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Anemia of Chronic Disease

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ABSTRACT

Introduction: Anemia of chronic disease has a widespread impact on patients with chronic disorders such as chronic inflammation, infection, malignancy etc. The pathophysiology behind it is largely due to involvement of hepcidin levels which are high as a result of the underlying chronic disorder, but negatively affects iron metabolism and erythropoiesis. **Aim of the work:** We tried to understand the pathogenesis, impact, diagnosis, and management of anemia due to chronic diseases. **Methodology:** We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from January 2001 to March 2017. The following search terms were used: anemia of chronic disease, anemia of inflammation, types of anemia, management of chronic anemia **Conclusion:** Since absolute treatment for the underlying chronic conditions are not available, various other modalities aimed at treating the anemia are developing. They include conventional and novel therapies. More researches must be done in order to manage the condition by treating the underlying cause, or for finding therapies with least side effects.

Keywords: anemia of chronic disease, anemia of inflammation, types of anemia, management of chronic anemia.

INTRODUCTION

The anemia of chronic disease (ACD) describes the impaired production of red blood cells associated with chronic inflammatory states, which includes cancer, autoimmune diseases, or chronic infection. Recent data show that anemia can also arise in the setting of severe, acute inflammation, which includes critical illness, or in case of milder but persistent inflammatory states that occur with aging, obesity, and kidney failure. Therefore, the name "anemia of inflammation" is more suitable compared to that of chronic disease. The National Health and Nutrition Examination Study (NHANES III) indicated that ~1 million Americans older than sixty-five years of age exhibit anemia due to inflammation. In NHANES III, anemia of inflammation was referred to low serum iron level (<10.74 μM or <60 μg/dL) without findings of low iron stores, that is, transferrin saturation >15%, along with serum ferritin >12 ng/mL, or an erythrocyte protoporphyrin concentration >1.24 μM. Other features of anemia of inflammation comprise in appropriately low levels of erythropoietin and high counts of inflammatory markers, for example C-reactive protein[1]. The anemia of inflammation is predominantly common in hospitalized patients. In CRIT study of anemia and blood transfusion for the critically ill, which was an observational cohort study of 4892 patients in intensive care units across the United States of America, average hemoglobin levels in these patients reduced over a 30-day period regardless of the administration of blood transfusions. Additionally, a base hemoglobin <9 g/dL was an autonomous predictor of increased mortality and length of hospital stay. In another recent study of 191 consecutive hospitalized senior patients with anemia, 70% of them were noted to have anemia of chronic disease. 16% of the patients suffering from anemia of chronic disease had simultaneous chronic renal failure. 71% of the patients ease was noted to have an acute infection, 12% of them had cancer, and 16% of the patients had a chronic inflammation mostly including pressure ulcer, or a chronic autoimmune inflammatory disease[2].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE, from January 2001 to March 2017. The following search

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terms were used: anemia of chronic disease, anemia of inflammation, types of anemia, management of chronic anemia.

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

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

DISCUSSION

The intersection of obesity, chronic inflammation, and metabolic derangements with anemia is an emerging area of interest. Obese patients exhibit higher plasma levels of pro-inflammatory cytokines and acute-phase reactants, as well as higher rates of iron-restricted erythropoiesis that can result in anemia. In patients with chronic inflammation, one would expect increased levels of serum ferritin, thus the concept of "functional iron deficiency" has been defined for patients with serum ferritin <100 ng/mL despite chronic inflammation. A recent cross-sectional study of 947 obese patients under evaluation for bariatric surgery revealed that 52.5% showed functional iron deficiency, demarcated as a serum ferritin of 12-100 ng/mL for women or 15-100 ng/mL for men with serum C-reactive protein >3 mg/L. 70% percent of obese patients with functional iron deficiency showed a transferrin saturation <20% .Additional suggesting an association between obesity and compromised iron metabolism, weight loss has been linked with arise in transferrin saturation in overweight persons[3].

Anemia frequently disturbs patients with neoplasia. Although while hematologic cancers are more probable to cause anemia through infiltration of the bone marrow with an abnormal cell population, solid tumors frequently cause anemia without bone marrow involvement. A recent prospective, observational analysis of 888 patients with a diversity of carcinomas showed that 63.4% of the patients were found to be anemic. The prevalence and degree of anemia rose with a more progressive stage of cancer.

Besides, advanced-stage patients had considerably increased average plasma levels of inflammation markers, including C-reactive protein ,interleukin (IL)-6, ferritin, hepcidin, fibrinogen, tumor necrosis factor α, IL-1β, , erythropoietin, and reactive oxygen species, paralleled with early-stage patients, while serum iron, glutathione peroxidase, leptin, and triglyceride levels were reduced significantly in advanced-stage patients[4].

Pathophysiology

Pathophysiology of ACD is intricate but can be précised as three main causations, based on the increase in pro-inflammatory cytokines. Rise in hepcidin plays a key role. Furthermore, inappropriate erythropoietin amount or hypo-responsiveness to erythropoietin, and decreased erythropoiesis in the bone marrow along with reduced red blood cell survival, all contribute to the anemia appreciated in chronic disease[2].

Iron Metabolism

Iron is a crucial micronutrient compulsory for heme biosynthesis, which is consequently incorporated into hemoglobin inside the red blood cells. Further, iron is available in proteins like cytochromes which are involved in respiration, in myoglobin, and in some other iron-containing proteins. The total iron amount in the body is strongly regulated because excess iron is toxic as it generates free radicals and has a propensity to deposit in numerous organs such as liver, heart, and endocrine organs[1]. The body needs more than 20 mg of iron every day, from which only 1 - 2 mg is resultant from intestinal absorption. The bulk of iron is delivered through recycling by the degradation of aged red blood cells inside macrophages of the liver, spleen, and bone marrow in the reticulo-endothelial system[5]. The chief iron storage locations are the hepatocytes and macrophages.

The duodenal enterocytes in the gastrointestinal tract are involved in iron absorption. They release iron into the extracellular fluid. However, since iron cannot be excreted from the body, the whole process of intestinal iron absorption along with release of iron from macrophages and hepatocytes is rigorously regulated by hepcidin, a peptide hormone. Chaotic iron metabolism is the hallmark of ACD as a result of amplified hepcidin levels.

This increase in hepcidin levels by either decreased clearance or by increased production leads to an increase in release of iron from iron storage cells which are enterocytes, macrophages, and hepatocytes, into the plasma causing hypoferremia, which results in functional iron deficiency[6].

Ferroportin and Iron Export

The discovery of the peptide hormone hepcidin and the iron exporter ferroportin transformed the understanding of anemia of inflammation. As erythroid progenitors develop to the poly- chromatophilic stage, they show increasing amounts of transferrin receptor 1 to obtain iron for the making of hemoglobin. Macrophages ingest the aged erythrocytes, degrade hemoglobin, and accumulate the liberated iron in ferritin for consequent release of iron to maturing erythrocytes. Ferroportin is essential for the export of iron from macrophages to maturing erythrocytes. When there is ferroportin-deficiency, iron remains seized in macrophages, causing in impaired delivery to the maturing erythrocytes[7].

Inflammation Induced Iron Sequestration

Responding to iron overload due to inflammation, human hepatocytes secrete hepcidin, the iron-regulatory peptide hormone. Hepcidin is a 25–amino acid peptide with anti-microbial characteristics. Overall, production of hepcidin is controlled by iron stores, pro-inflammatory cytokines, and the anemia response axis. Hepcidin binds to ferroportin and results in the internalization and degradation of both proteins. Hepcidin seems to be the fundamental regulator of iron homeostasis since mutations causing loss of its function in genes that regulate Hepcidin expression, for instance, HFE, Hemojuvelin, Transferrin receptor 2, or in Hepcidin itself, have all been associated with hereditary iron overload syndromes Upholding appropriate hepcidin levels rest on a complex interaction of regulatory factors, counting bone morphogenic proteins (BMPs), the BMP co-receptor hemojuvelin, inflammatory cytokines, and proteases such as furin and matriptase-2[8].

Inflammatory cytokines that elicit Hepcidin expression include IL-6 and IL-1β, while transcription factors that facilitate the effects of inflammation comprise Stat3, C/EBPα, and p53. IL-6 enhances JAK/Stat signaling, which leads to amplified phosphorylation of Stat3 and greater than before Stat3 binding to the Hepcidin promoter. IL-1β encourages Hepcidin expression through the C/EBPα and BMP/SMAD signaling pathways. Hepatocyte injury, due to endoplasmic reticulum stress or oxidation, improves C/EBPα or Stat3 activity, respectively, and upturns Hepcidin expression. Lipopolysaccharide (LPS) secreted by severe bacterial infection triggers toll-like receptor (TLR) 4 signaling, which increases production of IL-6 through macrophages. IL-6, sequentially, stimulates hepatocyte manufacture of hepcidin. The end effect is that iron cannot be released into the plasma and rests trapped inside the macrophages and hepatocytes, leading to an increase in iron stores mirrored in high levels of serum ferritin. Furthermore, hepcidin inhibits intestinal absorption of iron[5].

Hepcidin is not the only protein producing iron sequestration through bacterial infection. Recent studies specify that stimulation of TLR2 and TLR6 decreases expression of ferroportin in macrophages and causes hypoferremia without growing macrophage hepcidin expression. LPS stimulates macrophages to yield lipocalin 2, which seizes iron by binding bacterially formed siderophores. Additionally, infection or inflammation encourages neutrophil release of the iron binding protein lactoferrin, that can be internalized by bacteria, separate iron from pathogens, and inhibit microbial growth[9].

Obese individuals show increased plasma amount of metabolic regulatory hormones leptin and hepcidin, pro-inflammatory cytokines, and the iron-sequestering protein lipocalin-2. There are two suggested mechanisms by which obesity may add to functional iron deficiency and anemia centered on experimental models[7]:

(1) leptin and pro-inflammatory cytokines induce hepcidin production in hepatocytes and adipocytes

(2) adipocytes and peripheral blood mononuclear cells in obese individuals produce lipocalin 2, which limits iron availability to growing erythroid cells. Aside from the effects on iron metabolism, pro-inflammatory cytokines decrease erythropoietin production, damage the differentiation of erythroid progenitors, and cut the lifespan of mature red blood cells.

DIAGNOSIS

ACD is a mild to moderate form of anemia under the classification of normocytic normochromic, while less than 25% of cases portraying a microcytic hypochromic anemia, in which case the average corpuscular volume is infrequently less than 70 [2].This is in distinction to iron deficiency anemia, which is microcytic, hypochromic type with anisocytosis and poikilocytosisseen on peripheral blood film. Serum iron, transferrin saturation, and total iron binding capacity are all low in ACD, and are complemented by arise in serum ferritin and bone marrow iron

storage. Alternatively, in iron deficiency anemia, the serum iron, transferrin saturation, and ferritin are low, but there is an increase in total iron binding capacity. It is often puzzling to distinguish amongst ACD and iron deficiency anemia centered on available laboratory tests, and even more difficult are circumstances in which the two conditions co-occur[10]. Measurement of soluble transferrin receptor may be used to differentiate between the two types. In iron deficiency, soluble transferrin receptor levels are increased because the availability of iron is less, but in ACD soluble transferrin receptor levels are normal. The low transferrin levels are because of down regulation of transferrin synthesis on account of an increase in ferritin. Specified the vital role of hepcidin in regulating iron metabolism, determining serum hepcidin levels would aid to distinguish between the two types, but the question remains the lack of obtainability of a standard hepcidin assay. Hepcidin levels are decreased in iron deficiency, and amount of blood or urine hepcidin levels may be suggestive of factual iron deficiency.

Mass spectrometry and enzyme-linked immunoassays for quantitation of hepcidin in blood, plasma, and urine have been advanced[1]. A study of different assays for hepcidin found that in spite of noteworthy differences in the absolute value of each data, results for samples correlated well and analytical alteration was low. Additionally, issues in interpreting hepcidin levels comprise diurnal variations of hepcidin where it is lower in the morning, and higher in the afternoon; and relative sensitivity to the iron content of the diet. Therefore, ACD is defined by low serum iron, total iron binding capacity, and transferrin; by normal transferrin saturation; and by higher level of ferritin, in contrast to iron deficiency anemia[10].

There are numerous other parameters which are not essential for the diagnosis of ACD but which may considerably contribute to approximation of iron requirement for erythropoiesis and which may possibly turn out to be of importance for guessing the response to treatment of ACD with recombinant erythropoietin. Zinc protoporphyrin IX is made by erythroid progenitors when iron accessibility to these cells is decreased and thus the enzyme ferrochelatase combines iron as an alternative to zinc into the protoporphyrin ring. Zinc protoporphyrin is high in ACD patients with inflammatory disorders and reveals the request for iron for erythropoiesis. The same is true for finding the percentage of hypochromic red blood cells or reticulocytes; nevertheless, data for these measures in ACD are very inadequate. Finally, the assessment of serum erythropoietin levels does not add to the diagnosis of ACD but may have a suggestion towards the choice of treatment. Since ACD occurs in inflammatory diseases, high levels of cytokines are noted in serum of such patients, and these circulating cytokine concentrations are inversely associated to the grade of anemia[11].

Treatment

Treatment is principally directed at the original disease in the case of infections, malignancy, and autoimmune disorders, but most of these disorders are chronic and treatment of the underlying disease is difficult. Treatment of anemia contributes to enhancement in the quality of life of these patients. Presently available treatments may be classified either as conventional therapy or novel agents which are summarized in **(Table 1)[12].**

Conventional Therapy

Red blood cell transfusions must be provided for hemoglobin less than 8 g/dL, predominantly for patients with acknowledged coronary artery disease. It is to be remembered that repeated use of blood transfusions causes iron overload, hazard of transmission of infections, and allo-immunization[13].

Since ACD is associated with functional or absolute iron deficiency, iron supplementation might be of advantage particularly for patients with less ferritin and hypo-responsiveness to erythropoeisis-stimulating agents (ESAs). Instead of oral, intravenous iron can be used because of the increase in hepcidin levels which causes inhibition of intestinal iron absorption. ESAs such as epoetin-alpha, darbopoeitin-alpha, and epoetin-beta are extensively used in patients with anemia resulting from chronic renal failure. Conversely, studies have shown an increased possibility of cardiovascular events with use of ESAs. Thus, it is critical to regulate the ESA dose to keep hemoglobin less than 13 g/dL.

Moreover, ESA use has been associated with disease progression of many types of tumors. Since blood transfusions, ESAs, and iron therapy are not without adverse effects, the search continues for better therapies[14].

Novel Agents

Hepcidin antagonists (monoclonal antibodies, hepcidin binding proteins, small

interfering RNA [siRNA], antisense oligonucleotides, and aptamers) are being advanced. Anti-hepcidin monoclonal antibodies are under trials. These antibodies bind to hepcidin and stop it from binding to ferroportin. RNA interference (RNAi) and antisense oligonucleotides hinder either transcription or translation of hepcidin or its regulators including HJV and could possibly be beneficial therapeutic agents excluding technical challenges met in the delivery of RNAi. Moreover, hepcidin binding proteins, spiegelmers and anticalins are also being studied[15]. Spiegelmers are mirror image aptamers that are single-stranded synthetic oligonucleotides that join with high affinity and specificity to an extensive range of targets including peptides and proteins. The anti-hepcidin Spiegelmer NOX-H94 is in a phase IIa clinical trial to manage ACD. This phase IIa study was started following the efficacious completion of the clinical phase I program. The phase I study comprised of a comprehensive single and multiple ascending dose research in healthy volunteers and a following human pharmacodynamic study to evaluate the ability of NOX-H94 to prevent endotoxin-induced hypoferremia in healthy individuals. This endotoxemia study conveyed the first clinical evidence that NOX-H94 has the ability of neutralizing high levels of hepcidin in humans and upholding higher serum iron concentrations unlike subjects receiving placebo[16].

The augmented production of hepcidin in ACD serves as the foundation for development of inhibitors directing towards the BMP-HJV-SMAD and IL-6-JAK-STAT pathways which are involved in hepcidin synthesis. Dorsomorphin is a small-sized molecular inhibitor of BMP receptor, which is a derivative of dorsomorphin, while LDN-193189 is a highly selective BMP inhibitor. LDN-193189 has been shown to reverse anemia linked with chronic arthritis in rats. Other drugs include anti-BMP6 monoclonal antibody and soluble HJV. Furthermore, heparin also has been shown to reduce BMP-SMAD signaling and inhibit hepcidin transcription[15].

Regarding the IL-6-JAK-STAT pathway, monoclonal IL-6-R and IL-6 antibodies and the JAK2 and STAT3 inhibitors all have presented to down-regulate hepcidin expression. Vitamin D deficiency is related to an increased prevalence of ACD, and vitamin D replacement decreases hepcidin levels. As hepcidin excess blocks ferroportin by causing degrading, drugs that stabilize ferroportin or inhibit the interaction with hepcidin are an important target[17]. Our awareness of the interaction between inflammation, erythropoiesis, and iron metabolism has upgraded our ability to understand the pathogenesis of ACD. Although many drugs have not yet been permitted to treat this condition, several medications are under investigation, and some of them improve anemia of inflammation in patients with rheumatoid arthritis. In some cases, the anemia of inflammation can be a protective mechanism as observed in animal models of the anemia of critical illness that hepcidin-deficient mice exhibited considerably lower rates of survival than wild-type animals. Therefore, the best course of action continues to be to recognize and treat the underlying roots of the ACD[18].

Table 1: Treatment Modalities of Anemia of Chronic Disease

Therapy Types	Description	Dosing
Conventional	Red blood cell transfusion	1-2U
	IV Iron with erythropoesis-stimulating agents	iron sucrose 100 mg/dose
		Iron dextran 25 mg followed by 500-2000 mg
	Erythropoiesis-stimulating agent	Epoetin-alpha, -beta 20,000-60,000 U weekly
Novel	Direct hepcidin antagonists	*
	Monoclonal antibodies	mAb2.7, Ab12B9m
	siRNA	ALN-HPN
	Anticalins	PRS-080
	Spiegelmers	NOX-H94
	BMP-HJV-SMAD inhibitors	LDN-193189
	IL-6 antagonist	Tocilizumab
	JAK-STAT inhibitors	AG490, PpYLKTK
	Ferroportin agonist	Anti-ferroportin monoclonal antibody

CONCLUSION

Since absolute treatment for the underlying chronic conditions are not available yet, various

other modalities aimed at treating the anemia are present and developing. They include conventional methods which includes transfusion, intravenous iron, and inducing erythropoiesis; and novel therapies which include monoclonal antibodies, hepcidin binding proteins, small interfering RNA. More researches must be done in order to manage the condition by treating the underlying causes or for finding therapies with least side effects.

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