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IRON SUPPLEMENTATION IN BACTERIAL INFECTIONS: A SYSTEMATIC REVIEW

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Abstract: Iron is an essential mineral for several metabolic and physiological functions of the human body, playing a fundamental role in immunological function, such as cytokine production, cell proliferation and phagocytosis of pathogens. The characteristic paradox of iron supplementation during infections, which can often pose a risk of worsening the disease, has been widely discussed in order to clarify the effects of this practice and its relationship with anemia and infection. Therefore, through literature research, the objective of this work is to investigate the role of iron and its competition in pathogen-host interactions, highlighting its importance in human physiology and the microbial world. As a methodology, a bibliographic review was carried out in the PubMed and Scielo database, including scientific articles in Portuguese and English, based on the descriptors: iron, microbial resistance, siderophores and anemia. From this, it was identified that iron administration in patients with bacterial infections is questioned since this mineral can be sequestered by bacteria and supplementation becomes a risk factor and aggravation of infectious conditions. Therefore, it has been observed that iron supplementation worsens the infection, however, it is necessary to examine each situation individually, as the etiology of the bacteria, the patient's general condition and test results must be taken into account. laboratories.
Keywords: Iron; Microbial Resistance; Siderophores; Anemia.

INTRODUCTION

Iron is a fundamental mineral for a variety of metabolic and physiological functions in the human body, including tissue oxygenation, DNA synthesis, energy metabolism and immune function. Immune system cells require iron for important functions, such as cytokine production, cell proliferation and phagocytosis of pathogens. Iron uptake by immune cells occurs through specific transport proteins, such as transferrin, and storage occurs mainly in the form of ferritin.

Iron deficiency can lead to anemia, a condition in which the body does not produce enough hemoglobin and there are insufficient numbers of healthy red blood cells in the blood. Iron deficiency anemia can be caused by a low-iron diet, excessive blood loss, the body's inability to absorb iron properly, and other underlying conditions. Symptoms of iron deficiency anemia include fatigue, weakness, shortness of breath, dizziness, heart palpitations, pale skin, brittle nails, headaches and irritability. In severe cases, damage to vital organs such as the heart and brain can occur. Treatment of iron deficiency anemia includes iron supplementation in the form of tablets, injections, or intravenous supplements, or increasing your intake of iron-rich foods.

In microbiology, bacteria need to absorb important nutrients, such as iron, to survive in the human body. However, organic iron is generally transported in the blood in combination with transferrin and is therefore not readily available to microorganisms. To overcome this limitation, some bacteria produce siderophores, low molecular weight molecules with high affinity for iron, allowing them to capture extracellular iron. This allows bacteria to absorb available iron more efficiently than their competitors, giving them a competitive advantage in iron-depleted environments.

Administering iron supplements to patients with bacterial infections is often done incorrectly, giving rise to similar debates in the medical field. This practice aims to correct iron deficiency and treat anemia, but an important element is often forgotten. This is the potential risk that additional iron poses in an infected environment. The paradox of iron

supplementation in infectious diseases lies in the ability of bacteria to use excess iron for their own growth, which can exacerbate the infectious state.

Iron plays an important role in host-pathogen interactions, it is essential for the growth and reproduction of pathogens, but it is also necessary for the proper functioning of the host's immune system. Therefore, iron acquisition is one of the main battles occurring at the host-pathogen interface.

MATERIAL AND METHODS

Bibliographical surveys will be carried out, based on scientific articles taken from digital platforms, namely Scielo and Pubmed. From this bibliographic review, ideas, results and conclusions will be presented in order to conceptualize the objectives of this project.

To search for data and information, combinations with the following keywords will be used: anemia, siderophores, iron supplementation and bacterial infection.

RESULTS AND DISCUSSION

IMPORTANCE OF IRON FOR HUMANS

Iron plays an important role in heme synthesis and hemoglobin formation during erythroblast development. Approximately 90% of the iron required enters the mitochondria through a "kiss-and-run" mechanism, keeping Fe2+ concentrations in the cytoplasm low and preventing the formation of reactive oxygen species. In mitochondria, the protein mitoferlin 1 and its partner ABCB10 promote the uptake of iron, which is essential for the biosynthesis of the heme cluster and Fe-S. These clusters regulate cellular iron homeostasis, suppressing iron absorption and promoting iron storage, as well as regulating the activity of several enzymes, including those involved in the respiratory chain and the Krebs cycle, also playing an important role in sexuality. The regulation of heme synthesis by iron is specific to erythroid cells, and mutations in iron-related genes can cause various forms of anemia. Furthermore, after synthesis, heme is transported to the cytosol and pairs with alpha and beta chains to form hemoglobin, a key process in erythropoiesis. (SILVESTRI, 2021)

Iron is an important element in regulating the immune system because it affects macrophage polarization, NK cell activation, and control of B cell function. Macrophages, important components of the immune system, exhibit different polarities depending on the environment. Iron plays an important role in regulating these polarizations, influencing the ability of macrophages to respond to infection and inflammation. Furthermore, iron availability influences NK cell activation and serves as a shaper of natural killer cell function. Finally, low serum iron levels weaken antibody responses, which has important implications for vaccination and human immunity. (POWERS, 2019)

The mineral plays an important role in cellular respiration through the mitochondrial electron transport chain. In this process, electrons pass through a series of transporters. Most transporters are essential proteins with prosthetic groups that can accept and release electrons. There are three types of electron transfer in oxidative phosphorylation: direct electron transfer, transfer in the form of hydrogen atoms, and transfer as hydride ions. Cytochromes are proteins that contain heme groups containing iron atoms, and there are several types of cytochromes (a, b and c) in mitochondria. These proteins absorb visible light through heme and are incorporated into the inner mitochondrial membrane, where they play a special role in transporting electrons in the electron transport chain. Furthermore, iron-sulfur proteins contain

iron-sulfur complexes and are also involved in electron transport in the electron transport chain. Their complexity varies, but they all involve the oxidation and reduction of iron atoms within Fe-S clusters. These proteins play a fundamental role in mitochondrial electron transport and have different reduction potentials depending on the iron environment within the protein. (NELSON, 2019)

IRON METABOLISM

Iron is ingested through food and is absorbed mainly in the small intestine in organic or reduced form as iron salts. After absorption, iron is transported to the blood by the protein transferrin and stored in the liver and spleen in the form of ferritin and hemosiderin. The regulation of iron metabolism is complex and involves interactions between several regulatory proteins, such as hepcidin, ferroportin and transferrin. Hepcidin is a hormone produced by the liver that regulates the absorption of iron in the small intestine and the release of iron stores in the body. Ferroportin is an iron transport protein within cell membranes that releases iron into plasma. Transferrin is a plasma protein that transports iron from plasma to body tissues, such as red blood cells, which use iron to produce hemoglobin. (GROTTO, 2010)

IMPORTANCE OF IRON IN BACTERIAL PHYSIOLOGY AND METABOLISM

Iron plays important roles in diverse cellular reactions and biological processes, including the tricarboxylic acid cycle, the electron transport chain, oxidative phosphorylation, nitrogen fixation, and the biosynthesis of aromatic compounds. It is also essential for the formation of metabolites such as porphyrins, toxins, antibiotics and pigments. Important enzymes such as peroxidase, catalase and superoxide dismutase, which help protect cells from oxidative damage, contain iron as a cofactor. (KHASEII, 2021)

Iron availability affects DNA and RNA synthesis and bacterial growth. The virulence of some pathogenic bacteria is influenced by iron levels, and the expression of virulence factors can be regulated based on the concentration of available iron. Bacterial biofilm formation is also influenced by iron, which is necessary to stabilize the polysaccharide matrix and control surface activity. Under iron deficiency conditions, the hydrophobicity of microbial surfaces decreases, affecting biofilm formation.(KHASEII, 2021)

IRON UPTAKE MECHANISMS

The free iron content in the human body is very low and this is mainly due to the binding of iron through storage, transport and metabolic proteins. This creates competition between pathogens that require iron for growth and the host's iron regulatory system. To win this competition, Gram-negative and Gram-positive bacteria and some fungi secrete molecules called siderophores that have a high affinity for iron. Siderophores were first discovered in the 1950s and more than 500 different species have been identified since then. (HOLDEN, 2015)

These are low molecular weight compounds (400-2000 g/mol) and are excreted during iron deficiency. These chelating agents generally contain hydroxamic acids, catechols and/or α-hydroxycarboxylic acids as linking groups, which form stable five-membered chelate complexes with Fe(III). Although their primary affinity is for iron, some siderophores can also form stable complexes with other metal ions such as copper(II), aluminum(III), and other elements. These compounds play a fundamental role in the absorption of iron by various microorganisms and in the competition for this resource in the

environment. (BENITE, 2002)

IRON SUPPLEMENTATION AND INFECTIONS

EXPERIMENTAL MODELS

A study of mice infected with Salmonella Typhimurium reveals that iron supplementation led to higher bacterial loads in the spleen and liver, especially in the group of anemic mice supplemented with iron (AnmFe). There was a significant correlation between plasma iron levels and bacterial load in the spleen, indicating that low and high plasma iron levels were associated with an increase in bacterial load. Furthermore, iron supplementation had an impact on the survival of the mice, with the AnmFe group showing the worst outcome. The results suggest that plasma iron affects bacterial load and survival during Salmonella Typhimurium infection, highlighting the importance of iron in the host response to infection. (HOFFMANN, 2021)

Another study involving mice and Salmonella concluded that the iron-deficient group showed greater resistance to infection compared to mice that received iron supplementation or a normal diet. The results indicate that iron deficiency may have a protective effect against Salmonella infection in mice (PUSCHMANN, 1997)

Furthermore, the use of iron chelators, a substance with high affinity for iron, reduces systemic free iron and makes it difficult for microorganisms to capture iron. A study demonstrated the effectiveness of iron chelators in mice infected with the Acinetobacter baumannii strain. The use of iron chelators has been found to improve treatment effectiveness and reduce bacterial load in the lung, spleen and blood. (PARQUET, 2019)

CASE STUDY

Iron-deficient Somali nomads, an ethnic group living mainly in the Somali region, were analyzed, with 67 participants receiving a placebo and 71 receiving iron supplements. Higher rate ofinfections foiobserved in the iron-treated group, including activation of pre-existing malaria, brucellosis and tuberculosis. This suggests that iron deficiency may improve host defense against these infections. (MURRAY, 1978)

A study that investigated the relationship between increased iron stores and the risk of infections. Iron supplementation has been associated with an increased risk of infections, but these associations may be influenced by other factors. To circumvent these views, researchers used Mendelian randomization and genetic variants associated with iron biomarkers in studies with participants of European descent. The results showed that increasing iron was associated with elevated changes in the odds of bacterial infectious outcomes and modest odds for other infections. (BUTLER-LAPORT, 2023).

On the other hand, iron supplementation may have a positive effect on certain infections. For example, in a study of patients with chronic mucocutaneous candidiasis, oral and parenteral iron therapy showed improvement in 9 of 11 patients with iron deficiency, leading to regression of oral lesions and delayed Candida hypersensitivity. Similarly, another report reported that iron supplementation in patients with nonanemic iron deficiency resolved recurrent staphylococcal furunculosis after 3 to 4 weeks of treatment. Although these results suggest a benefit of iron supplementation in certain infections, it is important to note that these studies did not include a control group. Therefore, further investigations in controlled trials are needed to confirm these effects and better understand the underlying

mechanisms. (OPPENHEIMER, 2001)

CONCLUSION

The researched data shows controversial results, sometimes favoring the patient's recovery, sometimes determining the progression of the infection. Therefore, each case must be evaluated particularly, with careful monitoring so that any sign of activation of an infectious disease means that supplementation must be interrupted. Therefore, iron supplementation in patients diagnosed with infection must be considered potentially dangerous and, in principle, discouraged, unless there is scientific evidence that supports the decision and guarantees the safety of supplementation in a given clinical case.

REFERENCES

SILVESTRI L, Nai A. Iron and erythropoiesis: A mutual alliance. **Semin Hematol**. 2021 Jul;58(3):145-152. doi: 10.1053/j.seminhematol.2021.05.002. Epub 2021 Jun 15. PMID: 34389106.

GROTTO, Helena Zerlotti Wolf. Fisiologia e metabolismo do ferro. **Revista Brasileira de Hematologia e Hemoterapia**, v. 32, n. Suppl. 2, p. 08-17, 2010. DOI: 10.1590/S1516-84842010005000050.

POWERS, J. M.; BUCHANAN, G. R. Disorders of Iron Metabolism: New Diagnostic and Treatment Approaches to Iron Deficiency. **Hematol Oncol Clin North Am**, v. 33, n. 3, p. 393-408, jun. 2019. DOI: 10.1016/j.hoc.2019.01.006.

DELOUGHERY, Thomas G. Iron Deficiency Anemia. **Medical Clinics of North America**, v. 101, n. 2, p. 319-332, 2017. ISSN 0025-7125. DOI: 10.1016/j.mcna.2016.09.004

NAIGAMWALLA DZ, Webb JA, Giger U. Anemia ferropriva. **La revue veterinaire canadienne**. 2012 Março; 53(3):250-6. PMID: 22942439; PMCID: PMC3280776.

KHASEII , B., Mahmoodi, P., & Mohammadzadeh, A. (2021). Siderophores: Importance in bacterial pathogenesis and applications in medicine and industry. **Microbiological Research**, 250, 126790. https://doi.org/10.1016/j.micres.2021.126790.

HOLDEN, Victoria I, and Michael A Bachman. "Diverging roles of bacterial siderophores during infection." **Metallomics: integrated biometal science**, vol. 7,6 (2015): 986-95. doi:10.1039/c4mt00333k

BENITE, A. M. C., Machado, S. de P., & Machado, B. da C. (2002). Sideróforos: uma resposta dos microorganismos. **Química Nova**, 25(6b), 1155–1164. https://doi.org/10.1590/S0100-40422002000700016

HOFFMANN, Alexander et al. Baseline iron status and presence of anaemia determine the course of systemic Salmonella infection following oral iron supplementation in mice. **EBioMedicine**, v. 70, p. 103568, 2021. DOI: 10.1016/j.ebiom.2021.103568

NAIRZ, M.; Weiss, G. Infections Associated with Iron Administration. **Met Ions Life Science** 2019 Jan 14; v. 19.. DOI: 10.1515/9783110527872-011.

PUSCHMANN, M.; GANZONI, A. M. Increased Resistance of Iron-Deficient Mice to Salmonella Infection. Infection and Immunity, v. 17, n. 3, p. 663-664, set. 1977. **Copyright 1977 American Society for Microbiology**. Printed in U.S.A. 5 April 1977.

PARQUET, M. C., Selvage, D., Alan, O. D. S., Chen, T. M., Logan, E. M., Holbein, S. M., & Holbein, S. M. (2019). Iron Withholding by the Human Host as a Mechanism of Resistance Against Acinetobacter baumannii Infection. **Frontiers in Cellular and Infection Microbiology**, 9, 401. doi:10.3389/fcimb.2019.00401

MURRAY, M. J., Murray, A. B., Murray, M. B., & Murray, C. J. (1978). The adverse effect of iron repletion on the course of certain infections. **British Medical Journal**, 2(6145), 1113–1115. https://doi.org/10.1136/bmj.2.6145.1113

BUTLER-LAPORTE, G, Farjoun Y, Chen Y, Hultström M, Liang KYH, Nakanishi T, Su CY, Yoshiji S, Forgetta V, Richards JB. Increasing serum iron levels and their role in the risk of infectious diseases: a Mendelian randomization approach. **Int J Epidemiol**. 2023 Aug 2;52(4):1163-1174. doi: 10.1093/ije/dyad010. PMID: 36773317; PMCID: PMC10396421.

OPPENHEIMER, SJ. Iron and its relation to immunity and infectious disease. **J Nutrition** 2001 Feb;131(2S-2):616S-633S; discussion 633S-635S. doi: 10.1093/jn/131.2.616S. PMID: 11160594.