

## Relation between Iron Deficiency and Susceptibility to Bacterial Infections

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### ABSTRACT

Iron deficiency (ID) is a common deficit of the particular nutrient in the body and the top-ranking cause of anemia worldwide. It is a common cause of morbidity and accounts for 50% of anemia cases in the world. Symptoms of iron deficiency are subtle and nonspecific including severe anemia, fatigue, diminished work, gastrointestinal disturbances, associated with the impaired natural type of immunity and the cell-mediated type of immunity. Therefore, differentiating the term iron deficiency and the other term infection is essential. The process by which the microbes acquires iron supplement and the respectful virulence can be identified by the application of the different type of host mechanisms and also different microbial mechanisms, thus interfering with these respective mechanisms is likely to create the future therapy forms for the bacterial diseases that are infectious. In this review article, we summarized the mechanism of iron metabolism in the body, the characteristics of iron deficiency anemia, symptoms, epidemiology and etiology, host mechanism during bacterial infection, and the susceptibility to bacterial invasion in case of iron deficiency anemia.

**Keywords:** anemia; iron deficiency anemia, bacterial infection, iron, immunity.

### INTRODUCTION

Iron is considered to be the second most type of metal that is considered to be abundant in the crust of the earth, it's a substantial element for most living organisms and the one responsible for the maintenance of their health. Iron can be regarded to be a vital component of several body functions, primarily hemoglobin synthesis and transport of oxygen throughout the body. It is found in several different enzymes involved in maintaining cell integrity, such as catalases, peroxidases, and oxygenases. Proportionally higher iron concentrations are located in the basal ganglia of the human brain than in liver. In breastfeeding infants, brain parts, particularly the microglia, continue to develop, and therefore iron is vital for developing cognitive functions at this stage of life <sup>(1, 2)</sup>.

### IRON METABOLISM

In the body, iron is distributed into two compartments. The first is a functional compartment formed of a number of compounds, including hemoglobin, myoglobin, transferrin and enzymes, and all of which require iron as a cofactor or a prosthetic (ion or haem) group. The second is the storage compartment, formed of the ferritin and the hemosiderin, which constitute the body's mineral reserves <sup>(2)</sup>.

The absorption of iron takes place at the proximal duodenum, with the amount of the iron

absorbed being is dependent on the sufficiency of iron stores. Human iron metabolism is remarkably efficient, as only 0.5 – 1 mg of the approximately 4 – 5 g of the total amount of iron that is present in the body iron is lost on a daily basis <sup>(3)</sup>. In the individuals who are considered to be healthy, almost all the iron that is lost is taken into the plasma where it is bound to transferrin, and thus, limiting the catalysis of free radical production of iron. This facilitates the process of iron transportation to the cells of interest. The delivery process of the iron that is loaded with transferrin to the cells of interest where it is accomplished by the respective endocytosis that is receptor-mediated. The ferric type of iron that is released from the transferrin is then reduced into the endosome using the ferrireductase STEAP3 where it is also transported in a subsequent manner to the cytoplasm using the DMT1 <sup>(3)</sup>.

It from this location that we realize that the fate of iron mainly relies on the cellular requirements. One application of Iron it can be used for the heme biosynthesis, whereby heme is regarded as the tetrapyrrole-type of a molecule that serves both as the prosthetic group consisting of the metalloenzymes, also serving as the oxygen-binding moiety that is meant for hemoglobin. In the same case, iron is capable of being incorporated to the clusters of iron-sulfur, which are the redox cofactors that are mainly applied for the

metalloenzymes. In conclusion, it can be said iron is capable to be stored in an intracellular manner as a type of ferritin, which is said to be a form of spherical heteropolymer with an ability to store the atoms of iron that are more than 4000. A significant number of iron elements located in human is described to be located in the erythrocytes, whereby they are complexed to what is known as heme type of moieties that is located in the hemoglobin. The primary functions associated with hemoglobin are the delivering of the oxygen to the body tissues, removing carbon (iv) oxide from the body and also removing the carbon (ii) oxide from the same body, and carrying out the regulation of vascular tone by the use of the binding of the oxide of nitric. The HO-1 is responsible for releasing iron and also the carbon (IV) oxide from protoporphyrin ring, which is responsible for producing biliverdin also the shutting of iron to pools of the transferrin. The levels of iron are normally made in control by IRP1 and the IRP2, that are responsible for binding to the iron feedback components in the factors of mRNA encoding that are accompanied with the metabolism of this iron. Furthermore, it also performs the regulation of what is known as IRP that is mediated by the levels of the cellular type of iron, the respective metabolism of these iron is mainly regulated in a systemic manner<sup>(4)</sup>.

The lack of iron in the prospective body is a thing that is known to be everyone and is mainly observed in each and every country. The children, and mostly considering the case of the infants that live in the nations which are regarded to be developing one, are the one and the most common who are known to be very vulnerable and at risk of suffering from this type of infections that are considered to infectious<sup>(5)</sup>. Thus, having a clear understanding existing between the lack of iron and its infection is vital. The lack of Iron is normally accompanied with the interference of the innate type of immunity also called natural type of immunity and the cell-mediated type of immunity, therefore adding more contributions to the additional risk of the associated infections<sup>(6, 7)</sup>. The process by which microbes and the respective virulence acquire iron is mainly identified by applying the various mechanisms relating to host and those relating to microbial.

Iron is one mode of nutrient which can be omitted to microbes related to humans and those relating to pathogenic. It behaves as an essential type of cofactor in a number of biological processes that are considered to be vital. Its capability of existing in either single oxidation state of the two respective states is one responsible for making iron to be regarded as an ideal type of catalyst of redox responsible for carrying out different ranges of cellular processes which involves respiration processes and the processes of DNA replication. In addition, Iron can be said to be one the vital component that is consisting of different enzymes responsible for generating peroxide enzyme and also other types of enzymes responsible for generating nitrous oxide that evolves to become a critical component for the proper working of the enzymes in the respective cells located system of the immune. Iron regulates the cytokine that is produced and also the one involved in coming up with the immunity form that is said to be cell-mediated<sup>(9)</sup>.

However, the accompanied potential of the iron that consists of redox is capable of emerging to become toxic to body cells immediately the iron is presented at high molarities due to its capability of making it possible to form oxidative radicals that are destructive. Through the fact that the lack of iron and the presence of iron that is excess is likely to cause the compromising of the functions that are performed by the cellular and therefore, the molarity of iron and its respective distribution is required to be handled in a careful manner in addition to performing a precise regulation<sup>(9,10,11)</sup>.

Regulating the distribution of iron performs a big role of as a mechanism of the innate type of immune against the pathogens that tend to invade. If you are given a certain type of requirement for the respective iron that is absolute using the human type of pathogens that are virtually, forms an important form of the innate type of immune system which ensures the presence of iron in the body is limited by the invading type of microbes in the process entailing the nutritional immunity<sup>(3)</sup>.

**Hepcidin**, which is recognized as a peptide form of a hormone that is mainly produced by the human liver, it regulates the ferroportin in a

post-translational manner, therefore, controlling the entry of the respective iron to the human plasma following the absorption of the enterocyte. Increasing the amount of iron in the human body is the one that triggers the process of producing hepcidin that induces the degradation of ferroportin and the respective internalization in a subsequent manner<sup>(4)</sup>. Hepcidin is known as the main orchestrator that is responsible for the hypoferrenic type of response to any type of infection. This hepcidin had been initially categorized to be a form of the antimicrobial peptide that is located in the human urine, also in the ultrafiltrate of blood<sup>(12, 13)</sup>. The release of the hepcidin from the human liver is made possible by the cytokines that are pro-inflammatory, by the situation of the activation of the TLR, by the stimulation of the response of endoplasmic reticulum induction that is mainly made of the proteins that are unfolded<sup>(14)</sup>. (Adding to the production of hepcidin that takes place in the liver, also the neutrophils and the macrophages play a big role in synthesizing hepcidin in regard to the response that results from the agents that are infectious making it possible for the iron to be modulated on its availability on the infectious focus<sup>(15)</sup>).

**Lactoferrin** can be defined as the host that keeps glycoprotein which is known for binding the iron that is free with a level of affinity that is high like the Transferrin. It is considered that their concentration is said to be free from lactoferrin is normally removed from the inflammation places and also from the liver. The secretions of Mucosal consists mainly of the percentage of lactoferrin that is regarded to be high, entailing a type of mechanism known as constitutive that is meant to offer some limitation to iron at the surfaces of the mucosa. Furthermore, the neutrophils granules that are normally specific are made up of lactoferrin, that is mainly is eliminated at the respective infectious sites for the purpose of offering to the cytokines<sup>(16)</sup>. The lactoferrin normally maintains the capacity of binding iron at a pH that is low as compared to the case of transferrin which makes it be a more effective form of scavenger in the type of infectious foci that is acidotic<sup>(17)</sup>. For a long period of time, it has come to an appreciation that the host for the respective iron status consists of the status that comes up with a sign fact form of

impact to the susceptibility that is directed to the cause of this type of infectious disease<sup>(18)</sup>.

## IRON DEFICIENCY ANEMIA

Averagely, a 50% people suffering from in the whole world are argued are directed to be lacking iron. This is what makes the lack iron to be ranked in position 9 of the risk factors that are totaling 26 in the whole world that are recognized by the GBD.

Causes of iron deficiency in order of prevalence include:

1. Not taking enough iron. This normally takes place in a type of population is said to be pediatric in the children mostly in the growth spurts.
2. Chronic bleeding which involves the loss of iron in an abnormal manner.
3. Increase in the requirement of iron supplement. The main cause for this effect is a normal pregnancy and during the breastfeeding<sup>(19, 20, and 21)</sup>.

It is obvious that the metal necessity mainly relies on the remarkable form of capacity that involves engaging in the reactions pertaining electron transport that takes place in the biological systems<sup>(22)</sup>. It is vital to come up with a clear similarity pertaining the amount of iron available at the body fluids and the one available at the bacteria. The latest report suggests that infection risk has been recorded to decrease at a high level over the period in which the person lacks iron in the body. Malaria is a good example in this case<sup>(23, 24)</sup>.

Extracellular form of iron is normally bound with a percentage of affinity that is recorded to be high by the transferrin that is known to be saturated by the low iron percentage of 50% in normal individuals. When the binding capacity of the transferrin is exceeded, the iron is said to be chelated with a type of affinity that is lower by a big proportion of molecules which are located in the plasma which includes the albumin, the citrate, and the amino acids<sup>(3)</sup>. During the process of infection, more addition of the fortification of the respective iron having withholding type of immunity takes place. The process of Inflammatory, which entails the infections, is the one that initially causes the decrease of the serum type of the quantities of iron

commonly known as hypoferrremia finally, considering the chronic process case which leads to anemia <sup>(25)</sup>.

### HOST MECHANISM DURING INFECTION

Mechanisms which entails the creation of an opposing effect to the infections like those involving the features of antibacterial on the tissue fluids and also on the phagocytic capabilities of the tissues that are in need of a free type of environment to the virtual case of iron component for the purpose of carrying out its functions in a proper way <sup>(26)</sup>. For the case of a living body, it is realized that the iron component is not considered to be freely available. The bulk of the respective metal is mainly locked up in ferritin, the hemosiderin, the myoglobin, and also in hemoglobin that is located in the red cells <sup>(27)</sup>. The iron component meant for carrying out the process of binding the respective proteins, respective transferrin and the respective lactoferrin, that are known to be possessing only a very small quantity of the total amount of iron that is located in the body, in most cases are considered to be the saturated partly by the respective iron and also have an associated content that is said to be so high. In the first case, a big quantity of the iron that is available is normally sequestered in an intracellular manner, whereby it is then complexed in between the hemoglobin that is located in the erythrocytes. Thus, a few of the pathogens are said to have emerged with types of mechanisms that enable them to carry out the liberation of hemoglobin by applying the lysing of the erythrocytes for the purpose of extracting iron from the heme <sup>(3)</sup>.

### BACTERIAL MECHANISM TO SEQUESTER IRON

Human pathogens that are considered to be successful are the one that possesses the mechanisms of carrying out the circumvention of the nutritional type of immunity for the purpose of causing disease. It is said that bacteria are associated with different ways that can be applied for the purpose of withdrawing iron from the respective host environment that records a low concentration of iron.

In the tissue that is injured or the one that is dead, the situation is considered to be so different. The transferrin and also the lactoferrin,

either alone or more usually in concert with a specific antibody, can have a powerful inhibitory effect on bacterial growth. There is a suggestion from the recent type of work argues that the iron proteins that is responsible for binding in the polymorphs are capable of playing an essential role in the bactericidal activity of these cells <sup>(28)</sup>. This reinforces the idea that Fe occupies a central role in the battle between host and parasite, although it is important to point out that many other factors also contribute to resistance.

As far as cellular immunity is concerned, it appears that polymorphonuclear leukocytes are relatively impermeable to iron with the result that the partly saturated lactoferrin inside the specific granules is unlikely to be affected by the addition of soluble Fe to the external medium <sup>(28)</sup>. This observation again suggests that the unsaturated iron-binding protein provides the essential iron-free environment in which the bactericidal systems of the polymorphonuclear leukocyte can act <sup>(29)</sup>.

The antibacterial effects of serum appear to be due, in part at least, to the high affinity of transferrin for Fe+3 which makes it almost completely unavailable as the free ion <sup>(30)</sup>. With 20% saturated transferrin, for example, the amount of free ionic Fe is only about 10<sup>-18</sup>M. This is many thousand times too little Fe for normal growth. This is analogous to the reaction occurring between transferrin and the reticulocyte. A second possibility is a secretion by the organism of a low molecular weight iron chelator capable of removing Fe+3 from the transferrin molecule, the resulting iron-chelate then being taken up by the bacterial cell. Similarly, antibody and complement cannot function effectively against bacterial infections in the absence of unsaturated iron-binding proteins. This antibacterial system can also be bypassed by means of heme compounds which are not bound by transferrin or lactoferrin. In this case, the bacteria must possess a suitable heme-binding site. The unsaturated iron-binding protein provides the essential iron-free environment in which the bactericidal systems of the polymorphonuclear leukocyte can act. With these ideas in mind, the effect of iron compounds on the interaction of a variety of pathogenic bacteria with the defense systems of the host can now be considered.

Spear and Sherman <sup>(31)</sup> came up with a demonstration that indicated iron to be a component that is integral for myeloperoxidase (MPO) enzyme that is responsible for producing reactive oxygen which has a key role of the intracellular destroying of the pathogens.

There has been a detailed study on the humoral immunity and the cell-mediated immunity on the parts of vitro relating to the deficiency of iron in human beings and in the animals. The damaging of the immunity of cell-mediated has been normally associated with human beings experiencing iron deficiency. However, there is minimal evidence for the case pertaining the deficiencies of the major humoral immunity. A number of different abnormalities of the cellular defenses that are experienced for the cases of the deficiency are <sup>(31,32)</sup> the reduced functioning of the neutrophil with the decreased activity of the myeloperoxidase (MPO), the damaged activity of the bactericidal, the depression of the numbers of the T-lymphocyte with the thymic atrophy, the proliferative response of the defective T lymphocyte-induced, the damaged activity of the naturally killing cell, the damaged production of the interleukin-2 using the lymphocytes, the decreased production of the inhibition factor responsible for macrophage migration and the reversible damaging of the delayed type cutaneous hypersensitivity which includes the reactivity of tuberculin. The dysfunction of Neutrophil and that one of macrophage has been recorded to be having low quantities of iron, using the evidence involving a decrease of deficient nitrobluetetrazoleum and the formation of hydrogen peroxide formation in the said cell lines <sup>(32, 33, and 34)</sup>.

Murray et al. <sup>(23)</sup> studied the incidence associated with the infections in the deficient of iron components Somali nomads <sup>(23)</sup>. This suggested that host defense against these infections was better during iron deficiency than during iron repletion. In contrast, an argument by Higgs and also Wells <sup>(35)</sup> comes with a comment that of the thirty-one patients who were suffering from chronic mucocutaneous type of candidiasis, only twenty-three were said to be iron deficient while nine of the eleven recorded an improvement by the application of only oral form of iron therapy and also the parenteral form of iron

therapy <sup>(35)</sup>. The Furunculosis recorded a resolution in all the patients apart from one after a period of 3 to 4 weeks of the iron form of therapy <sup>(36)</sup>.

Similar study that was conducted by Harju and the colleagues, the postoperative type of infections that resulted after the surgery of the abdominal surgery observe to be a common effect in a number of patients who were 228 and were recorded to be having preoperative serum ferritin that was low in comparison to the 220 patients who were having the common ferritin <sup>(37)</sup>. The process by which the microbes acquires the net iron can be is determined using the existing balance amongst the microbial mechanisms for the purpose of acquiring iron and for hosting the defense system for depriving the microbes associated with iron. On the other hand the host comes up with its own mechanisms that are meant to deprive the microbes of the iron

## IRON-BINDING PROTEINS AND RESISTANCE TO INFECTION

**Lactoferrin** functions as the modulator of the immune. It is the one responsible for acting as the first line of ensuring that is a defense against the invading organisms by using its capability ability for sequestering iron <sup>(38)</sup>. Also, the sequence of lactoferrin sequence consists of the peptide that behaves as the defense system, the lactoferricin that has an activity of microbicidal against the *Candida albicans*, the *Streptococcus mutans*, the *Vibrio cholerae* and the different types of enterobacteria <sup>(39)</sup>. There are two major factors that have a greater contribution to the efficiency of lactoferrin in the sequestration of iron in the reticuloendothelial system. In the first case, because of its high percentage affinity of the iron that is lower than the physiological pH, the following factor is that it creates a binding of more iron as compared to transferrin located at the inflammation sites which are known to be having low pH <sup>(8)</sup>.

**Ferritin** is a type of molecule that has an ability to store irons atoms that are up to 4,500. Over the period of inflammation, the synthesis of ferritin is improved by the influence of what is known as the interleukin-1 factor and the factor of tumor necrosis. The Higher amount of ferritin



synthesis and the associated increment of the delivery of iron by the lactoferrin to the macrophages performs a vital role in the sequestration of iron<sup>(8)</sup>.

**Transferrin** is the iron responsible for a binding protein located in the blood, but, the protein affinity consisting of iron depends entirely on pH, which makes it ineffective when it comes to the presence of the acidosis<sup>(8)</sup>.

The host relies on other immune mechanisms that are activated during the infection and this involves the **Interleukin-6** (IL-6), the inflammatory cytokine which induces the synthesis of hepcidin. This hepcidin is the one that binds with the ferroportin (FPN), which is responsible for inducing the internalization and the degradation of EPN. Egressing of iron from the macrophages and the enterocytes is mainly caused by the said FPN, the identified sole iron exporter in the mammals, and therefore made a contribution to the increment of the levels of hepcidin by the degradation of the FPN, which limits egressing of the respective iron from the intestinal cells and the macrophage cells, which, in turn, results to hypoferrremia<sup>(8)</sup>.

It also depends entirely on the down-regulation of the gene transcription of FPN and also makes a contribution to the generated effect of hypoferrremia, making the ferritin gene transcription to be activated. The Apolactoferrin that is normally released from the neutrophils acts a big role in removing the iron from the invasion site, and also makes a contribution to the improved hepatic synthesis of the haptoglobin and the hemopexin that carry out the binding of the extracellular hemoglobin and the hemin. An increment in the lipocalins synthesis which has a role of binding the siderophores of the microbes and also performing a role of inactivating them, the nitric oxide that mainly disrupts the iron metabolism of the microbes and the natural resistance consisting of the accompanied proteins of macrophage (NRAMP) by the macrophages. The said NRAMP-1 is the one that withholds iron, and therefore the one responsible for preventing the uptake of iron and also its utilization by the respective microbes. The NRAMP-1 normally focuses on the membrane of the microbe-consisting of the phagosomes located in the

macrophages and in the monocytes. The B-lymphocytes normally start carrying out the production of the immunoglobulin against the microbial surface receptors of the cell, which creates the prevention of the uptake of iron by the microbes<sup>(8)</sup>.

The study was done after approval of the ethical board of King Abdulaziz University.

## CONCLUSION

It can be concluded that the deficiency of iron creates a depression of the certain specific aspects of the cell-mediated type of immunity and innate type of immunity which makes the human body to become more vulnerable to bacterial type of infection, however, the significance associated with the growth of hypoferrremia on the microorganisms is observed to remain uncertain. Therefore, it is quite essential to carry out a review pertaining the relationship existing between the deficiency of iron and the risk of any infection and the one relying on the increasing knowledge of iron-binding proteins interaction and biochemical studies a matrix is provided for understanding their role in resistance, showing how powerful these mechanisms could be.

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