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OVERVIEW OF ANEMIA OF CHRONIC DISEASE

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Abstract:
Anemia of Chronic Disease (ACD), an anemia of inflammation, is a variant of anemia that frequently manifests in persistent inflammatory conditions or specific chronic ailments. This particular manifestation of anemia is distinguished by a reduction in the generation of erythrocytes, otherwise known as red blood cells, and modifications in the process of iron metabolism, leading to hemoglobin and hematocrit levels below the typical range.

Introduction:
Anemia of chronic disease (ACD) is a form of anemia that manifests in individuals who suffer from a variety of chronic ailments, including but not limited to infectious diseases, autoimmune disorders, kidney diseases, neoplasia, inflammatory bowel disease, obesity, diabetes mellitus, congestive heart failure, and chronic lung disease[1,2]. This type of anemia is characterized by the disturbance of iron balance within the body, the inhibition of erythropoiesis by pro-inflammatory cytokines, and alterations in the erythrocyte membrane that decrease their lifespan. ACD commonly presents as microcytic or normocytic anemia with diminished levels of reticulocytes. The serum iron and transferrin levels are usually reduced or within the normal range, while serum ferritin levels correspond to either the reference values or are elevated. The pathophysiology of anemia of chronic diseases (ACD) is characterized by the activation of the immune system, which subsequently leads to the release of pro-inflammatory cytokines that instigate a cascade of events resulting in various manifestations. One of the key consequences of this immune activation is the upregulation of hepcidin production, a peptide hormone that plays a crucial role in iron homeostasis. The increased levels of hepcidin, in turn, lead to a state of hypoferremia, where iron availability is reduced, impairing the erythropoietic process. Moreover, the immune-mediated response also directly affects erythropoiesis

by suppressing the production of erythropoietin (EPO), the primary hormone responsible for red blood cell formation. Consequently, the life span of red blood cells is shortened, exacerbating the anemia. The mechanisms involved in the development of ACD are multifaceted and intricate, encompassing not only a decrease in endogenous EPO production but also the occurrence of absolute and/or functional iron deficiency and the presence of inflammation-induced elevation of hepcidin levels. ACD, the second most prevalent form of anemia following iron deficiency anemia, significantly diminishes the quality of life experienced by individuals affected by chronic diseases. It is frequently associated with abnormal iron metabolism, and the involvement of hepcidin, a pivotal regulator of iron metabolism, assumes a crucial role in the pathogenesis of this condition. The treatment objective is to manage the underlying disease and correct the anemia, with potential future therapeutic interventions targeting hepcidin for optimal outcomes.

The pathophysiology of ACD is complex, yet it can be summarized as three primary causes based on the elevation of pro-inflammatory cytokines. The increase in hepcidin plays a crucial role in this process. Moreover, an inappropriate level of erythropoietin or a decreased response to erythropoietin, along with reduced erythropoiesis

in the bone marrow and diminished survival of red blood cells, all contribute to the anemia observed in chronic disease [3].

Iron Metabolism

Iron metabolism plays a vital and essential role in developing and manifesting anemia of chronic disease (ACD), the second most prevalent form of anemia following iron deficiency anemia (IDA)[4]. This particular type of anemia is intricately linked to various chronic inflammatory diseases, further underscoring its significance in human health. Iron is found in multiple proteins, such as cytochromes, which play a crucial role in respiration, as well as myoglobin and other iron-containing proteins. The body tightly regulates the amount of iron present, as excessive iron can be harmful due to its ability to generate free radicals and its tendency to accumulate in multiple organs, including the liver, heart, and endocrine organs [5]. To meet its iron requirements, the body needs more than 20 mg of iron per day, but only a small portion, around 1 - 2 mg, is absorbed from the intestines. Most iron is obtained through recycling, where old red blood cells are broken down by liver, spleen, and bone marrow macrophages within the reticuloendothelial system[6]. The main sites for iron storage are hepatocytes and macrophages. Iron absorption in the gastrointestinal tract is facilitated by duodenal enterocytes, which release iron into the extracellular fluid. However, since iron cannot be excreted from the body, the entire process of intestinal iron absorption and the release of iron from macrophages and hepatocytes is tightly controlled by a peptide hormone called hepcidin. Hepcidin ensures that iron metabolism remains in balance. In cases of abnormal iron metabolism, such as in ACD, hepcidin levels are elevated. Due to decreased clearance or increased production, this increase in hepcidin levels leads to a higher iron release from iron storage cells, including enterocytes, macrophages, and hepatocytes, into the plasma. As a result, hypoferremia occurs, leading to functional iron deficiency [7].

The discovery of the peptide hormone hepcidin and the iron exporter ferroportin revolutionized the understanding of anemia of inflammation. This momentous discovery has significantly altered our comprehension of this condition. During the process of erythroid progenitor development, as they progress to the poly-chromatophilic stage, there is a noticeable increase in the presence of transferrin receptor 1. This receptor is crucial in obtaining the necessary iron to synthesize hemoglobin. Moving forward, macrophages play a pivotal role in this intricate process. They ingest aged erythrocytes, break down hemoglobin, and accumulate the freed iron in ferritin. This accumulation of iron in ferritin enables its eventual release to mature erythrocytes. The essentiality of ferroportin in this process cannot be overstated, as it is responsible for the export of iron from macrophages to mature erythrocytes. However, when ferroportin deficiency occurs, the iron becomes trapped within the macrophages, impairing delivery to the maturing erythrocytes [8].

Iron Sequestration due to inflammation:

In response to an excessive accumulation of iron caused by inflammation, human hepatocytes release hepcidin, an essential peptide hormone responsible for regulating iron levels in the body [9]. This particular hormone, hepcidin, comprises a chain of 25 amino acids and possesses antimicrobial properties. The overall process of hepcidin production is intricately controlled by various factors, including iron stores within the body, pro-inflammatory cytokines, and the response axis associated with anemia. Notably, hepcidin exerts its regulatory influence by binding to ferroportin, a protein involved in iron transport, leading to the internalization and subsequent degradation of both hepcidin and ferroportin. Given its crucial role in maintaining iron homeostasis, any disruptions or impairments in the function of hepcidin can result in hereditary iron overload syndromes. Mutations affecting the expression of hepcidin-regulating genes such as HFE, Hemojuvelin, Transferrin receptor 2, or the hepcidin gene itself have all been linked to these iron overload disorders. The maintenance of appropriate levels of hepcidin relies on a complex interplay of regulatory factors, including bone morphogenic proteins (BMPs), the BMP co-receptor hemojuvelin, inflammatory cytokines, and specific proteases like furin and matriptase-2.

Inflammatory cytokines regulate Hepcidin expression, such as interleukin-6 (IL-6) and interleukin-1β (IL-1β). These cytokines induce the production of Hepcidin through various signaling pathways. For instance, IL-6 enhances the JAK/Stat signaling pathway, resulting in the phosphorylation of Stat3 and subsequent binding of Stat3 to the Hepcidin promoter. This interaction amplifies the expression of Hepcidin. Similarly, IL-1β stimulates Hepcidin expression by activating the C/EBPα and BMP/SMAD signaling pathways. These transcription factors facilitate the effects of inflammation, further promoting the expression of Hepcidin. The expression of Hepcidin is also influenced by hepatocyte injury, which can be caused by endoplasmic reticulum stress or oxidative damage[6]. In these conditions, the activity of C/EBPα or Stat3 is enhanced, leading to an upregulation of Hepcidin expression. Additionally, lipopolysaccharide (LPS) secreted during severe bacterial infections triggers toll-like receptor 4 (TLR4) signaling. This activation stimulates the production of IL-6 by macrophages. Consequently, IL-6 acts on hepatocytes, promoting the synthesis of Hepcidin. As a result of these processes, iron cannot be released into the plasma and instead remains trapped within macrophages and hepatocytes. This leads to an accumulation of iron stores, which is reflected in elevated serum ferritin levels. Furthermore, Hepcidin exerts an inhibitory effect on iron absorption in the intestines. Doing so regulates the overall iron balance in the body. This intricate network of cytokines, transcription factors, and signaling pathways tightly regulates the expression of Hepcidin and maintains iron homeostasis. Understanding the mechanisms underlying the regulation of Hepcidin expression is crucial for unraveling the pathophysiology of iron-related disorders and developing targeted therapeutic interventions. Therefore, further research is warranted to elucidate the intricate interplay between inflammatory cytokines, transcription factors, and Hepcidin expression in health and disease [6].

Hepcidin is not the sole protein that is responsible for the production of iron sequestration during bacterial infection. Recent studies have specifically indicated that the stimulation of Toll-like receptor 2 (TLR2) and Toll-like receptor 6 (TLR6) leads to a decrease in the expression of ferroportin in macrophages [10]. This decrease in ferroportin expression subsequently results in hypoferremia without causing an increase in macrophage hepcidin expression. Furthermore, lipopolysaccharide (LPS) has been found to stimulate macrophages to produce lipocalin 2, a protein that binds to bacterially formed siderophores and sequesters iron. Moreover, in the presence of infection or inflammation, neutrophils release lactoferrin, an iron-binding protein that bacteria can internalize. Once internalized, lactoferrin can separate iron from pathogens and inhibit microbial growth. Therefore, it is evident that multiple proteins are involved in the process of iron sequestration during bacterial infection, each with its unique mechanisms of action.

Obese individuals exhibit an elevation in the plasma concentration of various metabolic regulatory hormones, such as leptin and hepcidin, as well as pro-inflammatory cytokines and the iron-sequestering protein known as lipocalin-2 [8]. The presence of these substances in excessive amounts in the bloodstream is believed to contribute to functional iron deficiency and anemia through two

proposed mechanisms. Firstly, it is hypothesized that leptin and pro-inflammatory cytokines stimulate hepcidin production in hepatocytes and adipocytes, further exacerbating the iron imbalance. Secondly, in individuals with obesity, adipocytes, and peripheral blood mononuclear cells have been found to produce lipocalin-2, a protein that restricts iron availability to emerging erythroid cells, thus aggravating the anemic state. In addition to their impact on iron metabolism, pro-inflammatory cytokines can diminish erythropoietin production, a red blood cell formation hormone. Furthermore, these cytokines can damage the differentiation process of erythroid progenitors and curtail the lifespan of mature red blood cells, further contributing to the development of anemia.

Diagnosis:

ACD is characterized as a mild to moderate form of anemia falling within the classification of normocytic normochromic. However, it is important to note that less than 25% of cases present microcytic hypochromic anemia, wherein the average corpuscular volume is rarely less than 70 [3]. This distinction sets ACD apart from iron deficiency anemia, characterized by a microcytic, hypochromic type with anisocytosis and poikilocytosis observed on the peripheral blood film. In individuals with ACD, serum iron, transferrin saturation, and total iron binding capacity are all found to be low, whereas there is an increase in serum ferritin and bone marrow iron storage. Conversely, in cases of iron deficiency anemia, the serum iron, transferrin saturation, and ferritin levels are low, but there is an elevation in total iron binding capacity. It can often be challenging to differentiate between ACD and iron deficiency anemia based on available laboratory tests, and even more complex are situations in which both conditions co-occur [11].

One method that can distinguish between the two types is the measurement of soluble transferrin receptors. In cases of iron deficiency, soluble transferrin receptor levels are elevated due to reduced iron availability, while in ACD, the soluble transferrin receptor levels remain within the normal range. The decreased levels of transferrin in ACD result from the downregulation of transferrin synthesis caused by an increase in ferritin. Given the critical role of hepcidin in regulating iron metabolism, determining serum hepcidin levels could be beneficial in distinguishing between ACD and iron deficiency anemia. However, one obstacle remains the need for a readily available standardized hepcidin assay. Hepcidin levels are found to be decreased in cases of iron deficiency, and the measurement of blood or urine hepcidin levels may provide indications of true iron deficiency. Researchers have made advancements in mass spectrometry and enzyme-linked immunoassays to quantify hepcidin in blood, plasma, and urine [5]. A study comparing different assays for hepcidin found that although there were significant differences in the absolute values obtained from each assay, the results for the samples correlated well, and the analytical variation was minimal. Furthermore, certain challenges are associated with interpreting hepcidin levels, including diurnal variations where hepcidin levels are lower in the morning and higher in the afternoon. Additionally, hepcidin levels can be influenced by the iron content of the diet, making it a relative measure of iron status. Therefore, ACD can be defined by low serum iron levels, total iron binding capacity, transferrin, and normal transferrin saturation. Furthermore, individuals with ACD exhibit higher ferritin levels than those with iron deficiency anemia[11].

There are a variety of additional factors that are not necessary for diagnosing ACD but may significantly contribute to estimating the iron needs for erythropoiesis and potentially be important for predicting the response to treatment of ACD with recombinant erythropoietin. When iron availability to erythroid progenitors is reduced, these cells produce zinc protoporphyrin IX instead of the usual protoporphyrin ring with iron. High levels of zinc protoporphyrin in ACD patients with inflammatory disorders indicate an increased demand for iron for erythropoiesis. Similarly, determining the percentage of hypochromic red blood cells or reticulocytes can provide insight, although data on these measures in ACD are limited. Lastly, assessing serum erythropoietin levels does not contribute to diagnosing ACD but may offer guidance in selecting the appropriate treatment. Since ACD is associated with inflammatory diseases, elevated cytokine levels are observed in these patients' serum, and these cytokine concentrations are inversely correlated with the severity of anemia [12].

Treatment:

The management of ACD involves the utilization of various approaches [13,14]. Currently, the treatment of ACD commonly consists of the application of erythropoiesis-stimulating agents (ESAs) and replenishing iron. Furthermore, the effective treatment of ACD in individuals with elevated levels of hepcidin can be achieved by inhibiting the BMP signaling pathway and the inflammatory response. To promote heme synthesis, the principal constituent of hemoglobin, treatment strategies should also prioritize the availability of precursor molecules such as glycine and succinyl-coenzyme A (CoA). New drug groups and substances are currently being developed to target different aspects of ACD. These include substances that impede hepcidin transcription, direct hepcidin inhibitors, and medications that enhance erythropoiesis by upregulating erythropoietin and inhibiting proinflammatory cytokines. Additionally, orally administered hypoxia-inducible factor (HIF) inhibitors have exhibited promise as a safer alternative to ESAs for the treatment of ACD.

Red blood cell transfusions are necessary when the hemoglobin level drops below 8 g/dL, primarily for individuals with known coronary artery disease. However, the repeated administration of blood transfusions can lead to excess iron, a risk of infection transmission, and allo-immunization [15].

Hepcidin antagonists, such as monoclonal antibodies, hepcidin binding proteins, small interfering RNA (siRNA), antisense oligonucleotides, and aptamers, are currently being developed[16]. Trials are being conducted on anti-hepcidin monoclonal antibodies, which inhibit hepcidin binding to ferroportin. RNA interference (RNAi) and antisense oligonucleotides can be effective therapeutic agents by interfering with hepcidin production and its regulators. However, challenges in delivering RNAi need to be addressed. Hepcidin-binding proteins, spiegelmers, and anticalins are also being investigated, with spiegelmers showing promise in a phase IIa clinical trial for managing ACD.

References:

1. Valitova AD, Kadyrova ZM, Oslopov VN, Oslopova YV, Khazova EV: Anemia of chronic diseases: a verdict or a protective reaction of the body? Kazan Medical Journal. 2023, 104:393-401.
2. de las Cuevas Allende R, Díaz de Entresotos L, Conde Díez S: Anaemia of chronic diseases: Pathophysiology, diagnosis and treatment. Medicina Clínica (English Edition). 2021, 156:235-242. https://doi.org/10.1016/j.medcle.2020.07.022
3. Weiss G: Pathogenesis and treatment of anemia of chronic disease. Blood reviews. 2002, 16:87-96.
4. Mi H-C, Cui F, YT D, Wang R-T, Zhang R, Shi M: Research progress on the regulation mechanisms of iron metabolism in anemia of chronic disease. Sheng li xue bao:[Acta Physiologica Sinica]. 2022, 74:639-647.
5. Fraenkel PG: Understanding anemia of chronic disease. Hematology 2014, the American Society of Hematology Education Program Book. 2015, 2015:14-18.
6. Thomas C, Thomas L: Anemia of chronic disease: pathophysiology and laboratory diagnosis. Laboratory hematology: official publication of the International Society for Laboratory Hematology. 2005, 11:14-23.
7. Cavill I, Auerbach M, Bailie GR, et al.: Iron and the anemia of chronic disease: a review and strategic recommendations. Current medical research and opinion. 2006, 22:731-737.
8. Ganz T, Nemeth E: Iron sequestration and anemia of inflammation. In Seminars in hematology. Volume 46. Elsevier; 2009:387-393.
9. Ganz T: Molecular pathogenesis of anemia of chronic disease. Pediatric Blood & Cancer. 2006, 46:554-557. https://doi.org/10.1002/pbc.20656
10. Weiss G: Iron metabolism in the anemia of chronic disease. Biochimica et Biophysica Acta (BBA)-General Subjects. 2009, 1790:682-693.
11. Cullis JO. Diagnosis and management of anemia in chronic disease: current status. British Journal of Haematology, 2011, 154:289-300.
12. Zarychanski R, Houston DS: Anemia of chronic disease: a harmful disorder or an adaptive, beneficial response? Cmaj. 2008, 179:333-337.

13. Quisel J, Beconi M, Robinette S, Macdonald B: Methods for treating anemia of chronic disease. Google Patents; 2022.
14. Michalak SS: Perspectives for the therapy of anemia of chronic diseases. Acta Haematologica Polonica. 2020, 51:125-132.
15. Weiss G: Anemia of chronic disorders: new diagnostic tools and treatment strategies. In Seminars in hematology. Volume 52. Elsevier; 2015:313-320.
16. Patel TV, Singh AK: Anemia in chronic kidney disease: new advances. Heart failure clinics. 2010, 6:347-357.