BHARATI INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH & DEVELOPMENT (BIJMRD)

(Open Access Peer-Reviewed International Journal)

DOI Link : https://doi.org/10.70798/Bijmrd/03120013

Available Online: www.bijmrd.com|BIJMRD Volume: 3| Issue: 12| December 2025| e-ISSN: 2584-1890

Mechanisms and Molecular Insights into Iron Deficiency Anemia: From Hematology to Cellular Biology

Kalyani Jana[1] & Dr. Abha Kumari[2]

1. Research Scholar, Department of Food and Nutrition, YBN University
2. Assistant Professor, Department of Food and Nutrition, YBN University

Abstract:

Iron Deficiency Anemia (IDA) is the most common micronutrient deficiency globally, affecting over two billion individuals and representing a major public health concern. It disproportionately impacts children, adolescents, and women of reproductive age, contributing to increased morbidity, impaired cognitive and physical development, and adverse maternal and perinatal outcomes. IDA arises from a multifactorial etiology, including inadequate dietary intake, increased physiological iron requirements, chronic blood loss, malabsorption syndromes, and genetic predispositions. At the cellular and molecular levels, iron deficiency impairs hemoglobin synthesis, resulting in microcytic, hypochromic erythrocytes, and triggers compensatory erythropoietic and systemic responses. The hepcidin-ferroportin axis serves as a central regulatory pathway controlling iron absorption and mobilization, while iron regulatory proteins (IRPs) modulate intracellular iron homeostasis. Clinical manifestations include fatigue, pallor, cognitive dysfunction, restless leg syndrome, and impaired immune function. Diagnosis relies on a combination of hematologic indices, serum ferritin, transferrin saturation, soluble transferrin receptor levels, and emerging molecular biomarkers. Management strategies encompass dietary and lifestyle interventions, oral and intravenous iron supplementation, and novel therapies targeting hepcidin modulation, iron absorption, and gut microbiome interactions. Understanding the pathophysiology, molecular mechanisms, and systemic consequences of IDA is essential for designing personalized interventions, optimizing therapeutic efficacy, and guiding future research in nutritional anemia.

Keywords: *Iron Deficiency Anemia, Hemoglobin, Hepcidin, Ferroportin, Erythropoiesis, Iron Metabolism, Nutritional Deficiency, Molecular Mechanisms, Gut Microbiome.*

Introduction:

Iron is an essential micronutrient required for numerous biological processes, including oxygen transport, DNA synthesis, cellular respiration, and enzymatic reactions. Iron deficiency represents a global public health challenge and is the leading cause of anemia, particularly in developing countries where dietary insufficiency, infections, and malabsorption are prevalent (McLean et al., 2009). IDA results from an imbalance between iron requirements, intake, absorption, and losses, leading to impaired erythropoiesis and diminished hemoglobin synthesis. Beyond hematologic manifestations, iron deficiency affects immune function, cognitive development, energy metabolism, and organ systems, underscoring its systemic impact (Beard, 2001).

Recent advances in molecular biology and genomics have provided insights into the regulation of iron homeostasis at the cellular and systemic levels. Understanding the molecular mechanisms, including hepcidin regulation, ferroportin-mediated iron transport, and erythroid iron utilization, is critical for precise diagnostics, therapeutic interventions, and development of targeted treatments (Nemeth & Ganz, 2006).

Objectives: This review explores the multifactorial etiology, pathophysiological mechanisms, molecular pathways, and cellular dynamics underlying IDA. The review also examines diagnostic biomarkers, clinical consequences, and emerging therapeutic approaches, integrating hematological, biochemical, and molecular perspectives.

Etiology and Risk Factors of Iron Deficiency Anemia

Nutritional Deficiency: Dietary iron insufficiency is the most common cause of IDA. Heme iron, found in animal sources, is readily absorbed, while non-heme iron from plant sources has limited bioavailability and is influenced by dietary inhibitors such as phytates, polyphenols, and calcium (Hurrell & Egli, 2010). Populations with low meat consumption, strict vegetarians, and economically disadvantaged communities are particularly susceptible.

Increased Iron Requirements: Physiological states with elevated iron demand, including infancy, childhood, adolescence, pregnancy, and lactation, increase the risk of deficiency. Rapid growth or blood loss during menstruation also contributes to iron depletion (Milman, 2006).

Blood Loss and Chronic Disease: Gastrointestinal bleeding due to ulcers, gastritis, or malignancy, and chronic blood loss during menstruation, represents a major cause of iron depletion. Chronic inflammatory diseases, infections, and parasitic infestations (e.g., hookworm) further exacerbate iron loss and impair absorption (WHO, 2008).

Malabsorption Syndromes: Celiac disease, inflammatory bowel disease, and post-gastrectomy states reduce intestinal iron absorption. Gastric acidity is essential for converting ferric (Fe^3+) to ferrous (Fe^2+) iron, facilitating uptake via duodenal enterocytes. Hypochlorhydria or proton pump inhibitor use can impair this process (Gibson et al., 2017).

Iron Metabolism and Molecular Mechanisms

Iron Absorption and Transport: Iron absorption occurs primarily in the duodenum and proximal jejunum. Non-heme iron is reduced from Fe^3+ to Fe^2+ by duodenal cytochrome B (Dcytb) before transport via divalent metal transporter 1 (DMT1) into enterocytes. Heme iron is absorbed intact through the heme carrier protein 1 (HCP1) pathway. Within enterocytes, iron is either stored as ferritin or exported into circulation via ferroportin (FPN), the only known iron exporter, regulated by hepcidin (Andrews, 2000; Nemeth et al., 2004).

Systemic Regulation: Hepcidin-Ferroportin Axis: Hepcidin, a liver-derived peptide hormone, is the master regulator of systemic iron homeostasis. It binds to ferroportin, triggering internalization and degradation, thereby reducing intestinal absorption and macrophage-mediated iron release. Hepcidin synthesis is influenced by iron stores, erythropoietic activity, inflammation, and hypoxia. In IDA, hepcidin levels are typically suppressed to enhance absorption and mobilization of iron for erythropoiesis (Ganz & Nemeth, 2012).

Cellular Iron Utilization: Iron is transported in plasma bound to transferrin and delivered to tissues via transferrin receptors (TfR1/TfR2). In erythroid progenitors, iron is incorporated into protoporphyrin IX to form heme, essential for hemoglobin synthesis. Inefficient utilization or disruption in iron transport leads to iron-restricted erythropoiesis, characteristic of IDA (Hentze et al., 2010).

Molecular Signaling Pathways: At the cellular level, iron metabolism is regulated by iron regulatory proteins (IRPs) that bind iron-responsive elements (IREs) on mRNAs encoding ferritin, transferrin receptor, and DMT1. Low intracellular iron increases IRP binding, enhancing iron uptake and reducing storage, while high iron levels suppress IRP activity (Rouault, 2006).

Pathophysiology of Iron Deficiency Anemia

Impaired Erythropoiesis: Iron is an essential component of hemoglobin, and its deficiency directly limits hemoglobin synthesis, leading to the production of microcytic (small) and hypochromic (pale) red blood cells. This reduction in hemoglobin compromises oxygen delivery to peripheral tissues, triggering compensatory physiological responses such as increased cardiac output and elevated erythropoietin (EPO) secretion to stimulate erythropoiesis (Camaschella, 2015; Weiss & Goodnough, 2005). Over time, chronic iron deficiency exhausts iron stores and results in ineffective erythropoiesis, where red blood cell production is insufficient to meet tissue oxygen demands. Clinically, this manifests as fatigue, reduced exercise tolerance, and pallor. Prolonged iron deficiency may also lead to structural changes in erythroid precursors, further impairing red blood cell maturation and survival (Ganz, 2013).

Systemic and Cellular Effects: Iron plays a pivotal role beyond hemoglobin synthesis, acting as a cofactor in numerous enzymatic processes. Iron-dependent enzymes are crucial for mitochondrial oxidative phosphorylation, neurotransmitter synthesis (including dopamine, serotonin, and norepinephrine), and DNA replication and repair (Beard & Connor, 2003; Oexle et al., 1999). Consequently, iron deficiency impairs cellular energy metabolism, leading to lethargy, cognitive deficits, and developmental delays in children. The immune system is similarly affected, as iron is required for proliferation and differentiation of lymphocytes and for the generation of reactive oxygen species used in pathogen clearance. Deficiency may therefore increase susceptibility to infections and impair overall immune competence (Wintergerst et al., 2007).

Molecular Adaptations: Cells respond to iron deficiency through finely tuned molecular mechanisms. Transferrin receptor (TfR1) expression is upregulated on cell surfaces to maximize iron uptake from transferrin-bound plasma iron. Conversely, intracellular ferritin expression is downregulated to mobilize stored iron for essential metabolic and erythropoietic functions. At the systemic level, hepcidin, the key regulator of iron homeostasis, is suppressed during iron deficiency, increasing intestinal iron absorption and iron release from macrophages (Ganz, 2013; Nemeth & Ganz, 2006). Despite these adaptations, persistent dietary insufficiency, chronic blood loss, or malabsorption can overwhelm compensatory mechanisms, leading to progressive anemia with associated tissue hypoxia and systemic manifestations.

Clinical Manifestations and Hematologic Features

Symptoms: Iron deficiency anemia (IDA) presents with a spectrum of clinical symptoms reflecting decreased oxygen delivery and systemic iron depletion. Common manifestations include pallor, fatigue, weakness, dizziness, shortness of breath, palpitations, and reduced exercise capacity. Chronic or severe deficiency may lead to neurocognitive impairment, particularly in children, manifesting as poor concentration and developmental delays. Other classical signs include restless leg syndrome, brittle nails (koilonychia), angular cheilitis, glossitis, and pica—a craving for non-nutritive substances such as ice or dirt (Georgieff, 2017; Beard, 2001). In infants and toddlers, IDA can impair motor development and learning capacity, emphasizing the need for early recognition and intervention.

Hematologic Findings: Laboratory evaluation of IDA typically reveals characteristic red blood cell abnormalities. Microcytosis (low mean corpuscular volume, MCV) and hypochromia (low mean corpuscular hemoglobin, MCH) are hallmark features. Peripheral blood smears often demonstrate anisopoikilocytosis—variations in red blood cell size and shape—and reduced reticulocyte counts, reflecting inadequate

erythropoietic response. As anemia progresses, red blood cells may become markedly pale and small, sometimes with target cells and pencil-shaped forms. Chronic deficiency may also cause mild leukopenia and thrombocytosis in some cases, reflecting systemic marrow stress (Camaschella, 2015; Cook & Skikne, 1989).

Diagnostic Biomarkers: Laboratory assessment of iron status integrates multiple parameters:

- **Serum ferritin:** Primary indicator of iron stores; low in IDA, though may be elevated during inflammation or infection due to its acute-phase reactant properties (Camaschella, 2015).
- **Transferrin saturation (TSAT):** Reflects circulating iron available for erythropoiesis; values below 20% are suggestive of deficiency.
- **Serum iron:** Measures iron bound to transferrin; often reduced in IDA.
- **Total iron-binding capacity (TIBC):** Elevated in iron deficiency as the body increases transferrin production to capture more iron.
- **Soluble transferrin receptor (sTfR):** Elevated in IDA; reflects erythroid demand for iron and is relatively unaffected by inflammation, making it a sensitive marker to differentiate IDA from anemia of chronic disease (Camaschella, 2015; Cook et al., 2003).

Combining these biomarkers provides a comprehensive assessment of iron status, guiding diagnosis and monitoring of therapeutic response. Advanced molecular markers, including hepcidin and erythroferrone, are increasingly studied for their potential to refine diagnostic precision and monitor iron metabolism dynamically (Ganz, 2013).

Management Strategies for Iron Deficiency Anemia

Dietary and Lifestyle Interventions: Dietary modification remains the cornerstone of both prevention and management of iron deficiency anemia (IDA), particularly in mild or early cases. Emphasis is placed on the inclusion of iron-rich foods such as red meat, liver, poultry, fish, legumes, green leafy vegetables, and iron-fortified cereals (WHO, 2016). Vitamin C-rich foods (e.g., citrus fruits, tomatoes, bell peppers) enhance non-heme iron absorption by reducing ferric iron (Fe^{3+}) to the more readily absorbed ferrous form (Fe^{2+}). Conversely, dietary inhibitors—including tea, coffee, phytates from whole grains, and calcium-rich foods—should be limited around iron-containing meals to optimize absorption. In populations at high risk, such as pregnant women, infants, and adolescents, fortification of staple foods with iron is recommended to prevent deficiency. Lifestyle measures, including management of chronic blood loss, treatment of parasitic infections, and addressing conditions causing malabsorption, complement dietary strategies and enhance therapeutic efficacy (WHO, 2016; Camaschella, 2015).

Pharmacological Therapy: When dietary measures are insufficient, pharmacological supplementation is required to replenish iron stores.

- **Oral Iron Supplementation:** Ferrous salts—such as ferrous sulfate, gluconate, or fumarate—are first-line therapy. Typical regimens provide 100–200 mg of elemental iron daily, administered in divided doses. Oral therapy is cost-effective and generally safe, though gastrointestinal side effects like nausea, constipation, and abdominal discomfort may reduce adherence. Newer formulations, including slow-release tablets and liposomal iron, aim to improve tolerability and bioavailability (Auerbach & Ballard, 2010).
- **Intravenous Iron Therapy:** IV iron is indicated in cases where oral supplementation fails, is not tolerated, or when rapid correction of anemia is necessary—such as in chronic kidney disease,

inflammatory bowel disease, or severe IDA. Preparations include iron sucrose, ferric carboxymaltose, and iron dextran. IV therapy allows direct replenishment of iron stores but requires careful monitoring for hypersensitivity reactions and adherence to dosing protocols (Auerbach & Ballard, 2010; Pavord et al., 2012).

Monitoring and Follow-Up: Monitoring is essential to ensure treatment efficacy and prevent recurrence. Hemoglobin levels are typically rechecked every 2–4 weeks after initiating therapy to assess hematologic response. In addition, serum ferritin, transferrin saturation, and other iron studies should be evaluated periodically to confirm replenishment of iron stores and resolution of deficiency (Camaschella, 2015). In cases of persistent anemia despite adequate iron therapy, further investigation into underlying causes, such as occult blood loss or malabsorption syndromes, is warranted.

Emerging and Advanced Therapies: Recent research has focused on innovative strategies to improve iron bioavailability and regulate systemic iron metabolism.

- **Hepcidin Antagonists:** These agents target the master regulator of iron homeostasis, hepcidin, promoting intestinal iron absorption and mobilization from macrophage stores. They hold promise for patients with functional iron deficiency due to chronic inflammation (Nemeth & Ganz, 2021).
- **Improved Oral Formulations:** Novel iron salts, including ferric maltol and liposomal iron, offer enhanced absorption with reduced gastrointestinal adverse effects, improving adherence in chronic therapy (Cancelo-Hidalgo et al., 2013).
- **Gene and Molecular Therapies:** Experimental approaches targeting iron regulatory pathways aim to correct genetic defects in iron metabolism or modulate hepcidin expression, potentially offering curative interventions for refractory cases of IDA or inherited iron-refractory anemia (Nemeth & Ganz, 2021).

Overall, a multifaceted approach combining dietary modification, pharmacotherapy, and emerging molecular strategies ensures effective management of IDA, addressing both hematologic deficits and systemic complications associated with iron deficiency. Timely intervention, individualized therapy, and diligent follow-up are critical for restoring iron homeostasis and improving patient outcomes.

Recent Research and Molecular Insights into Iron Deficiency Anemia

Hepcidin Modulation: Hepcidin, a liver-derived peptide hormone, is the master regulator of systemic iron homeostasis. It controls iron absorption from the intestine and iron release from macrophages by binding to the iron exporter ferroportin and inducing its internalization and degradation. In iron deficiency anemia (IDA), hepcidin levels are typically suppressed to enhance iron absorption. However, in inflammatory or chronic disease states, elevated hepcidin can cause functional iron deficiency, rendering conventional iron supplementation less effective (Ganz, 2013).

Recent research has focused on hepcidin-targeted therapies, including hepcidin antagonists, anti-hepcidin antibodies, and modulators of hepcidin expression, which hold promise for refractory or inflammation-associated IDA. Erythroferrone, a hormone secreted by erythroblasts during increased erythropoietic activity, suppresses hepcidin, thereby promoting iron mobilization for hemoglobin synthesis. Understanding the dynamic interplay between erythroferrone, inflammatory cytokines such as IL-6, and hepcidin is pivotal for designing precision therapies that restore iron homeostasis while minimizing adverse effects (Ganz, 2013; Nemeth & Ganz, 2021).

Genetic and Epigenetic Studies: Genetic predisposition plays a significant role in IDA susceptibility, particularly in cases of impaired iron absorption or chronic blood loss. Polymorphisms in genes such as

TMPRSS6, which encodes a serine protease involved in hepcidin regulation, HFE, associated with iron sensing, and TFR2, the transferrin receptor 2, have been linked to altered iron metabolism and increased risk of IDA (Finberg & Heeney, 2014).

Epigenetic regulation, including DNA methylation and histone modifications, is emerging as an important mechanism affecting the expression of iron transporters (DMT1, ferroportin) and storage proteins (ferritin). Environmental factors, diet, and chronic inflammation can influence these epigenetic marks, thereby modulating iron absorption and utilization. Such insights open avenues for **personalized interventions** targeting molecular pathways specific to individual genetic and epigenetic profiles (Finberg & Heeney, 2014; Camaschella, 2015).

Iron and the Gut Microbiome: The gastrointestinal tract plays a central role in iron absorption, and iron availability significantly affects the composition and function of the gut microbiota. Iron supplementation can alter microbial diversity, favoring pathogenic bacteria and potentially contributing to gastrointestinal side effects such as constipation, diarrhea, and inflammation (Zimmermann & Hurrell, 2007).

Recent studies indicate that modulating the gut microbiome may enhance iron bioavailability and reduce adverse effects. Strategies under investigation include co-administration of prebiotics and probiotics with iron therapy, using iron formulations with controlled release to minimize luminal iron excess, and exploring microbial metabolites that promote iron absorption and systemic utilization. These interventions not only optimize therapeutic outcomes but also highlight the intricate link between micronutrient status and host-microbiome interactions, positioning the gut microbiome as a promising target in IDA management (Zimmermann & Hurrell, 2007; Kortman et al., 2014).

Conclusion

Iron Deficiency Anemia is a multifactorial condition with complex hematologic, molecular, and systemic implications. Advances in understanding iron metabolism, cellular regulatory mechanisms, and molecular pathways provide opportunities for precise diagnostics, personalized therapy, and innovative interventions. Early recognition, combined with dietary, pharmacological, and molecular strategies, is critical for preventing complications and improving health outcomes. Ongoing research into hepcidin modulation, gene therapy, and microbiome interactions promises to transform the management of IDA, bridging traditional hematology with cellular and molecular biology for optimized patient care.

Reference

- Andrews, N. C. (2000). Iron homeostasis: insights from genetics and animal models. *Nature Reviews Genetics*, 1(3), 208–217.
- Auerbach, M., & Ballard, H. (2010). Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology/Oncology Clinics of North America*, 24(2), 345–362.
- Beard, J. L. (2001). Iron biology in immune function, muscle metabolism and neuronal functioning. *The Journal of Nutrition*, 131(2), 568S–580S.
- Beard, J. L., & Connor, J. R. (2003). Iron status and neural functioning. *Annual Review of Nutrition*, 23, 41–58.
- Camaschella, C. (2015). Iron-deficiency anemia. *New England Journal of Medicine*, 372(19), 1832–1843.
- Cancelo-Hidalgo, M. J., et al. (2013). Tolerability of different oral iron supplements: a systematic review. *Current Medical Research and Opinion*, 29(4), 291–303.

- Cook, J. D., & Skikne, B. S. (1989). Iron deficiency: definition and diagnosis. *Journal of Internal Medicine*, 226(5), 349–355.
- Cook, J. D., Flowers, C. H., & Skikne, B. S. (2003). The quantitative assessment of body iron. *Blood*, 101(9), 3359–3364.
- Finberg, K. E., & Heeney, M. M. (2014). Iron-refractory iron deficiency anemia. *Hematology/Oncology Clinics of North America*, 28(4), 637–652.
- Ganz, T. (2013). Systemic iron homeostasis. *Physiological Reviews*, 93(4), 1721–1741.
- Ganz, T., & Nemeth, E. (2012). Hepcidin and iron homeostasis. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, 1823(9), 1434–1443.
- Gibson, R. S., Perlas, L., & Hotz, C. (2017). Improving the bioavailability of nutrients in plant foods at the household level. *Proceedings of the Nutrition Society*, 63(2), 243–250.
- Georgieff, M. K. (2017). Iron deficiency in pregnancy and early childhood. *The Lancet*, 390(10097), 2492–2502.
- Hentze, M. W., Muckenthaler, M. U., & Andrews, N. C. (2010). Balancing acts: molecular control of mammalian iron metabolism. *Cell*, 142(1), 24–38.
- Hurrell, R., & Egli, I. (2010). Iron bioavailability and dietary reference values. *The American Journal of Clinical Nutrition*, 91(5), 1461S–1467S.
- Kortman, G. A., Raffatellu, M., Swinkels, D. W., & Tjalsma, H. (2014). Nutritional iron turned inside out: intestinal stress from a gut microbial perspective. *FEMS Microbiology Reviews*, 38(6), 1202–1234.
- Milman, N. (2006). Iron and pregnancy—a delicate balance. *Annals of Hematology*, 85(9), 559–565.
- Nemeth, E., & Ganz, T. (2006). Regulation of iron metabolism by hepcidin. *Annual Review of Nutrition*, 26, 323–342.
- Nemeth, E., & Ganz, T. (2021). Anemia of inflammation: molecular mechanisms and therapeutic targets. *Hematology/Oncology Clinics of North America*, 35(2), 329–345.
- Oexle, H., Gnaiger, E., & Weiss, G. (1999). Iron-dependent changes in cellular energy metabolism: influence on oxygen utilization and reactive oxygen species formation. *Free Radical Biology and Medicine*, 26(9–10), 1122–1129.
- Pavord, S., et al. (2012). UK guidelines on the management of iron deficiency in pregnancy. *British Journal of Haematology*, 156(5), 588–600.
- Rouault, T. A. (2006). The role of iron regulatory proteins in mammalian iron homeostasis and disease. *Nature Chemical Biology*, 2(8), 406–414.
- Weiss, G., & Goodnough, L. T. (2005). Anemia of chronic disease. *New England Journal of Medicine*, 352(10), 1011–1023.
- Wintergerst, E. S., Maggini, S., & Hornig, D. H. (2007). Contribution of selected vitamins and trace elements to immune function. *Annals of Nutrition & Metabolism*, 51(4), 301–323.

- World Health Organization (WHO). (2008). Worldwide prevalence of anaemia 1993–2005. WHO Global Database on Anaemia. Geneva: WHO.
- World Health Organization (WHO). (2016). Guideline: Daily iron supplementation in infants and children. Geneva: WHO.
- Zimmermann, M. B., & Hurrell, R. F. (2007). Nutritional iron deficiency. *Lancet*, 370(9586), 511–520.

Citation: **Jana. K. & Kumari. Dr. A.,** (2025) "Mechanisms and Molecular Insights into Iron Deficiency Anemia: From Hematology to Cellular Biology", *Bharati International Journal of Multidisciplinary Research & Development (BIJMRD)*, Vol-3, Issue-12, December-2025.