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The Interplay between Chronic Diseases and Anemia: Pathophysiological Mechanisms and Clinical Implications

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ABSTRACT

Anemia is a common comorbidity in chronic diseases and significantly contributes to reduced quality of life, impaired functional status, and poor clinical outcomes. Chronic disease–associated anemia, often referred to as anemia of chronic disease (ACD) or anemia of inflammation, is distinct in its pathophysiology from nutritional anemia. It is mediated by a complex interplay of inflammatory cytokines, disrupted iron homeostasis, blunted erythropoiesis, and reduced erythropoietin production. This review explores the mechanisms linking anemia to chronic conditions such as chronic kidney disease (CKD), heart failure, cancer, rheumatoid arthritis, and inflammatory bowel disease. Emphasis is placed on the role of hepcidin, the master regulator of iron metabolism, and how chronic inflammation alters iron distribution and utilization. The article also discusses diagnostic challenges and emerging therapeutic approaches, including erythropoiesis-stimulating agents (ESAs), iron supplementation, and novel anti-hepcidin therapies. A better understanding of the molecular and clinical interconnections between chronic disease and anemia is essential for improving patient-centered treatment strategies and outcomes.

Keywords: Anemia of chronic disease, hepcidin, erythropoiesis, inflammation, chronic kidney disease

INTRODUCTION

Anemia is a multifactorial clinical condition marked by a reduction in hemoglobin concentration or red blood cell mass, resulting in compromised oxygen transport to tissues [1]. It presents with symptoms such as fatigue, pallor, weakness, and reduced exercise tolerance. In patients with chronic diseases, anemia is a common and clinically significant complication that contributes to deteriorating health outcomes and worsens the underlying disease trajectory [2]. It often leads to functional impairment, increased healthcare utilization, and a decline in quality of life. Anemia in chronic disease states differs from nutritional or iron-deficiency anemia in both its pathophysiological mechanisms and management [2]. Known as anemia of chronic disease (ACD) or anemia of inflammation, it is typically associated with sustained immune activation and is characterized by altered iron homeostasis, impaired erythropoiesis, and blunted erythropoietin response [3]. Unlike iron-deficiency anemia, ACD generally occurs in the presence of adequate iron stores, but iron becomes functionally unavailable for red blood cell production [4]. ACD is prevalent in patients suffering from chronic infections, autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus, chronic kidney disease (CKD), congestive heart failure, and malignancies [5]. The chronic inflammatory milieu characteristic of these conditions initiates a cascade of molecular events that disrupt normal hematopoiesis and iron utilization. The severity and persistence of anemia often correlate with the intensity of the inflammatory process and disease progression. Despite its high prevalence and negative impact on patient outcomes, ACD remains under-recognized and undertreated. Many clinicians may overlook mild to moderate anemia in chronic disease settings, considering it a secondary concern. However, studies have demonstrated that even modest reductions in hemoglobin levels are associated with increased morbidity, reduced physical capacity, poor response to therapy, and elevated mortality risk [6]. Therefore, understanding the underlying mechanisms of ACD is essential for clinicians to develop targeted, evidence-based management strategies aimed at improving patient care.

2. Pathophysiological Mechanisms

2.1 Role of Inflammation

Inflammation plays a central and initiating role in the development of anemia of chronic disease. During prolonged immune activation, the body produces a range of pro-inflammatory cytokines, most notably interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) [7]. These cytokines disrupt red blood cell production in multiple ways. Firstly, they impair the differentiation and proliferation of erythroid progenitor cells in the bone marrow [8]. Under normal physiological conditions, erythropoiesis is stimulated by erythropoietin, a hormone primarily produced by the kidneys in response to hypoxia [9]. However, during inflammation, cytokines suppress the bone marrow's responsiveness to erythropoietin, leading to a reduced rate of red cell production [10]. Additionally, cytokines increase apoptosis of erythroid precursors, further compounding the anemia.

2.2 Hepcidin and Iron Sequestration

One of the hallmark mechanisms of ACD is iron sequestration [11]. Hepcidin, a peptide hormone synthesized in the liver, is the master regulator of systemic iron homeostasis [12]. Under inflammatory conditions, particularly those involving IL-6, hepcidin expression is significantly upregulated [13]. Elevated hepcidin levels lead to internalization and degradation of ferroportin, the only known cellular iron exporter located on macrophages, hepatocytes, and enterocytes [15]. With ferroportin activity inhibited, iron becomes trapped within storage sites in macrophages and the liver, and intestinal iron absorption is reduced [14]. As a result, iron is rendered unavailable for incorporation into hemoglobin, despite being present in sufficient or even elevated quantities in the body. This creates a condition known as functional iron deficiency, where serum ferritin may be normal or high, but transferrin saturation is low and iron supply to the erythron is inadequate.

2.3 Impaired Erythropoiesis

Beyond iron metabolism, chronic inflammation also directly impairs erythropoiesis. Cytokines such as TNF-α and IFN-γ suppress erythroid colony-forming units and limit erythropoietin secretion by the kidneys [16]. This is especially relevant in patients with chronic kidney disease, where anemia is further compounded by reduced renal mass and diminished erythropoietin synthesis. Additionally, chronic disease states often increase oxidative stress and result in the accumulation of toxic metabolic byproducts such as uremic toxins, especially in renal failure [17]. These substances interfere with red blood cell survival and maturation. In cancer-related anemia, the picture is even more complex, with factors such as bone marrow infiltration by malignant cells, chemotherapy-induced myelosuppression, and chronic inflammation all playing roles in suppressing hematopoiesis [18].

Taken together, the interplay between inflammation, iron restriction, and impaired bone marrow activity creates a self-sustaining cycle that contributes to the persistence and severity of anemia in chronic disease.

3. Anemia in Common Chronic Diseases

Anemia commonly coexists with several chronic illnesses and can significantly influence their progression, symptom burden, and overall prognosis [19]. Although the underlying mechanisms may vary depending on the disease, the shared feature is chronic inflammation, which disrupts normal hematopoiesis and iron metabolism [20]. Below are key examples of chronic conditions commonly associated with anemia.

3.1 Chronic Kidney Disease (CKD)

Anemia is a frequent and early complication of CKD, often appearing as kidney function begins to decline. The primary cause is reduced production of erythropoietin by the damaged kidneys, which leads to insufficient stimulation of red blood cell production in the bone marrow [21]. In addition to erythropoietin deficiency, patients with CKD experience chronic systemic inflammation, shortened red blood cell lifespan, and functional or absolute iron deficiency due to impaired iron absorption and blood loss during dialysis [22]. Anemia in CKD is a major contributor to cardiovascular morbidity and mortality [22]. Management typically includes the use of erythropoiesis-stimulating agents (ESAs) and intravenous iron supplementation, particularly when oral iron is ineffective or poorly tolerated [23].

3.2 Heart Failure

In patients with chronic heart failure, anemia is a well-recognized comorbidity associated with increased hospitalizations, reduced exercise tolerance, and higher mortality [24]. Several mechanisms contribute to anemia in this population, including chronic inflammation, renal dysfunction, reduced erythropoietin production, and hemodilution [25]. Moreover, heart failure can lead to intestinal edema, impairing nutrient absorption, including iron [26]. Clinical studies suggest that treating anemia in heart failure patients-especially with intravenous iron—can improve quality of life, exercise capacity, and overall functional status [27]. However, the use of ESAs in this setting remains controversial due to potential thromboembolic risks.

3.3 Cancer

Anemia in cancer patients can result from multiple interacting factors. These include direct bone marrow infiltration by malignant cells, myelosuppression due to chemotherapy or radiotherapy, chronic blood loss, and systemic inflammation [28]. Tumor-induced cytokine production, particularly interleukin-6, also elevates hepcidin levels, leading to iron sequestration and functional deficiency [29]. Anemia contributes to fatigue, reduced performance status, and poor tolerance to treatment, ultimately impacting prognosis [30]. Management may involve iron supplementation (often intravenous), ESAs, and red blood cell transfusions in severe cases, with careful consideration of risks versus benefits.

3.4 Autoimmune and Inflammatory Diseases

Chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease frequently lead to ACD [31]. Persistent inflammation promotes hepcidin overproduction and bone marrow suppression, resulting in decreased iron availability and erythropoiesis [32]. Additionally, gastrointestinal blood loss and malabsorption may coexist, particularly in inflammatory bowel disease. Treatment of anemia in these conditions requires a comprehensive approach focused on controlling the underlying disease activity, correcting iron deficiency when present, and possibly using ESAs in select cases [33].

4. Diagnostic Challenges

Distinguishing anemia of chronic disease from other types, particularly iron-deficiency anemia, presents a diagnostic challenge due to overlapping laboratory features. Serum ferritin is typically normal or elevated in ACD because it is an acute-phase reactant, even though iron availability is low [34]. In contrast, transferrin saturation tends to be reduced due to restricted iron release and absorption [35]. The soluble transferrin receptor (sTfR) test, which remains normal in ACD but is elevated in iron-deficiency anemia, can help differentiate between the two [36]. Additionally, newer biomarkers such as serum hepcidin, when available, offer valuable insights into iron regulation status. Accurate diagnosis relies not only on laboratory interpretation but also on comprehensive clinical evaluation, including assessment of underlying chronic diseases, nutritional status, history of bleeding, and treatment history [37]. Recognizing the type and cause of anemia is critical to guiding appropriate treatment strategies and improving clinical outcomes.

5. Clinical Implications and Management Strategies

Anemia in the context of chronic disease carries significant clinical implications, including reduced physical performance, increased fatigue, poor quality of life, and higher morbidity and mortality. Its presence often complicates disease management, contributes to hospitalization, and worsens overall prognosis, particularly in patients with chronic kidney disease, heart failure, cancer, and autoimmune disorders. Effective management begins with addressing the underlying chronic condition, as disease control often leads to partial or complete correction of anemia. In patients with functional iron deficiency, especially those with elevated hepcidin levels, intravenous iron therapy is preferred over oral supplementation due to better bioavailability and tolerability [38]. This is particularly important in inflammatory states where oral absorption is impaired. Erythropoiesis-stimulating agents (ESAs) are commonly used in anemia associated with chronic kidney disease and certain cancers [39]. However, they must be used with caution, balancing the benefits of hemoglobin improvement against risks such as thromboembolic events and, in some cancers, potential tumor progression. Emerging therapies offer new hope. Agents targeting the hepcidin-ferroportin axis, including hepcidin antagonists and hypoxia-inducible factor (HIF) stabilizers, are being developed to restore normal iron metabolism and stimulate endogenous erythropoietin production [40]. These novel treatments may offer safer and more targeted alternatives for patients who do not respond adequately to conventional therapy.

A tailored, patient-centered strategy that incorporates disease-specific factors, laboratory evaluation, and therapeutic risk-benefit analysis is essential for optimal management of anemia in chronic disease.

CONCLUSION

Anemia is both a consequence and contributor to the progression of many chronic diseases. Its pathogenesis involves a dynamic interplay of inflammation, iron sequestration, and impaired erythropoiesis. Early recognition and targeted treatment of anemia can significantly improve clinical outcomes and patient quality of life. Continued research into hepcidin modulation, inflammation control, and individualized treatment strategies will be pivotal in addressing the burden of anemia in chronic disease contexts

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