Anemia of chronic disease: A comprehensive review

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Abstract
Iron has varied importance in the biological activity of cells. Supraphysiologic levels of iron are deleterious for cellular survival. Besides, iron also plays a significant role in the immunologic surveillance. Anemia of chronic disease (ACD) is the anemia that is caused not due to marrow deficiency of iron, but due to an underlying chronic inflammatory disease. ACD is caused due to factors, which impede the availability of iron stores in the body. Identification of the condition requires meticulous hematologic work up. Therapy for ACD involves manipulating the inflammatory process and the resultant inflammatory cytokines, which are a major source for inhibition of iron availability.

Keywords
Anemia of chronic disease, chronic inflammation, hepcidin

Introduction
Anemia of chronic disease (ACD) is defined as anemia present in chronic infectious and inflammatory conditions or neoplastic disorders, which is not due to marrow deficiencies and occurs even though the presence of iron stores and vitamins is adequate. It is the most common form of anemia observed next to iron deficiency anemia.¹ The common conditions associated with ACDs are acute and chronic infections, cancer, autoimmune disorders, chronic kidney diseases (CKDs), and chronic inflammatory conditions. The estimated prevalence of ACD caused due to chronic inflammation accounts to 23-50%. The condition has thus been termed “anemia of inflammation.”² A number of different pathways have been presumed to cause ACD like aversion of iron traffic, reduced erythropoiesis, decreased response to erythropoietin, erythrophagocytosis and invasion of bone marrow by tumor cells and pathogens.

ACD is a commonly present, poorly understood condition that affects patients with a variety of diseases, including chronic infections, malignancies and rheumatological diseases.³ It is characterized by impaired erythropoietin response, diminished red blood cell (RBC) survival and an impairment in iron absorption and macrophage iron retention, which hinders iron delivery to erythroid precursor cells.

Iron Homeostasis
Iron is an essential compound for all living beings. It is a co factor for enzymes in mitochondrial respiration chain, citric acid cycle and is a binding moiety for oxygen transport by hemoglobin (Hb) and myoglobin.⁴ However on the other hand, cellular accumulation of iron in supraphysiologic limits may be detrimental to survival of cells since iron is also able to catalyze the formation of highly toxic hydroxyl radicals by Haber Weiss reaction.⁵ Hence, a stable regulation of iron homeostasis is essential for maintaining cellular functions. Maintenance of iron homeostasis is exerted at post transcriptional level by cytoplasmic proteins i.e. iron regulatory proteins (IRP) with iron responsive elements (IRES). Iron deficiency in cells stimulates binding affinity of IRP to IRES thus resulting in blockage of ferritin.⁶

On the contrary, when cells harbor sufficient amounts of metabolically active iron, the target binding affinity of IRP to IRES is reduced.

Iron and Immunity
IRP binding affinity to IRES is not only controlled by the need of iron, but also by labile radicals produced by activated immune cells.⁷ An adequate supply of iron is of prime importance for...
immune surveillance because of its growth-promoting function of immune cells and its intrusion with cell-mediated effector pathways and cytokine activities.\[6] Besides, iron deficiency and iron overload can exert certain effects on immune status by varying the proliferation and activation of NK cells, T-cells and B-cells. Cellular iron availability controls the differentiation and proliferation of T helper cells, monocytes and macrophages.\[9,10]

Pathophysiology of ACD

ACD is a clinical entity, which is commonly observed in patients with various underlying diseases that includes anemia of chronic infection, anemia of cancer, anemia associated with rheumatoid arthritis, and anemia in chronic CKDs.\[11] The etiology of ACD are many and is categorized by an activation of immune cell and response of inflammatory cytokine that blunts erythropoietin production, decreases erythropoiesis, impaired red cell life span, and dysregulated iron homeostasis.\[12]

Inflammatory cytokines induce changes in the pattern of iron distribution. Patients with ACD have low serum iron concentration, low or normal total iron binding capacity, and low transferrin saturation and low reticulocyte counts.\[13] The primary feature of ACD is an accumulation of iron in the reticuloendothelial macrophages despite decreased circulating iron levels.\[5] Thus, a reduced circulating iron is available for Hb synthesis in spite of the presence of adequate or high body iron stores.\[14] It was hypothesized that humans evolved this mechanism to sequester iron as an act of defense against certain invading pathogens, many of which require iron for growth and survival.\[15] Recent research has indicated possible role of hepcidin in functional iron deficiency present in ACD.\[16]

Overexpression of hepcidin in mice causes classic features of ACD like hypoferrremia and iron retention in macrophages.\[17]

ACD and Hepcidin

Hepcidin is produced in the liver and detectable in the serum and urine. It has intrinsic antimicrobial activity. The expression of hepcidin increases in response to inflammatory stimuli.\[18] Until recently there was no indication that hepcidin has additional role in iron metabolism until 2001, when mouse studies were published showing that hepatic hepcidin mRNA synthesis was induced by iron loading. Hepcidin is a negative regulator of intestinal iron absorption and macrophage associated iron release. Interleukin (IL) 6 acts on the hepatocytes and promotes the release of hepcidin.\[19] Hepcidin is the key regulatory protein that regulates the iron absorption in intestine and distribution of iron from various body stores including reticuloendothelial macrophage cells. Hepcidin acts by compounding and initiating the degradation of the only known iron exporter like ferroportin.\[20] Presence of ferroportin on the cell surface of hepatocytes, duodenal enterocytes and macrophages makes it an important transporter of cellular iron. Thus, a depletion of ferroprotein will stop the transfer of cellular iron into the plasma.

High serum hepcidin levels decreases the intestinal iron absorption and inhibits iron export from tissue stores into the bloodstream. This is done to protect the body against excess total body iron built up and increased distribution of iron into the circulation. In contrast, limited circulating iron levels downregulate the hepcidin synthesis, thus allowing an influx of bioavailable iron from the duodenal enterocyte cells and tissue iron stores.

Regulation of hepcidin

Inflammation due to infection, autoimmune disease and oral cancers stimulates the synthesis of many pro inflammatory cytokines, such as interferon, IL-1, and IL-6 and proinflammatory cytokines which have been shown to induce excess hepcidin production.\[21] Hepcidin has the ability to reduce the function of ferroportin on duodenal enterocytes and macrophages, which leads to impaired iron absorption from the gut and exaggerated iron retention, which is a hallmark of ACD. Thus, long-term release of hepcidin causes ACD.\[18]

The molecular mechanism by which inflammation regulates hepcidin is the Janus kinase (JAK) - signal transducer and activator of transcription (STAT) pathway. IL-6/JAK2-STAT3 pathway controls the production of hepcidin.\[19] Ligand binding to the IL-6 receptor activates JAK2. This in turn phosphorylates the transcription factor STAT3. The upregulation of hepcidin gene expression is brought about by translocation of phosphorylated STAT3 into the nucleus and binding to the canonical STAT3 binding site in the proximal hepcidin promoter.

Diagnostic parameters to detect ACD

Detection of the type of anemia is important to execute a correct treatment plan. Peripheral blood picture shows ACD as normochromic, normocytic anemia that is characteristically mild (Hb level, 9.5 g/dl) to moderate (Hb level, 8 g/dl). Patients with ACD usually have a decreased reticulocyte count, which indicates under production of RBCs.\[22,23] Evaluation of ACD includes determination of whole body iron store status in order to rule out iron-deficiency anemia, which is usually characterized by microcytic and hypochromic. It is imperative to differentiate between ACD and iron deficiency anemia keeping in view their pathogenesis and treatment approach.

Hematologic differences between iron deficiency anemia and ACD

The levels of transferrin are an indicator of serum iron stores. The depleted levels serum transferring in ACD a reflection of the same.\[24] In iron deficiency anemia, the transferrin saturation may be even reduced because of the relevant increase in serum concentrations of transferring. But on the contrary transferrin levels may remain normal or are decreased in ACD.\[25] Ferritin is an acute-phase reactant which is commonly increased in chronic inflammation, autoimmune disorders, chronic infection and chronic liver diseases. Apart from being an acute phase protein, ferritin also plays a crucial role in iron storage and recycling.\[26]
Besides its function as an iron storage protein, ferritin plays an important role in macrophages where it recycles iron from old RBCs and transfers it to apoferritin. The iron in transferrin is transported to immature RBCs in the bone marrow in order to complete the cycle.\[27\]

Ferritin plays a crucial role in host immune response. This is evident from increased concentration of ferritin during chronic infectious diseases. This happens in order to counter the binding of the infective agent that attempts to combine with iron from the host tissue. A hyper immune response compliments the migration of ferritin from the plasma to within the cells, so that iron is not available to the infective agent.

Ferritin is considered as a marker of iron storage. A level of 15 ng/ml is generally indicative of absent iron stores. A better positive predictive value of iron deficiency is reflected with ferritin level of 30 ng/ml. In patients with ACD, there is increased storage and retention of iron within the reticulo endothelial system, along with increased ferritin levels due to immune activation.

The levels of soluble transferrin receptor are increased in iron deficiency, when the availability of iron for erythropoiesis is low.\[1\] In contrast, the levels of soluble transferrin receptors in ACD are not significantly different from normal, because the inflammatory cytokines negatively affect the transferring receptor expression. The evaluation of the levels of soluble transferrin receptors is helpful to differentiate between patients with only ACD and patients with ACD accompanied by iron deficiency.\[34\]

The ratio of concentration of soluble transferrin receptors to the log of the ferritin level may also be helpful in differentiating iron deficiency anemia with ACD. A ratio of <1 suggests ACD, whereas a ratio of more than 2 suggests absolute iron deficiency coexisting with ACD.

**Treatment of ACD**

Anemia often complicates the underlying chronic diseases. It is considered a predictor of poor prognosis of the disease.\[36\] There is a marked improvement in the quality of life and energy levels in patients of ACD associated with hemodialysis, cancer, and rheumatoid arthritis after correction of anemia. An ideal treatment for ACD is to reduce the underlying chronic disease; however, this is not possible for many ACD patients.\[29\] Present therapeutic management of ACD involves increasing Hb levels by blood transfusions or iron administration. However, the treatment changes according to the underlying systemic disease. ACD with CKD involves improving the erythropoietin levels by administration of epoetin alpha.\[30\] Due to the functional iron deficiency in ACD, iron supplementation is frequently administered either alone or in combination with erythropoietin stimulating agents. Although oral iron tablets are easily available and are of low cost, but their effectiveness is diminished due to hepcidin mediated iron block in the intestine. Hence, intravenous iron therapy is more effective.\[29\] However, supraphysiologic levels of iron can be deleterious as it is believed that certain organisms require iron for their growth and survival. Hence, over supplementation of iron can be detrimental in such cases.

**Recent Advances in Treatment of ACD**

The recent advances in treatment of ACD targets the hepcidin – ferroprotein axis. Pharmacologic agents that reduce hepcidin production and increase ferroportin activity would improve iron bioavailability from the diet and would mobilize existing body iron stores for erythropoiesis, without causing the adverse risks from supraphysiologic iron supplementation.\[30\] A number of new strategies like direct hepcidin antagonists, hepcidin production inhibitor or ferroportin agonists/stabilizers are currently under investigation. Anti-hepcidin monoclonal antibodies are direct hepcidin antagonists.\[31\] Another approach to treat ACD is RNA interference and gene silencing antisense oligonucleotides that target transcription or translation of hepcidin. It is a known fact that IL6 promote the production of hepcidin. Hence, IL6 inhibitors have known to inhibit hepcidin production. Administration of anti-IL-6R antibody therapy has shown to substantially lower hepcidin levels, decrease C-reactive protein levels within 1 week and improve other hematological parameters over a treatment period of 4 weeks.

**Future Course**

There has been an active research in the field of hematology pertaining to ACDs in the past few decades. The future of research on this field should strengthen our knowledge about the transmembrane iron transporters like ferroprotein, divalent metal transporter 1, natural resistance-associated macrophage protein 1, membrane bound enzymes for redox reactions like hephaestein and new circulating IRPs like hepcidin.\[32\] Research should be directed toward elucidating how these factors induce the disturbance in iron metabolism under inflammatory conditions.

Research should also be directed at finding new hematologic and serologic markers to distinguish ACD from iron deficiency status.\[33\] Parameters that are under investigation are soluble transferrin receptor, zinc protoporphyrin IX and possibly hepcidin. Concomitant to these, research should also be targeted at therapeutic options to interfere with hematological and immunological network in ACD. Such agents are cytokine inhibitors, anti-tumor necrosis factor, hormones like testosterone, iron chelators and stem cell factors.\[34\]

**Conclusion**

ACD is quite distinct due to the fact that it is caused not due to deficiency, but due to factors impeding the availability of iron. Inflammation is one such impeding factor causing ACD. Mere removal or reduction of inflammation may not correct the anemic status. It has to be supported with appropriate therapy. Hepcidin has emerged as one such molecule which has caught...
the attention of researchers. Further evaluation of this acute phase protein along with other hematologic parameters will throw light on this common, yet intriguing disease called ACD.

References