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Review Article

Iron deficiency anemia as a multisystem disorder: linking molecular dysregulation to clinical outcomes

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ABSTRACT

Iron deficiency anemia (IDA) is the most prevalent nutritional deficiency worldwide and remains a major public health challenge affecting children, women of reproductive age, pregnant women, and individuals with chronic diseases. Although traditionally regarded as a hematological disorder characterized by impaired hemoglobin synthesis and reduced oxygen-carrying capacity, increasing evidence indicates that iron deficiency produces multisystem dysfunction through disturbances in cellular metabolism, mitochondrial function, neurotransmitter synthesis, immune regulation, and iron homeostasis. This review summarizes the epidemiology, etiology, molecular pathophysiology, clinical manifestations, diagnostic evaluation, treatment strategies, and complications of IDA. Central to its pathogenesis is dysregulation of the hepcidin–ferroportin axis, leading to impaired iron absorption, defective erythropoiesis, and altered tissue iron utilization. Beyond anemia, iron deficiency contributes to cognitive impairment, reduced physical performance, cardiovascular stress, immune dysfunction, adverse pregnancy outcomes, and diminished quality of life. Early diagnosis using appropriate hematological and biochemical markers, together with timely identification of the underlying cause and individualized iron replacement therapy, is essential to prevent irreversible complications. A comprehensive understanding of the molecular mechanisms linking iron deficiency to systemic clinical manifestations may facilitate earlier diagnosis, optimize therapeutic strategies, and improve long-term patient outcomes.

Keywords: Iron deficiency anemia, Iron metabolism, Microcytic hypochromic anemia, Ferritin, Transferrin saturation, Hepcidin, Malabsorption

INTRODUCTION

Iron deficiency anemia (IDA) does not affect all populations equally. The risk of developing IDA is determined by the balance between iron intake, absorption, physiological requirements, and chronic iron loss. Certain demographic groups and clinical conditions substantially increase the likelihood of iron deficiency because of increased iron demand, reduced bioavailability, impaired absorption, or chronic blood loss. Early identification of these high-risk populations is essential for timely screening, prevention, and intervention.

The progression of IDA occurs in distinct stages. Initially, iron depletion is characterized by a reduction in iron stores while hemoglobin levels remain within the normal range. With further depletion, the bone marrow is unable to adequately hemoglobinize developing erythrocytes, resulting in microcytic and hypochromic red blood cells (RBCs). As the deficiency worsens, overt anemia develops, marked by a significant decrease in hemoglobin concentration and the emergence of clinical symptoms, including pallor, fatigue, shortness of breath, and dizziness. This staged pathophysiology underscores the importance of early detection and intervention in preventing the progression of IDA.[1]

The widespread prevalence of IDA is attributed to its diverse etiologies. In women, excessive menstrual blood loss is a frequent cause, while gastrointestinal blood loss due to ulcers, polyps, or chronic use of certain medications (such as NSAIDs) also contributes significantly. Dietary insufficiency, particularly diets deficient in iron-rich foods, and malabsorption syndromes-including celiac disease and post-surgical states-further increase susceptibility. Additionally, periods of increased physiological demand, such as pregnancy and rapid growth during infancy or adolescence, markedly elevate the risk of iron deficiency due to heightened iron requirements.[2]

Traditionally, IDA has been regarded primarily as a hematological disorder characterized by impaired hemoglobin synthesis and reduced oxygen transport. However, emerging evidence demonstrates that iron plays indispensable roles in mitochondrial oxidative phosphorylation, DNA synthesis, neurotransmitter production, immune-cell proliferation, skeletal muscle metabolism, and epithelial cell integrity. Consequently, iron deficiency affects multiple organ systems even before significant reductions in hemoglobin become apparent. These observations have shifted the understanding of IDA from a simple nutritional deficiency to a complex multisystem disorder involving widespread molecular dysregulation.[2]

Although numerous reviews have separately discussed the epidemiology, diagnosis, or management of IDA, relatively few have comprehensively integrated the molecular mechanisms responsible for tissue dysfunction with the diverse systemic clinical manifestations. A better understanding of these molecular pathways may facilitate earlier recognition of iron deficiency, improve risk stratification, and identify potential therapeutic targets beyond conventional iron replacement.

The consequences of IDA extend well beyond hematologic changes. Individuals with IDA frequently experience persistent fatigue, difficulty concentrating, headaches, and dizziness due to impaired oxygen delivery to tissues. Immune function is compromised, increasing susceptibility to infections. In children, IDA can adversely affect growth and cognitive development, while in adults, it can impair productivity, work performance, and overall quality of life. Early recognition and treatment of IDA are crucial to mitigate these systemic effects and prevent long-term complications.[3]

Therefore, this review aims to provide a comprehensive overview of IDA by integrating current knowledge regarding iron metabolism, molecular pathophysiology, multisystem clinical manifestations, diagnostic evaluation, treatment strategies, and future therapeutic perspectives. Particular emphasis is placed on the relationship between molecular dysregulation and systemic clinical outcomes.

EPIDEMIOLOGY

IDA remains the most common nutritional deficiency and the leading cause of anemia worldwide. According to the Global Burden of Disease (GBD) 2021 study, anemia continues to affect more than 1.9 billion people globally, with iron deficiency accounting for the largest proportion of cases. Despite substantial improvements in healthcare delivery and nutritional interventions, IDA remains a significant contributor to disability, particularly in low- and middle-income countries where nutritional deficiencies, infectious diseases, parasitic infestations, and limited healthcare access coexist.

The burden of IDA is not uniformly distributed across populations. Women of reproductive age, pregnant women, infants, young children, adolescents, and older adults represent the most vulnerable groups because of increased physiological iron requirements or chronic blood loss. In women, menstrual blood loss and pregnancy are major contributors, whereas rapid growth increases iron demand in infants and adolescents. Older adults frequently develop IDA secondary to gastrointestinal bleeding, malignancy, or chronic inflammatory disorders.

Regional differences also exist. The prevalence is highest in South Asia and Sub-Saharan Africa, where dietary iron deficiency, parasitic infections, recurrent pregnancies, and limited healthcare infrastructure remain major public health challenges. Conversely, developed countries report lower prevalence rates, although iron deficiency remains common among women, older adults, patients with chronic kidney disease, inflammatory bowel disease, heart failure, and those undergoing bariatric surgery.

Beyond its hematological consequences, IDA imposes substantial socioeconomic and healthcare burdens by reducing physical productivity, impairing cognitive performance, increasing maternal and childhood morbidity, and decreasing quality of life. These observations emphasize the need for population-based nutritional interventions, early screening of high-risk individuals, and timely therapeutic strategies to reduce the global burden of disease.[4,5]

ETIOLOGY

IDA develops when iron loss or physiological demand exceeds intestinal iron absorption, resulting in depletion of body iron stores and impaired erythropoiesis. Although the mechanisms leading to iron deficiency vary, all etiologies ultimately disturb iron homeostasis by reducing iron availability for hemoglobin synthesis. The major etiological factors include chronic blood loss, inadequate dietary intake, impaired intestinal absorption, increased physiological demand, parasitic infestations, chronic inflammatory disorders, and certain genetic or acquired conditions.

Chronic blood loss is the leading cause of IDA in adults. Persistent blood loss gradually depletes iron stores because each milliliter of blood contains approximately 0.5 mg of elemental iron. Menorrhagia remains the most common cause in premenopausal women, whereas occult gastrointestinal bleeding due to peptic ulcer disease, colorectal carcinoma, inflammatory bowel disease, hemorrhoids, angiodysplasia, or long-term use of nonsteroidal anti-inflammatory drugs is more common in older adults. Unless the source of bleeding is identified and corrected, iron supplementation alone is unlikely to prevent recurrence of anemia.[6]

Insufficient dietary iron intake contributes significantly to iron deficiency, particularly in populations consuming diets low in heme iron. Animal-derived iron (heme iron) is absorbed more efficiently than non-heme iron from plant sources. Vegetarian and vegan diets are therefore associated with an increased risk of deficiency unless appropriately supplemented or combined with dietary enhancers of iron absorption, such as vitamin C. Conversely, phytates, calcium, polyphenols, and tannins present in cereals, tea, and coffee reduce intestinal iron absorption.[7]

Iron is absorbed predominantly in the duodenum and proximal jejunum. Disorders affecting these regions including celiac disease, Crohn's disease, autoimmune gastritis, Helicobacter pylori infection, and bariatric surgery reduce intestinal iron absorption. Long-term proton pump inhibitor therapy may further impair absorption by decreasing gastric acidity, which is required for reduction of ferric iron to the more absorbable ferrous form.[8]

Physiological states associated with rapid growth or increased erythropoietic activity markedly increase iron requirements. Pregnancy represents one of the highest-demand states because iron is required for maternal erythropoiesis, placental development, and fetal growth. Similarly, infancy, adolescence, and lactation increase iron utilization, predisposing individuals to deficiency when dietary intake fails to meet these increased physiological demands.[9]

Parasitic infestations, particularly hookworm infection, remain important causes of IDA in tropical and resource-limited regions. Hookworms attach to the intestinal mucosa, producing chronic gastrointestinal blood loss that progressively depletes iron stores. Recurrent parasitic infections may also impair nutrient absorption and contribute to chronic inflammation, further aggravating iron deficiency.[10]

Additional causes include repeated blood donation, chronic kidney disease, chronic inflammatory disorders, malignancy, inherited disorders of iron metabolism, and medications that either reduce iron absorption or increase gastrointestinal blood loss. Functional iron deficiency may also develop in chronic inflammatory diseases because elevated hepcidin concentrations inhibit ferroportin-mediated iron release despite adequate body iron stores.[11]

Although these etiological factors differ considerably, they all converge on a common pathogenic pathway characterized by depletion of body iron stores, impaired iron transport, reduced hemoglobin synthesis, and defective cellular metabolism. Consequently, successful management requires not only iron replacement but also identification and correction of the underlying cause to prevent recurrence.

RISK FACTORS

IDA is particularly prevalent among high-risk populations. Women of reproductive age with menorrhagia experience substantial iron loss, predisposing them to deficiency. Pregnant and lactating women are at increased risk due to heightened physiological iron demands. Infants and young children, especially those exclusively breastfed beyond 6 months or with diets deficient in iron, are susceptible due to rapid growth and elevated iron requirements. Individuals adhering to vegetarian or vegan diets may be at higher risk if their intake of bioavailable iron, particularly heme iron, is inadequate.[2]

Chronic blood loss, including gastrointestinal bleeding, frequent blood donation, or regular use of medications such as aspirin or NSAIDs, significantly increases the risk of IDA. Malabsorption disorders, such as celiac disease, Crohn’s disease, atrophic gastritis, and post-bariatric surgery, impair iron absorption and predispose affected individuals to deficiency. In tropical regions, parasitic infections-particularly hookworm-are common etiologies due to chronic blood loss and impaired nutrient absorption. Chronic diseases, including kidney disease, heart failure, and inflammatory conditions, further contribute to iron deficiency. Additionally, genetic factors, such as mutations affecting iron metabolism, may predispose certain individuals to IDA.[3]

PATHOPHYSIOLOGY

IDA occurs when the body's iron stores are insufficient to support normal hemoglobin synthesis, leading to impaired erythropoiesis and reduced oxygen-carrying capacity. The pathophysiology progresses through three main stages: depletion of iron stores, iron-deficient erythropoiesis, and ultimately microcytic hypochromic anemia, all driven by defective heme synthesis. The underlying mechanisms involve disturbances in iron absorption, transport, storage, and regulation, with hepcidin acting as the master hormone that controls systemic iron homeostasis.

Iron homeostasis is maintained through a tightly regulated balance between intestinal iron absorption, transport, storage, utilization, and recycling. Unlike many other minerals, iron has no physiological mechanism for active excretion; therefore, systemic iron balance depends primarily on intestinal absorption and macrophage-mediated iron recycling. Central to this regulation is the hepcidin–ferroportin axis, which controls iron availability for erythropoiesis and tissue metabolism. Disruption of this regulatory pathway results in progressive depletion of iron stores and widespread cellular dysfunction that extends beyond impaired hemoglobin synthesis.

Depletion of iron stores

IDA begins with the progressive depletion of iron stores in the liver, spleen, and bone marrow. The earliest laboratory sign is a decrease in serum ferritin, reflecting reduced iron reserves. During this phase, the body mobilizes iron from macrophages to maintain serum iron levels, so serum iron often remains normal despite declining stores. This initial stage is typically asymptomatic, with individuals not experiencing noticeable symptoms. However, continued depletion sets the stage for subsequent phases of iron deficiency, eventually leading to impaired hemoglobin synthesis and the development of clinical anemia if left untreated.

During the initial stage, iron is mobilized from ferritin stored within hepatocytes and macrophages to maintain circulating transferrin-bound iron. Although hemoglobin concentration remains normal during this phase, intracellular iron-dependent enzymatic processes gradually become impaired, particularly in tissues with high metabolic activity such as skeletal muscle, myocardium, and the nervous system.[12]

Impaired iron transport and utilization

As iron stores become depleted, the transport and utilization of iron in the body are significantly impaired, leading to inadequate supply of iron to developing erythrocytes. This results in key changes in iron-related laboratory markers: serum iron levels decrease, and transferrin saturation (the proportion of iron-binding sites on transferrin that are occupied) also falls. In response, the body increases transferrin levels to maximize iron transport, and transferrin receptor (TfR1) expression on erythroid precursors rises to capture more available iron from the circulation. Despite these compensatory mechanisms, insufficient iron delivery ultimately reduces heme synthesis, resulting in defective hemoglobin production and the characteristic features of IDA.

Iron uptake into developing erythroblasts depends on transferrin receptor-1 (TfR1), while intracellular iron is released through endosomal reduction by STEAP3 and transported by divalent metal transporter-1 (DMT1). Progressive iron depletion reduces iron availability for heme synthesis, limiting hemoglobin production despite compensatory upregulation of transferrin receptors.[13]

Hepcidin dysregulation and increased absorption attempt

Hepcidin, a hormone produced by the liver, plays a central role in regulating iron homeostasis by inhibiting iron absorption in the gut and blocking iron release from macrophages. In iron deficiency, hepcidin levels decrease, leading to increased ferroportin activity, which enhances intestinal iron absorption and greater release of iron from macrophages, thereby helping to restore iron supply for erythropoiesis. However, in the presence of inflammation, hepcidin levels remain inappropriately elevated, suppressing ferroportin activity. This results in a functional iron deficiency, where iron is trapped in stores and unavailable for hemoglobin synthesis, even if total body iron stores are adequate.

Hepcidin, synthesized by hepatocytes, serves as the master regulator of systemic iron homeostasis. It binds to ferroportin, the only known cellular iron exporter, inducing its internalization and degradation. Consequently, intestinal iron absorption and macrophage iron release decrease. During iron deficiency, suppression of hepcidin expression allows ferroportin to remain active, thereby increasing dietary iron absorption and mobilization of stored iron. Conversely, inflammatory cytokines, particularly interleukin-6 (IL-6), stimulate hepcidin production, producing functional iron deficiency despite adequate body iron stores.[14]

Iron-deficient erythropoiesis

Inadequate iron availability leads to structural and functional abnormalities in RBCs. In the bone marrow, erythroblasts become microcytic (smaller than normal) and show poor hemoglobinization, with cytoplasmic vacuolization observed in severe deficiency. These morphological changes are directly linked to defective hemoglobin synthesis due to insufficient iron. In peripheral blood, red cell indices reflect these defects: mean corpuscular volume (MCV) decreases, indicating microcytosis; mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are reduced, showing hypochromia; and red cell distribution width (RDW) increases, reflecting anisocytosis due to the presence of mixed populations of RBCs. These laboratory findings are hallmark features of IDA and confirm impaired hemoglobin production.[14]

Development of microcytic hypochromic anemia

When iron supply cannot meet erythropoietic demand, RBCs undergo extra cell divisions, resulting in the production of smaller RBCs known as microcytes. Due to reduced hemoglobin content, these RBCs appear pale, a condition referred to as hypochromia. This ineffective erythropoiesis further worsens the anemia, leading to a decreased hemoglobin concentration and compromised oxygen delivery to tissues. These changes are direct consequences of insufficient iron for hemoglobin synthesis and are characteristic features of IDA.[15]

Systemic physiological consequences

The drop in hemoglobin and impaired oxygen-carrying capacity in IDA stimulate several compensatory responses in the body. Systemic effects include an increased heart rate and cardiac output, as well as vasodilation, which help improve oxygen delivery to tissues. RBCs also increase their production of 2,3-diphosphoglycerate (2,3-DPG), enhancing oxygen unloading to tissues. Iron is essential for cellular metabolism, and its deficiency leads to a range of symptoms such as fatigue, weakness, impaired cognitive function, restless legs syndrome, and epithelial changes like koilonychia and glossitis. These effects highlight the broad impact of iron deficiency on both systemic and cellular functions.[15]

Etiological factors leading to pathophysiologic changes

Although the pathophysiology of IDA is uniform, the underlying causes can vary significantly. Major contributors include chronic blood loss (such as gastrointestinal bleeding or menorrhagia), malabsorption due to conditions like celiac disease, post-gastrectomy, or bariatric surgery, increased demand during pregnancy or periods of rapid growth, and dietary deficiency. These factors create a mismatch between iron intake, absorption, storage, and utilization, driving the progression through the stages of iron depletion, iron deficiency erythropoiesis, and ultimately IDA. Each cause disrupts the delicate balance of iron homeostasis, leading to the characteristic hematologic and systemic manifestations of IDA.[16]

Collectively, these molecular disturbances demonstrate that IDA is considerably more than a disorder of erythropoiesis. Defective iron-dependent enzymatic activity affects virtually every organ system, explaining why neurological, cardiovascular, muscular, immune, and epithelial manifestations frequently develop before severe anemia becomes clinically apparent.

This broader understanding provides the biological basis for considering IDA a multisystem disorder rather than simply a hematological disease.

Table 1: Molecular mechanisms underlying IDA and their multisystem clinical manifestations.

Molecular abnormalities	Key mediator	Cellular effect	Clinical manifestation
Decreased hepcidin	Ferroportin activation	Increased iron absorption	Compensatory response
Iron depletion	↓ Ferritin	Reduced iron stores	Early iron deficiency
Impaired heme synthesis	↓ Hemoglobin	Microcytic hypochromic RBCs	Anemia
Mitochondrial dysfunction	↓ ATP	Reduced cellular energy	Fatigue, muscle weakness
Neurotransmitter impairment	↓ Dopamine	Neuronal dysfunction	Cognitive impairment, restless legs syndrome
Immune dysfunction	↓ T-cell function	Reduced host defense	Increased infection risk

EVALUATION

Accurate diagnosis of IDA requires integration of clinical history, physical examination, hematological indices, and biochemical markers of iron metabolism. Because several laboratory parameters may be influenced by inflammation, chronic disease, pregnancy, and liver disorders, interpretation should always be made within the appropriate clinical context. Early diagnosis before the development of overt anemia allows timely intervention and prevention of irreversible systemic complications.

Laboratory evaluation is essential for the diagnosis of IDA. A complete blood count typically reveals decreased hemoglobin, microcytic and hypochromic RBCs, and an elevated red cell distribution width, reflecting impaired erythropoiesis. Peripheral blood smear often demonstrates microcytosis, hypochromia, and occasionally elongated "pencil cells," further supporting the diagnosis. Iron studies are critical: serum ferritin, a marker of iron stores, is usually reduced, while serum iron is low, total iron-binding capacity (TIBC) is increased, and transferrin saturation is less than 15%, confirming inadequate iron availability.

Serum ferritin remains the most sensitive indicator of iron stores under non-inflammatory conditions. However, because ferritin is an acute-phase reactant, normal or elevated ferritin concentrations do not exclude iron deficiency in patients with chronic inflammation, infection, liver disease, obesity, or malignancy. In such situations, transferrin saturation, soluble transferrin receptor (sTfR), reticulocyte hemoglobin content (Ret-He), and inflammatory markers such as C-reactive protein (CRP) should be interpreted together to improve diagnostic accuracy.

In cases where inflammation or chronic disease may confound ferritin interpretation, additional tests such as soluble transferrin receptor (sTfR) and the sTfR/log ferritin ratio can help differentiate IDA from anemia of chronic disease. Reticulocyte hemoglobin content (Ret-He/CHr) serves as a sensitive indicator of iron-restricted erythropoiesis. Bone marrow examination with Prussian blue staining, which demonstrates absent iron stores, is rarely required but may be considered in diagnostically challenging cases. Among red cell indices, an increased red cell distribution width (RDW) is often one of the earliest abnormalities, reflecting anisocytosis before significant reductions in mean corpuscular volume (MCV) occur. However, similar hematological findings may also be observed in thalassemia trait and anemia of chronic disease, necessitating further biochemical evaluation.[17,18]

Once iron deficiency is confirmed, clinical evaluation must focus on identifying the underlying etiology. Diagnostic investigations may include testing for occult gastrointestinal bleeding through fecal occult blood tests and endoscopic examinations to assess for sources such as ulcers, polyps, or malignancies. Additionally, evaluation for malabsorption syndromes, including celiac disease and Helicobacter pylori infection, is warranted. For women, obtaining a comprehensive menstrual history and conducting appropriate gynecologic assessments are critical due to the commonality of menstrual blood loss as a contributing factor. A positive hematologic response to iron therapy, characterized by an increase in reticulocyte count and rising hemoglobin levels, further supports the diagnosis of IDA and the effectiveness of treatment.[19,20]

Table 2: Laboratory evaluation and diagnostic biomarkers of IDA.

Investigations	Typical finding in IDA	Clinical significance
Hemoglobin	↓	Confirms anemia
MCV	↓	Microcytosis
MCH	↓	Hypochromia
RDW	↑	Early anisocytosis
Serum ferritin	↓	Best indicator of iron stores
Serum iron	↓	Reduced circulating iron
TIBC	↑	Increased iron-binding capacity
Transferrin saturation	↓ (<15–20%)	Functional iron deficiency
Soluble transferrin receptor	↑	Differentiates IDA from anemia of chronic disease
Reticulocyte hemoglobin (Ret-He)	↓	Early marker of iron-restricted erythropoiesis
Bone marrow iron stain	Absent iron stores	Gold standard (rarely required)

TREATMENT

The primary goals of treatment in IDA are to restore hemoglobin concentration, replenish iron stores, correct the underlying cause of iron deficiency, and prevent recurrence. Treatment should be individualized according to the severity of anemia, the underlying etiology, patient comorbidities, inflammatory status, and the urgency of iron replacement.[21]

Oral iron remains the first-line treatment for most patients because it is inexpensive, widely available, and effective. However, gastrointestinal adverse effects including nausea, abdominal discomfort, constipation, diarrhea, and metallic taste remain major causes of poor adherence. Recent evidence demonstrates that alternate-day dosing improves fractional iron absorption by minimizing hepcidin-mediated inhibition of intestinal iron uptake while simultaneously reducing gastrointestinal side effects.

Most patients start to feel better within a week or two, and doctors look for a rise in reticulocyte count (young RBCs) within 7-10 days, followed by a steady increase in hemoglobin-usually about 1 gram per deciliter every 2-3 weeks until levels return to normal. Intravenous iron is recommended for patients who cannot tolerate oral iron, have impaired gastrointestinal absorption, inflammatory bowel disease, chronic kidney disease, ongoing blood loss, severe iron deficiency requiring rapid correction, or an inadequate response to oral therapy. Modern intravenous preparations-including ferric carboxymaltose, ferric derisomaltose, iron sucrose, and ferumoxytol-permit administration of larger iron doses with improved safety profiles compared with older high-molecular-weight iron dextran formulations.

For those who can't tolerate oral iron, have conditions that impair absorption (like celiac disease or inflammatory bowel disease), or need iron replaced quickly (such as in severe deficiency or chronic kidney disease), intravenous iron therapy is a safe and effective option. Newer IV iron formulations, such as ferric carboxymaltose and iron sucrose, are well-tolerated and allow for faster repletion. Blood transfusions are reserved for emergencies when anemia is severe and causing dangerous symptoms or instability.[22,23]

But treatment doesn't stop at iron replacement. It's crucial to identify and treat the underlying cause, whether it's heavy menstrual bleeding, gastrointestinal bleeding, infection (like Helicobacter pylori), or another condition. Addressing these issues helps prevent iron deficiency from recurring. After hemoglobin levels normalize, ongoing follow-up is important. Doctors will check ferritin and transferrin saturation to make sure iron stores are fully replenished and to guide further care if needed. This comprehensive approach ensures not just a quick fix, but lasting recovery and better health in the long run.[24-26]

Table 3: Current therapeutic strategies for IDA and their clinical indications.

Treatments	Indications	Advantages	Limitations
Oral iron	Mild-moderate IDA	Inexpensive, effective	GI side effects, poor adherence
Alternate-day oral iron	Most stable patients	Better absorption, fewer side effects	Slower correction in severe anemia
Intravenous iron	Malabsorption, CKD, IBD, severe deficiency	Rapid iron replacement	Higher cost, infusion monitoring
Blood transfusion	Severe symptomatic anemia	Immediate correction	Does not replenish iron stores
Emerging therapies	Functional iron deficiency	Target underlying molecular pathways	Limited clinical availability

COMPLICATIONS

Cardiovascular complications

Chronic iron deficiency reduces oxygen delivery to tissues, resulting in compensatory tachycardia, increased cardiac output, and ventricular remodeling. Persistent severe anemia may eventually lead to high-output cardiac failure, worsen pre-existing cardiovascular disease, and reduce exercise tolerance. Patients with chronic heart failure frequently experience poorer functional status and increased hospitalization rates when iron deficiency coexists.[6]

Neurological and cognitive

Iron is essential for dopamine synthesis, myelination, and mitochondrial function within the central nervous system. Iron deficiency therefore contributes to impaired attention, memory deficits, reduced cognitive performance, developmental delay in children, restless legs syndrome, and impaired academic achievement. Some neurodevelopmental abnormalities occurring during early childhood may not be completely reversible despite subsequent iron replacement.[27]

Musculoskeletal effects

Iron deficiency impairs mitochondrial oxidative phosphorylation and ATP production within skeletal muscle, resulting in fatigue, muscle weakness, reduced endurance, diminished exercise tolerance, and impaired physical performance. These manifestations may occur before severe anemia develops.[27]

Behavioral and psychosocial issues

Altered neurotransmitter metabolism contributes to irritability, depression, anxiety, sleep disturbances, poor work productivity, and reduced QoL. Persistent fatigue further amplifies psychosocial impairment in affected individuals.[27]

Immune system impairment

Iron deficiency adversely affects both innate and adaptive immunity by reducing neutrophil bactericidal activity, impairing T-cell proliferation, and altering cytokine production. Consequently, affected individuals may demonstrate increased susceptibility to infections and delayed immune responses.[28]

Pregnancy-related

Iron deficiency during pregnancy increases the risk of maternal fatigue, preterm delivery, low birth weight, postpartum hemorrhage, impaired fetal neurodevelopment, and increased perinatal morbidity. Adequate antenatal screening and timely iron supplementation substantially reduce these adverse outcomes. [29]

Epithelial and mucosal changes

Iron deficiency impairs epithelial cell turnover, producing characteristic manifestations such as koilonychia, brittle nails, brittle hair, angular cheilitis, atrophic glossitis, and pica. These findings often reflect long-standing iron deficiency and should prompt evaluation for the underlying cause. [30]

Gastrointestinal

Long-standing iron deficiency may lead to Plummer-Vinson syndrome, characterized by dysphagia, esophageal webs, and IDA. This condition is associated with an increased risk of upper esophageal squamous cell carcinoma, highlighting the importance of early diagnosis and treatment. [31]

Impact on chronic diseases

Iron deficiency negatively influences outcomes in chronic kidney disease, chronic heart failure, inflammatory bowel disease, and other chronic illnesses by worsening fatigue, reducing functional capacity, increasing hospitalization, and impairing overall quality of life. [32]

Collectively, these complications emphasize that IDA is a multisystem disorder extending far beyond reduced hemoglobin synthesis. Many manifestations arise from impaired iron-dependent cellular metabolism and may develop before advanced anemia becomes clinically apparent. Early diagnosis and correction of iron deficiency therefore remain essential to prevent irreversible organ dysfunction and improve long-term clinical outcomes.

Table 4: Multisystem complications of IDA and their underlying mechanisms.

Organ systems	Major complication	Underlying mechanism
Cardiovascular	Tachycardia, heart failure	Tissue hypoxia, increased cardiac output
Nervous system	Cognitive impairment, restless legs	Reduced dopamine synthesis, impaired myelination
Skeletal muscle	Fatigue, weakness	Mitochondrial dysfunction, reduced ATP production
Immune system	Increased infections	Impaired neutrophil and T-cell function
Pregnancy	Preterm birth, low birth weight	Increased iron demand, placental dysfunction
Skin & mucosa	Glossitis, koilonychia, angular cheilitis	Impaired epithelial regeneration
Gastrointestinal	Plummer–Vinson syndrome	Chronic epithelial iron deficiency
Chronic disease	Reduced functional capacity	Persistent tissue iron deficiency

CONCLUSION

IDA is far more than a disorder of reduced hemoglobin synthesis; it is a complex multisystem disease resulting from dysregulation of iron homeostasis and impaired cellular metabolism. Disturbances in the hepcidin–ferroportin axis, iron transport, and intracellular iron utilization affect numerous physiological processes, including erythropoiesis, mitochondrial energy production, neurotransmitter synthesis, immune function, and tissue repair. Consequently, many clinical manifestations of iron deficiency extend beyond anemia and may develop before significant reductions in hemoglobin become apparent.

Early diagnosis requires careful interpretation of hematological and biochemical markers together with identification of the underlying cause. Although oral and intravenous iron replacement remain the cornerstone of therapy, successful long-term management depends on correcting the underlying etiology and ensuring complete restoration of iron stores. Advances in the understanding of iron metabolism have also led to the development of novel diagnostic biomarkers and emerging therapeutic strategies targeting the hepcidin–ferroportin pathway, which may further improve patient outcomes in the future.

A comprehensive understanding of the molecular mechanisms linking iron deficiency to multisystem clinical manifestations will facilitate earlier diagnosis, individualized treatment, and prevention of long-term complications. Future research should focus on validating emerging biomarkers, optimizing personalized iron replacement strategies, and developing targeted therapies capable of improving both hematological and systemic outcomes.

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