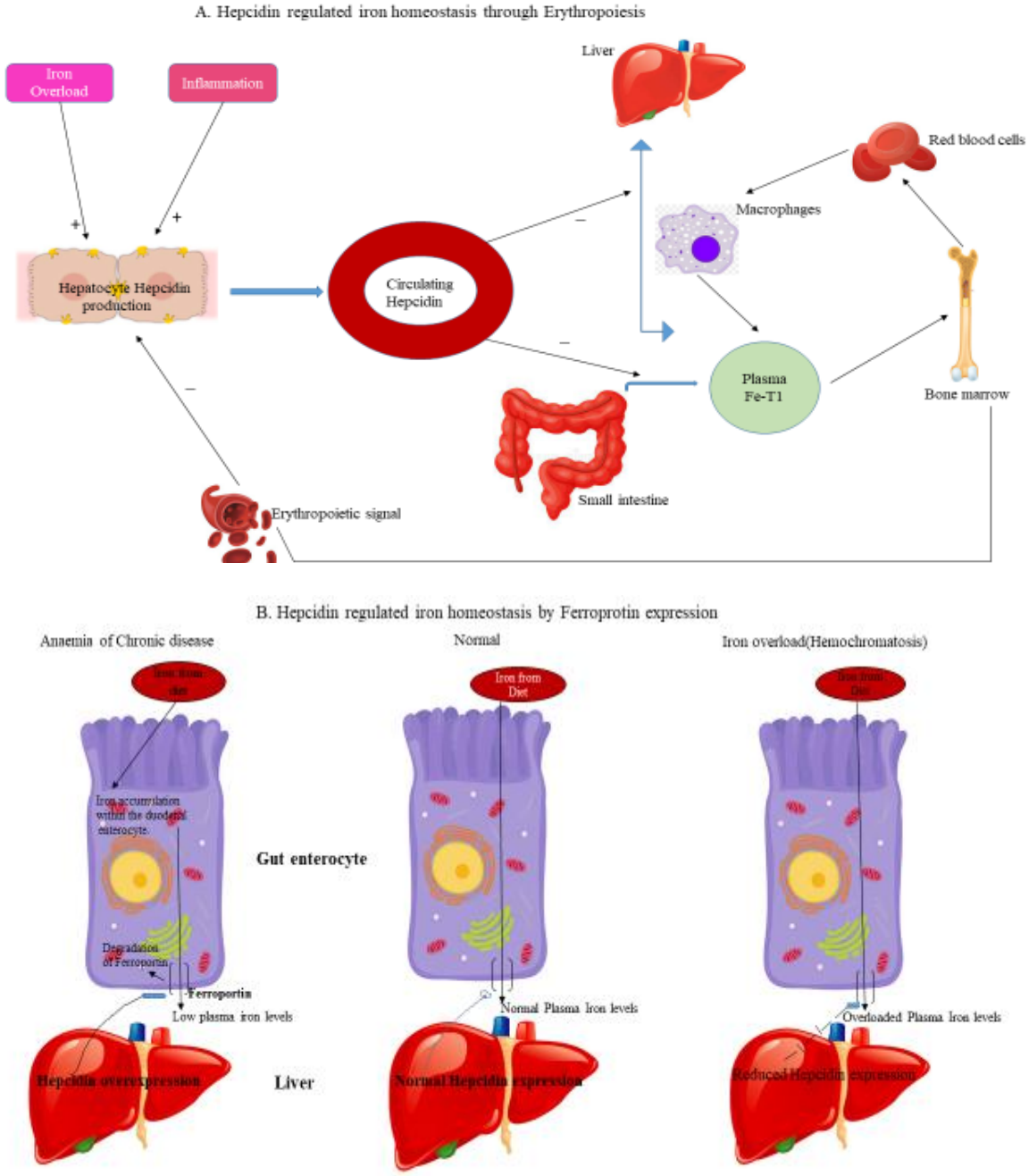

Figure1: Hepcidin Mediated Iron Homeostasis

II. IRON IN BODY

In human iron is present in numerous organs and in numerous forms. Usually a person will have 4000mg of iron(in food),out of this seventy percent is in erythrocytes, twenty percent in renal and internal organ macrophages and rest is bound together with numerous proteins like hemoglobin, myoglobin, cytochromes, ferroprotein for correct functioning of body. For the mobilisation of iron to numerous intracellular iron stores plasma globulin is

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required, iron is additionally found in plasma transferrin within the variation of around 3mg. At least 1-2 mg of iron gets excreted on regular basis via evaporation through skin. The regular excretion and viscus absorption facilitate to take care of the iron balance within the body, that is why iron usage through iron-homeostasis is very important in humans. The balance of usage of iron stores,Hb levels and proteins all are haphazard in emission section, iron deficiency being the most typical issue. During the state of gestation things intensify as there is accumulated iron demand for correct growth of a vertebrate. Similarly, within the bounds of infancy,childhood and pubescence iron is critical for growth[7].

III.ANEMIA AND HEPCIDIN

Anemia happens due to improper functioning of iron within the body. Anemia additionally results in several chronic infections and plenty of diseases. Iron deficiency anemia may be a major downside in developing countries. Iron deficiency will happen in cases of bronze diabetes anemia that is additionally quite common world wide. Anemia is a manifestation not solely in iron deficiency or overload however additionally in chronic infections and in inflammatory diseases-this condition is termed as anemia of chronic disease(ACD). Hepcidin participate in maintaining the physiological state of the iron metabolism upto its depleted level when anemia occurs [6,8].

Anemia is the most typical medical specialty disorder worldwide. Anemia is common in growing years, puberty, gestation and also found in elders. Anemia additionally happen in a large number of physiological disorders like Protein Energy Malnutrition(PEM), nephrosis, inflammatory disease, where primarily Hb level is measured distinctively. These days, the protein globulin is also used to determine the severity of the condition. The most important physiological downside is when the body gets barren of iron which cannot be discovered until the hepcidin level gets measured. The hepcidin level identification is a necessary act to treat anemia properly [9].

There are many different types of anemia like- iron deficiency anemia, bronzed diabetes anemia, mixed anemia among the notable ones of concern- of these types many are directly related to hepcidin level of the body. In some cases hepcidin level is low and in others high. Hepcidin thus plays a task in iron physiological state [6],(Vide Figure2).

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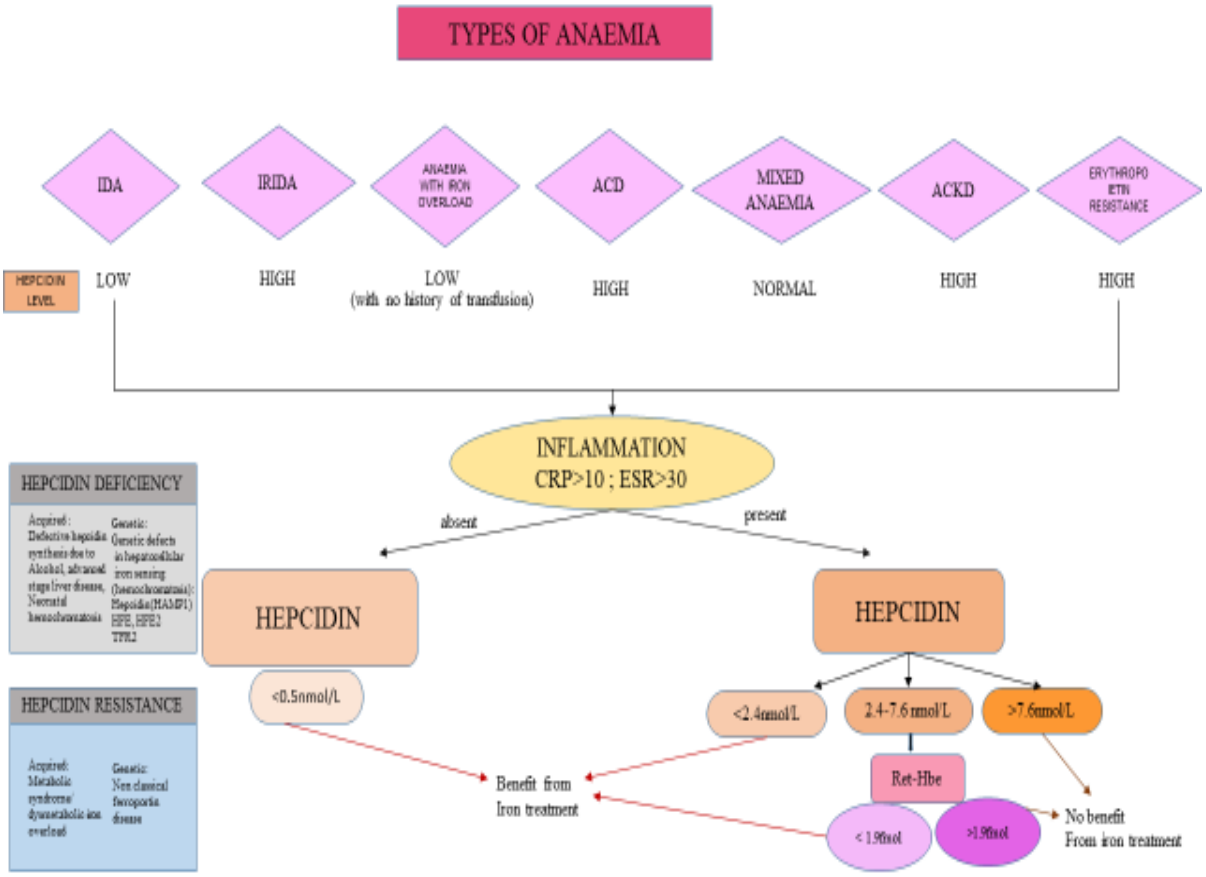

Figure 2: Proposed Algorithm for Hepcidin and Anaemia Interrelationship

IDA=Iron deficiency anaemia, IRIDA=Iron- refractory iron deficiency anaemia, ACD=Anaemia of chronic disease, ACKD= Anaemia of chronic kidney disease, CRP=C-reactive protein, ESR= Erythrocyte sedimentation rate, Ret-Hb=Reticulocyte-hemoglobin equivalent

IV. HEPCIDIN

Organically, hepcidin is created from twenty five organic compound proteins within the body. These amino acids are made of eight aminoalkanoic acid residues, those are Homojuveline, hereditary iron overload macromolecule, globulin receptor, a pair of, bone morphogenic macromolecule, six, matripase-2, neogenin, bmp receptor, transferrin. In body primarily in biological fluids hepcidin is present as twenty five organic compound isoforms principally. There are 2 different variants of hepcidin particularly hepcidin twenty two and hepcidin twenty. Hepcidin twenty five is the main participator in iron metabolism. Hepcidin as an internal secretion that acts as presecretion and prohormone, the pre internal secretion hepcidin has eighty four amino acids and prohormone has sixty amino acids. once hepcidin was discovered it absolutely was marked as Liver Expressed Antimicrobial amide (Leap 1), as a result of its anti-microbial and anti-fungal activities in liver.The name Hepcidin was given, as derived from Hep(liver) and cidin(anti-bacterial).Then step by step hepcidin's work was known, it's main role in iron physiological state was found much later. Hepcidin has an

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associate oligopeptide and its main activity are within enterocytes, hepatocytes and macrophages for maintenance of the dominant iron physiological state [10,11].

The hepcidin factor found in the body encodes a prepropeptide of eightyfour amino acids that undergoes cleavage to provide the sixty aminoacid containing pro-hepcidin, followed by another cleavage to produce the final product of 25 aminoacid hepcidin.[11].

V. THE GENETIC ROLE IN HEPCIDIN LEVEL MAINTENANCE

Iron overload within the tissue of the body happens once the hepcidin production step by step decreases to improper iron absorption and release from the iron enclosure. Hepcidin regulation within the body relies on some genes, they are HFE, HJV, TFR2, HAMP, TMPRSS6. Hereditary iron overload and ineffective organic process leads to anemia thaat happen in hepcidin deficiency. During this state of affairs mutation in genes HFE, HJV are seen primarily.

These genes encode proteins within the regulative pathway of iron and as a result hepcidin synthesis decrease in bronze diabetes. Mutations of these genes ends up in accumulated viscus absorption of iron and limitless iron gets released from macrophages.
On the other side Hepcidin deficiency results from mutation in β-globin factor and cause briefly hepcidin deficiency which results in improper formation of β-globin and therefore simple protein tetramers are fashioned in blood corpuscle as progenitors far more than precipitating and causing premature death of corpuscles [12].

VI. THE ROLE OF HEPCIDIN IN IRON HOMEOSTASIS: (FOCUSSING ON FERROPORTIN EXPRESSION)

Hepcidin and its regulation in body iron physiological state, is the study that continues to draw in interest in the last decade. Body iron demand is accumulated to such a large extent that all the phases of iron demand was dependent on diet iron content as well as on the extent of hepcidin. The action of hepcidin is established by targeting the downstream cell and therefore the release of iron from these cells to the plasma. The downstream target cells are derived from hepatocytes, enterocytes and macrophages. Ferroportin may be an internal secretion that determines the presence of iron in intracellular areas, that helps maintaining the iron physiological state. Hepcidin limits the cellular binding of iron with ferroportin. Hepcidin is also concerned in aminoalkanoic acid phosphorylation pathway of ferroportin that plays a direct role in physiological state of iron metabolism [13].

The general iron physiological state was studied in the last decade to know the dynamics of iron metabolism in detail. These studies showed the importance of an internal amide secretion named as Hepcidin and its performance in iron metabolism and host defense. Hepcidin is secreted from its primary site the liver, and maintain the extent of iron in the current iron status and the iron stores. Hepcidin usually circulates in the blood serum plasma, and is excreted through the excretory organs quickly. Hepcidin transcription have a correlation at the macromolecular level that regulates hepcidin outcome [14].

Efflux of iron in plasma is regulated by the ferroportin internal secretion placed within the tissue. The feroportin is found in the majority of tissues from enterocytes,

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macrophages and hepatocytes. If the ferroportin level is reduced then iron efflux it can diminish in plasma concentration. During this method hepcidin actually works negatively in ferroportin synthesis and reduces iron level in blood,therefore anemia happens. Hepcidin additionally works in regulation of iron stores and on the iron present within the body by participating in an organic process. Once the body demands additional iron, hepcidin production gets diminished in order that ferroportin synthesis increases with additional and iron absorption. Once iron level increase in the body the condition triggers infections within the body.At that point hepcidin will increase and act as an antimicrobial element that stop the work of ferroportin and then the iron absorption decreases. That is how hepcidin deals with iron level within the body and becomes a parameter in determing the degree of lack of iron in the body [15,16].

Furthermore, hepcidin concentrations markedly influence iron absorption and may have an effect on the efficaciousness of iron repletion via supplemental or from dietary sources [17].

So hepcidin levels works with iron level in body by the following mechanisms: (chart1)

- accumulated hepcidin expression by the liver, leading to high level of hepcidin in blood stream, in addition leading to the degradation of the iron related ferroportin that successively ends up in diminished phagocyte iron loading,low plasma iron level, decreased erythropoiesis and diminished transferrin-bound iron finally leading to anemia.
- traditional hepcidin levels fluctuates in response to traditional levels of iron within the body.
- depleted hepcidin ends up in iron overloading and excess iron deposition within the liver [12].

Chart 1: Relationship of Hepcidin and Serum Iron level

Level of Hepcidin	Serum Level of Iron
Increased	Iron insufficiency
Normal	Normal level of iron
Decreased	Iron overload

VII. HEPCIDIN REGULATION

1. **Hepcidin Production by Hepatocytes is Transcription Regulated and Mediated by Iron:** Hormones are regulated by a feedback mechanism in order that their concentration level will remain balanced within the body. Hepcidin is additionally regulated by this mechanism and in addition works as an iron device in intracellular and living fluids of the cells. This feedback regulation has one or additional pathways to control the hepcidin synthesis from hepatocytes. Two globulin receptors, TfR1 and TfR2 primarily work along and move with membrane macromolecule HFE that functions as a holotransferrin device,

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serving to increase hepcidin production. First of all HFE biochemically makes contact with MHC category I, binds with Tfr1 and initiate the pathway with the assistance of holotransferrin. The free HFE move with TfR2 and therefore the combined HFE and TfR1 gets displaced with increase in holotransferrin level. This whole method stimulates hepcidin expression to the BMP and MAPK pathway [18].

2. **The BMP Pathway Regulates Hepcidin Transcription:** After feedback regulation BMP pathway is initiated by the assistance of cytoplasmatic Smad, that is that the main regulative pathway for hepcidin transcription. In human co receptor hemojuvelin helps to induce the hepcidin expression. This hemojuvelin synthesis regulates this BMP pathway in liver together with several different pathways. If the hemojuvelin receptor gets mutated then hepcidin deficiency occurs and as a result bronze diabetes related anemia happen. Mutation in BMPs like BMP2,BMP4, BMP5, BMP7 and BMP9 are connected with hepcidin expression. Erythroferrone is also an element during this pathway. The hepcidin expression imbalance can be cited as samples of genetic iron disorder like- Hereditary Hemochromatosis(HH), Iron Refractory Iron Deficiency Anemia(IRIDA) and Anemia of Inflammation(AI). BMP-SMAD pathway primarily controlled by BMP2 and BMP6 happens in endothelial cells of liver ALK2 and ALK3.These two receptors are measured equally and are accountable for basal hepcidin expression through BMP pathway. These 2 receptors facilitate in BMP pathway by one method with the assistance of HH supermolecule and therefore the responsive BMP2 receptor and BMP6 conjointly works in an increased potential to increase the tissue iron store. JAK2-STAT3 signalling conjointly plays a key role in the BMP-SMAD pathway [19,20].

   Inflammation in JAK2-STAT3 signalling give the required signal to provide hepcidin production through the BMP-SMAD pathway. Pharmacologically the boosting of hepcidin synthesis works in this BMP-SMAD pathway in order that genetic iron dysfunction in absorption may be treated to keep up hepcidin level in body [19]

3. **Hepcidin Regulation by Inflammation Through IL6 Pathway:** IL6 pathway is an associate upstream tracker that regulates hepcidin production by inflammation. IL6 pathway in the main pathway in making balance of hepcidin expression in reference to body fluid iron saturation. This pathway happens in hepatocytes. This pathway starts with the formation of hexameric advanced IL6 then it binds with the compound protein 130(gp 130) that helps in downstream signalling. The intrinsic enzyme activity triggers JAK2 element shaped with the assistance of amino acid enzyme following this mechanism. Once JAK2 gets activated, then downstream phosphorylation of STATs method conjointly gets initiated. These STATs after translocating the nucleus induce HAMP cistron transcription. Studies show that hepatocyte STAT3 is accountable for hypoferremia and anemia [21].

4. **Hepcidin Regulation by Stat3 Sign Pathway:** Stat3 sign pathway is a crucial regulative pathway for hepcidin through inflammation. This pathway helps in production of IL6 and IL22, that helps in regulating hepcidin in the IL6 pathway. Stat3 sign pathway involves the promoter of HAMP cistron, binding to the stat3 site. Hepcidin transcription may decrease if siRNA mediate stat3 is not operating properly. Altogether these inflammatory processes involving stat3 works as a regulator of hepcidin. Stat3 signalling creates inflammatory conditions and conjointly IL6-Stat3 pathway helps in hepcidin expression

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in baseline. This pathway helps to mix IL6 to IL6 receptor and activate Stat3 phosphorylation then helps in transcription of HAMP cistron. This HAMP cistron is additionally a crucial think about hepcidin regulation within the body [22].

5. **Hepcidin Regulation by Sex Hormones:** The main two sex hormones particularly androgenic hormone and progestogene, have important role in hepcidin regulation. Androgenic hormone, the male endocrine component regulates the assembly of hepcidin by initiating the signalling of stratum protein Receptor (EGFR) and conjointly contributes in BMP-SMAD pathway. On the other hand, the feminine hormone estrogen contributes its role in down-stream regulation of HAMP organic phenomenon (23). Steroid hormone receptor component suppresses the 17β-Estradiol and promotes hepcidin transcription in hepatocarcinoma cells as seen in experimental studies(24). Throughout gestation, monthly emission cycles and in biological time the 17β-Estradiol relates with hepcidin production negatively and iron absorption in positive..A recent study instructed that progestogen receptor, conjointly contributes to hepcidin regulation [18].

6. **Hepcidin Regulation by Vitamin- D:** In recent times studies have shown the relation of anemia and vitamin-D. This association acts as a semiconductor diode of the condition of inflammatory anemia. The most pressing reason behind vitamin-D association is - vitamin-D is required in formation of hepcidin and its deficiency results in anemia. The shape of vitamin-D, 1, 25$(OH)_2D_3$ interacts with the hepcidin- cistron in monocytes and hepatocytes and suppresses hepcidin forming RNA transcription. Vitamin-D actively participates in pro-inflammatory protein production serving in suppression of hepcidin expression, that is more accountable for hepcidin production in inflammation. The erythropoietic biological process conjointly desires active role of 1,25$(OH)_2D_3$. Synthesis of hepcidin requires eight proteins from hepatocytes and macrophages. Out of those eight proteins cathelocidin is one that has antibacterial drug component[25,26].Cathelocidin is additionally a spinoff of ergocalciferol. IL6, the vital pathway for regulation of hepcidin conjointly needs ergocalciferol[27].

7. **Excretory Mechanism of Hepcidin:** The kidney is the major clearance route for hepcidin excretion. Hepcidin appears to specifically target the distal nephron rather than the proximal tubule . Several groups have shown that hepcidin is significantly elevated in dialysis patients. Most groups found that hepcidin levels were directly correlated with serum ferritin, and some reported a correlation with C- Reactive protein, a marker of inflammation. Hepcidin levels have been shown to be inversely related to erythropoetin dose and decrease with initiation of erythropoetin therapy[28]. These relationships are consistent with regulatory mechanisms and the relationships are observed in animal studies[29].

VIII. MEASURING METHOD OF HEPCIDIN

Measurement of hepcidin tiers has been difficult.(16) Some of the issues involve evaluation of the techniques and the shortage of standardization involved. The maximum definitive test is with hepcidin-25 that can be used on blood samples. These try-outs presently encompass surface-superior laser desorption/ionization time-of-flight mass spectrometry and enzyme-connected immunoassays.[29,30]

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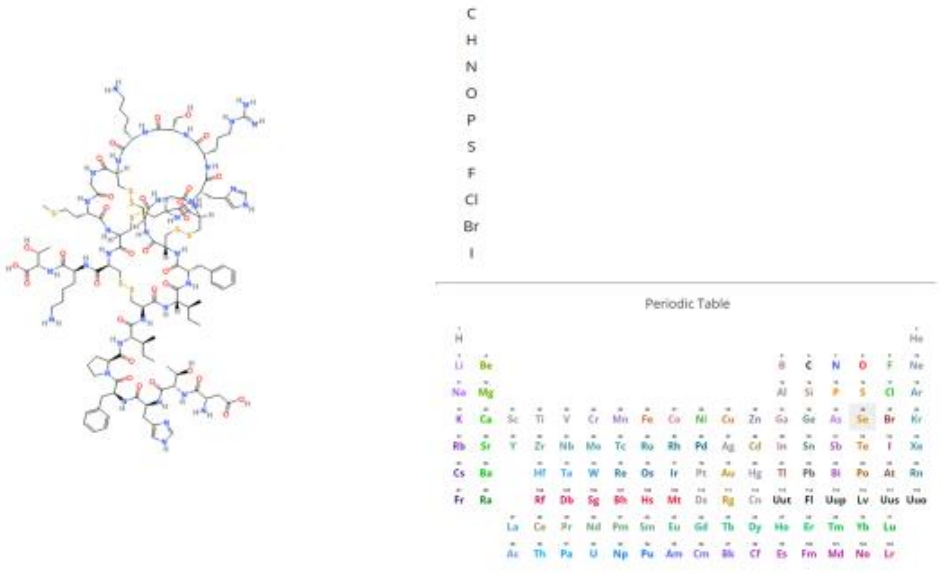

Figure 3: Structure of Hepcidin Molecule JMol View

IX. THERAPEUTIC IMPLICATIONS OF HEPCIDIN- THE CONCEPT OF HEPCIDIN AGONISTS AND ANTAGONISTS

Hepcidin as already established before is a key hormonal regulator of whole-body iron homeostasis and its expression is induced by iron or inflammatory stimuli.Studies based on structural genetics of Hepcidin is of much use in present times(Figure 3). Genetic defects in iron signaling to hepcidin lead to 'hepcidinopathies' ranging from hereditary hemochromatosis to iron-refractory iron deficiency anemia, diseases caused by hepcidin deficiency and excess, respectively. Furthermore, hepcidin dysregulation is a pathogenic cofactor in iron anemia and inflammatory anemia with ineffective erythropoiesis. Experiments in preclinical animal models have provided evidence that restoring adequate hepcidin levels can be used to treat these diseases. This accelerated the fast-growing segment of hepcidin therapeutics. To date, several hepcidin agonists and antagonists, as well as inducers and inhibitors of hepcidin expression, have been identified. Several of these have been further developed and are currently being evaluated in clinical studies.[31].

In recent time this new medical aid referred to as hepcidin agonist medical aid is developed to assist anemic patients. This method helps to manage iron absorption and ameliorate bronzed diabetes. This take a look at is currently in its initial section, thus more tests and trial are going to be required to boost it [3

Hereditary pathology, paediatric pathology and anemia because of chronic disease square measure all samples of iron –overload anaemia,and altogether this sort of cases hepcidin agonists may be an useful fruitful method [33,34].In β-thalassemia, Iron deficiency anemia this medical aid can facilitate in iron absorption. more studies ought to be done to live the pertinence and end in anemia treatment in addition as in blood corpuscle production[35].

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X. CONCLUSION

Both iron deficiency anaemia(IDA) and and anaemia of chronic disease (ACD) are harmful states. Thus, body iron levels measurement is strictly maintained by controlled absorption of dietary iron and release of stored iron by the internal endocrine organs. Hepcidin and its impaired regulation is related to all iron connected disorders. Over the past 20 years, a great number of progress has been made in the understanding of iron physiological condition and hepcidin regulation. In developing countries where anemia is one of the commonly seen disorders, we should always try to understand meticulously its causes and look for the therapeutic ways that to forestall it. Not only haemoprotein is the reason behind the different types of anemias , the different biochemical parameters like- IL6, complete blood count (CBC), c-reactive protein(CRP),hepcidin etc needs attention in thorough study of the patterns of anaemia. . Hepcidin is that the endocrine biomarker that decides the iron level in plasma and in the liver storage,also in intracellular and extracellular storage, thus Hepcidin level ought to be measured in anemia and poses as an effective biosignature with both diagnostic and therapeutic potential[36,37].

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