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Review Article:

The Relationship between Iron-Deficiency Anemia (IDA) and the Function of the Immune System

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Abstract

Context: Iron deficiency anemia is a common types of anemia in the world with harmful effects on various organs of the body without any diagnostic symptoms. This review article aimed to review the observational studies and clinical trials conducted on the effect of iron deficiency anemia on the immune system.

Evidence Acquisition: The results mentioned in this review are obtained from relevant studies published from January 1980 to January 2024 and indexed in PubMed, Google Scholar, Ovid and Scopus. The keywords were iron deficiency anemia, innate and adaptive immune system, cellular and humoral immunity.

Results: Iron deficiency anemia can affect the killing of phagocytes and the function and proliferation of T and B lymphocytes. Various factors including the number, gender, and age of the studied samples, the host's immune system, and the severity of iron deficiency anemia can be influential factors in the reported results.

Conclusion: Iron is essential in the function of different organs of the body, especially the immune system. Therefore, the regulation of iron metabolism against pathogenic factors is important in preventing or treating the disease. In individuals suffering from iron deficiency anemia, taking iron supplements through diet or by injection can strengthen their immune system and minimize their vulnerability to infectious diseases.

Keyword: Iron-Deficiency Anemia (IDA), Immune system, Innate immunity, Adaptive immunity.

1. Context

Anemia occurs with deficiency of red blood cells that are responsible for transporting oxygen to the tissues and organs of the body. Anemia can be seen in different types and with different causes, each of which causes a decrease in the number of circulating red blood cells. One of the types of anemia discussed in the research and the most common cause of anemia is iron deficiency anemia (IDA). Iron deficiency anemia is one of the most common types of anemia and micronutrient deficiency in the world among children and women (especially pregnant women) [1].

This type of anemia occurs due to the reduction of iron reserves in more severe cases [2].

In iron deficiency anemia, due to the decrease in the amount of iron in the body and bone marrow, the synthesis of hemoglobin is disturbed, which causes a decrease in red blood cells and the formation of microcytosis (small size) and hypochromic red blood cell [3].

Iron deficiency anemia (IDA) is usually a chronic disease without specific symptoms. In many asymptomatic patients, iron deficiency anemia can be diagnosed with blood tests [4]. In general, in some patients, specific symptoms such as yellow skin, fatigue and lack of energy, tingling and numbness, increased heart rate, decreased breathing or chest pain during activity, pica (bite eating and eating dirt or ice), fragile and spoon-shaped nails, chronic gastritis, restless leg syndrome, glossitis (inflammation of the tongue) and swallowing disorders due to the formation of webs at the junction of the esophagus and hypopharynx [4,5].

Iron, as one of the important elements in the functioning of body organs, can be used for various reasons, including the physiological conditions of the body (increasing the need for iron in infancy, growing age, pregnancy and blood donation), environmental conditions (such as insufficient absorption and malnutrition), pathological conditions (decreased absorption and chronic bleeding), drugs and genetics. When its amount is reduced and if it is not replaced, it makes the person prone to iron deficiency anemia [2]. To eliminate it, measuring the serum level of ferritin can be a sensitive and specific test. In patients with iron anemia, the serum level of hemoglobin/hematocrit, iron, ferritin and transferrin saturation percentage reduction and level of the total iron-binding capacity (TIBC) is low due to the compensation of iron deficiency [6].

Figure1. CBC results in IDA patients and control group [7].

Hematology indexes	Control Mean ± SD	IDA Mean ± SD
Hemoglobin (g/dl)	14.00 ± 0.80	10.93 ± 1.17
Hematocrit (l/l)	41.48 ± 2.24	35.57 ± 4.35
MCV (fl)	85.94 ± 4.19	73.57 ± 4.70
MCH (pg)	28.60 ± 1.98	23.10 ± 2.77
MCHC (g/dl)	33.38 ± 1.48	30.85 ± 1.77
RBC ($\times 10^{12}$/l)	4.85 ± 0.37	4.40 ± 0.22
PLT ($\times 10^{9}$/l)	245.62 ± 46.47	339.82 ± 105.56
WBC ($\times 10^{9}$/l)	7.02 ± 1.33	5.93 ± 1.21
Neutrophils (%)	58.93 ± 10.73	60.60 ± 10.89
Lymphocytes (%)	35.64 ± 8.68	34.05 ± 10.80
Monocytes (%)	2.71 ± 1.27	3.84 ± 1.22

Nutrients and their absorption through diet are important and necessary for all living organisms and maintaining their health, growth, cell function and tissue expansion, energy supply and immune defense. Many studies show that the mechanism of the effect of these nutrients on the function of the immune system and macronutrients (such as protein, carbohydrates and fatty acids) and micronutrients (such as vitamins, minerals, antioxidants and probiotics) in the diet are critical [8].

Supplying micronutrients is necessary for the development of the immune system at different stages of development, and the lack of any of them can increase the risk of respiratory and intestinal infections, allergies, asthma, nervous system development disorders, and infant death [9-11].

One of the most important micronutrients is iron which is essential for DNA synthesis, ATP production, cellular respiration, oxidation and reduction processes, play a role as a cofactor for electron transfer, enzyme function and immune system [12]. Dietary iron can be taken as heme or non-heme iron and in two forms ferrous (Fe^{2+}) and ferric (Fe^{3+}) enter the body. Non-heme iron is usually absorbed through grains and vegetables and is found in wide and diverse forms (such as iron in low molecular weight complexes and stored iron in ferritin). On the other hand, heme iron has a more effective absorption and its absorption is less dependent on other food items in the diet than non-heme iron[12].

The metabolism of iron is highly regulated and the amount of its input into the blood circulation is provided by two routes: by macrophages by retrieving iron from red blood cells and epithelial cells of the duodenum by absorption of iron from the diet. The released iron (Fe^{2+}) from macrophages enters the cytoplasm of duodenum cells through the phagosome lumen and passing through the divalent metal transporter 1 (DMT1). When there is no need for iron in the intestinal cells, it is stored inside the ferritin protein. Finally, when iron is needed, it is converted to Fe3+ and exits the enterocytes through the ferroportin channel (FPN) [13]. The level of ferroportin and the amount of iron released into the circulation are regulated in response to the need for iron. To deliver Fe^{3+} to the cells, the iron bound to transferrin, by binding to the transferrin receptors (TFRs), enters the cell membrane as an endosome and is separated from transferrin in the acidic environment and depending on the needs of the cells, it can have a different fate[13,14].

Due to the prevalence of iron deficiency anemia (IDA) and the harmful effects of iron deficiency on

different parts of the body, especially the responses of the immune system and the increased vulnerability of these people to various diseases, in this research, an attempt was made to determine the role of iron and its deficiency on the defense function, cells and responses of the immune system against the pathogen that have been discussed in previous articles will be investigated and the results will be reported so that these people can be prevented from contracting diseases by ensuring the effects of iron deficiency anemia on the immune system. In addition, by preventing and treating iron deficiency anemia, the immune system of these people is strengthened and the risk of infectious diseases is reduced.

2. Evidence Acquisition

For this review article, we searched PubMed, Google Scholar, Ovid and Scopus for studies published between January 1980 and January 2024. The keywords and phrases included iron deficiency anemia, innate and adaptive immune system, cellular and humoral immunity. A variety of articles were extracted from the journals in immunology, hematology and nutrition. A total of 42 relevant studies were reviewed. The criterion for selecting the final articles was the articles with the highest number of citations.

3. Result

Iron deficiency anemia can have different effects on innate and adaptive immune responses, which are detailed below on innate immune cells that include phagocytes, dendritic cells (DC) and natural killer cells (NK cells) and acquired immunity involving lymphocytes and the humoral immune response are described [15].

In infectious diseases, iron is considered one of the most important elements for maintaining the function, metabolism and proliferation of immune cells of the host and pathogens. In other words, stopping the access of pathogens to iron can be one of the ways to defend the host as food immunity. The pathogen also needs iron for its metabolic pathways; As a result, different forms of iron are used in the interaction between microorganism and body organs in symbiosis and infection [16]. It was first stated in 1946 about the importance of iron in the host against infections and pathogens, which was observed to decrease within 48 hours in patients with Staphylococcus aureus [16, 17]. Regulating the amount of iron in the blood circulation by the peptide hormone called Hepcidin is done, and its primary synthesis takes place in the liver [18].

This hormone prevents the increase of iron absorption by intestinal cells and the release of iron from macrophages in the spleen in people whose blood and tissue iron levels are high or who have systemic infection and inflammation. As a result, it can cause anemia resulting from chronic diseases in persistent infections [19, 20]

In contrast, in erythropoiesis, iron deficiency and tissue hypoxia, the amount of production of this hormone is reduced and causes the release of iron from its reserves, which can increase the risk of infection in these people due to the access of the pathogen to iron.

Pathogens take iron from the host for their growth and metabolism through siderophore and specific receptors, but the cells of the immune system play an important role in the lack of access to iron due to various proteins [18]. For example, lactoferrin is the first protein bound to iron in the face of pathogenic agents, which is produced in the secondary granules of neutrophils, secretions of exocrine glands and liver, and causes the breakdown of extracellular iron. Also, by producing in the liver, it can release inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor (TNF-α) and interferon gamma (IFN-γ) and plays its role in diseases such as diabetic ketoacidosis by acting in acidic pH [18, 21, 22]. Also, by producing lipocalin-2, which is an iron-retaining protein, it can be attached to the siderophore of bacteria and prevent them from absorbing iron [23]. Ferritin is another protein that has an antimicrobial effect by absorbing iron, by chemotaxis, increasing the secretion of interleukin 6 and TNF-α due to the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), can also have a pro-inflammatory effect [24, 25].

The effect of iron deficiency anemia on innate immunity

Innate immunity is considered as the first line of defense against pathogens, and iron deficiency can have many effects on its function.

The effect of iron deficiency anemia on the function of phagocytes

One of its effects is on the phagocytosis of leukocytes, which disrupts their bactericidal function. Especially in neutrophils by reducing the activity of the myeloperoxidase enzyme (MPO), which is an iron-containing enzyme and in the production of reactive oxygen intermediates that contribute to the death of intracellular pathogens by converting Fe^{3+} to Fe^{2+}, their germicidal properties are weakened [26].

The effect of iron deficiency anemia on monocyte/macrophage function

According to studies conducted on the effect of iron on macrophages/monocytes, which are one of the most important cells in innate immunity, it can disrupt their activity [26]. The effect of iron on monocyte-macrophage differentiation has been reported as iron is needed to carry out antimicrobial mechanisms. Macrophages can express two phenotypes M1 which causes the production of pro-inflammatory factors and M2 which causes the production of anti-inflammatory factors, depending on the relevant cytokine environment. Changes in iron levels can also affect the proliferation of macrophages. In iron deficiency, macrophages proliferate more toward their alternative phenotype (M2) because iron deficiency in M2 macrophages prevent the formation of functional iron-containing enzymes in arachidonic acid metabolism. In addition, Iron may affect the biosynthesis of the iron-containing enzyme, tyrosine hydroxylase, which catalyzes the rate-limiting step in catecholamine biosynthesis and, consequently, the inflammatory response[27, 28].

Investigating the effect of iron deficiency anemia on the body is a little more difficult, but it has been shown in laboratory animals that the activity of macrophages can be impaired [29]. In a study that examines the level of two factors, MIF (macrophage migration inhibitory factor), which is a pro-inflammatory cytokine that causes systemic inflammation and monocyte chemoattractant protein-1 (MCP-1), which is a chemokine involved in macrophage/monocyte infiltration and migration. The experiment showed that the level of both decreases due to the decrease TNF-α [29, 30]. In animal models and tissue culture with iron chelation by Defroxamine, inhibition of the oxidase activity of phagocytes and the death of bacteria with the production of reactive oxygen intermediates were observed. It can also affect the expression of other antimicrobial molecules such as nitric oxide (NO) produced by the enzyme inducible nitric oxide synthase (iNOS) [31, 32].

The effect of iron deficiency anemia on natural killer cells (NK cells)

Iron deficiency can affect the function of natural killer cells (NK cells) because the activity of these cells increases the expression of transferrin receptors. It can also reduce the release of interferon gamma in viral infections. The role of iron on these innate immune cells (NK cells) is clear, especially in tumor cells. In the tumor environment (TME), natural killer cells play a role in tumor destruction by producing cytotoxic cytokines, by increasing the expression MHC1 due to the presence of inhibitory receptors, the activity of NK cells decreases, but on the contrary, when the amount of iron and ferritin heavy chain (FTH) decreases, the level of MHC1 expression also reduced and the vulnerability of cancer cells to NK cells increases. Therefore, this issue can be used to increase the antitumor activity of natural killer cells by chelating iron, although using iron chelators such as deferoxamine (DFO) is limited due to side effects on other cells [33, 34].

No results were reported in the studies about the effect of iron deficiency anemia on dendritic cells.

The effect of iron deficiency anemia on complement system function

The complement system is a collection of serum glycoproteins activated by cell receptors from 3 classical, alternative and lectin pathways and with cascade activities lead to the induction of inflammatory response, chemotaxis of phagocytes and opsonization [35]. C3 and C4 proteins play an important role in the activation of other members of the complement system, and when their activity decreases, the vulnerability to bacterial infections increases [36]. In a study conducted on adolescents, by determining the activity of the complement system especially C3 and C4 using nephrometric method, it was found that the level of these two proteins decreases with iron deficiency anemia, but there is no significant statistical difference. The results of this study were consistent with the findings of a study by Galan and Tang conducted in pregnant women and children with iron deficiency anemia. The effect of iron on the activity of the complement system is not clear, but it has been stated that the role of iron can be similar to the role of calcium and magnesium on the proteins of the complement system [37, 38].

The effect of iron deficiency anemia on the function of inflammatory cytokines

Little is known about the effect of iron deficiency anemia (IDA) on the secretion of cytokines, which are one of the key factors in many immunological processes and the interface between cells of the immune system. changes in the levels of interleukins and cytokines (IL-1, IL-2-IL-6, TNF-αIL-4, IFN-γ, IL-10) can be a causes of immune system dysfunction in iron deficiency anemia [39, 40]. While the secretion of cytokines is affected by iron deficiency, they can play an important role in maintaining the balance of intracellular iron [41]. Many studies show that in iron deficiency anemia, , the level of interleukin 6 (IL-6) decreases significantly due to a decrease in the function of T lymphocytes and there is a positive correlation between serum iron and interleukin-6 [6]. In the

study by Galan et al, it was reported that the level of interleukin 2, which is produced by active T lymphocytes and is necessary for their clonal expansion, decreased[42, 43]. In contrast, in other studies such as a study by Bergman et al., there was no change in the production of cytokines in people with iron deficiency anemia and the control group [44].

The effect of iron deficiency anemia on adaptive immunity

Adaptive immunity includes humoral and cellular responses that include lymphocytes B, lymphocytes T helper (Th) and T cytotoxic (CTL) becomes Iron in acquired immunity in growth factors for the clonal expansion of lymphocytes T are used, has a role. In studies, the flow cytometry technique is used to calculate and determine the number of lymphocytes and their type in the samples in question, and one of the advantages of this approach is the rapid counting of cells in high numbers.

The effect of iron deficiency anemia on cellular immunity

To investigate the effect of iron deficiency anemia on cellular immunity, counting different subgroups of T lymphocytes such as $CD3^+$ for total T-cells, $CD4^+$ for T-helper, $CD8^+$ for T cytotoxic lymphocytes and $CD4^+/CD8^+$ ratio as important parameters in cellular immunity are performed.

The effect of iron deficiency anemia on T Helper and T cytotoxic lymphocytes (Th, CTL)

Initially in 1972, Johnson expressed the effect of iron deficiency on the function of T lymphocytes and cellular immunity. In his research, there was a reduction in DNA synthesis in lymphocytes activated with PPD. the formation of macrophage migration inhibitory factors, which delay the development of an immune response against stimulatory factors such as antigens and PPD can be done, its effect was expressed on lymphocytes [45, 46]. Iron deficiency can affect the function, differentiation and proliferation of T helper lymphocytes, especially Th1, due to the difference in transferrin iron absorption and its greater sensitivity to iron deficiency, have an effect and inhibit their synthesis. Hoffbrand reported that the reason for their reduction in synthesis is the decrease in the function of ribonucleotide reductase enzyme (RNR), which is involved in the S phase of DNA cell cycle and iron is its cofactor [28]. Also, a decrease in $CD4^+/CD8^+$ has been reported in many studies. Of course, in the studies conducted by Ekiz, Hassan and Thibault with their colleagues, it has been reported that most of the functions of lymphocytes are affected by iron deficiency anemia and no significant change in their number is observed [6, 47, 48].

Also, in a study by Attia et al., the effect of iron deficiency anemia on the maturation of lymphocytes was studied [49]. The results showed an increase in the ratio of two markers CD71 (sTfR) and CD1a. CD71 is a soluble transferrin receptor sensitive to the reduction of iron in the tissue and its concentration level increases significantly in iron deficiency [10, 20]. CD1a is another marker for the population of immature lymphocytes. There appear to be a positive effect on the proliferation and maturation of lymphocytes, and the event of iron deficiency, the amount of immature lymphocytes increases [26, 50].

The effect of iron deficiency anemia on regulatory T lymphocytes (Tregs)

Effect of iron on regulatory T lymphocytes (Tregs) states that its chelation can directly affect the expression of the transcription factor (FoxP3) which directs the differentiation towards the production of these lymphocytes, and reduces the level of CD25 and STAT5 phosphorylation [27,51-54]. Indirectly, during the research, it was found that the iron in the heavy chain of ferritin (FTH) affects the function of Tregs in malignant myeloma patients because FTH in these patients, is secreted from the myeloma cells and enters the plasma, then on the antigen-presenting cells (APC) is presented and induces the expression of CD86 and B7-H1 and activates Tregs lymphocytes [55, 56]. In case of iron deficiency and FTH reduction, the response of antitumor effects of regulatory T lymphocytes (Tregs) can be analyzed [6, 16, 48, 49].

The effect of iron deficiency anemia on humoral immunity

During past studies, it has been suggested that iron deficiency anemia has a lesser effect on humoral immunity than cellular immunity, and contradictory findings has been stated in the articles. , For example, in some studies on the level of IgG, IL-6 and IL-2 which is used to communication between lymphocytes and NK cells, they decrease with iron deficiency and no changes was observed in the IgA and IgM levels. In contrast, in a study by Ekiz et al., there was no significant difference in the serum level of different types of antibodies except for IgG4 which was significantly reduced in people with iron deficiency anemia. In addition, in studies by Bagchi, Macdougall and Walter that examined the humoral immunity, IgG levels were reported to be normal in iron deficiency anemia [17, 57-59].

Finally, in several studies on selected samples, the results were compared before and after taking iron supplements by injection or through diet. In these

studies, after treatment with iron supplements and absorption of iron through diet, the findings showed that the function and responses of the immune system are reversible and the immune system can recover its function.

4. Conclusions

Iron can have various effects on innate and acquired immune system, the response of T lymphocytes to extracellular and intracellular signals, effective functions, proliferation and the death of the programed cell death. Considering the prevalence of iron deficiency anemia in the world and its harmful effects on various organs of the body, , its effects can be prevented with more extensive studies and the development of treatment methods. According to the studies conducted in laboratory conditions and tests done on the blood of individuals at different ages, there were inconclusive findings. due to the influence of different conditions such as the severity of iron deficiency anemia, different geographical conditions and nutritional status, differences in the number, age and gender of the subjects studied in each research, the host's immune responses and the presence of factors affecting the immune system. Conducting more extensive studies with larger sample sizes could help obtaining more reliable findings.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Author's contributions

Conceptualization and Supervisions: Dr. Hamid Chegni; Data collections: Maryam Shaker Taheri;

Conflict of interest

The Authors declare that there is no conflict of interest.

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