Pakistan Journal of Advances in Medicine and Medical Research (PJAMMR)
ISSN: (Online) 2957-5893
Website: https://www.pjammr.com/index.php/pjammr/homepage

Open Access
Volume 4, Issue 2, 2026

A Comprehensive Narrative Review

Iron Deficiency anemia: A Comprehensive Narrative Review

Muhammad Ahsan[1], Hammad Nasir[2], Ali Ahmad[3], Hammad Babur[4], Zuriya Amjad[5], Uswah Khan[6]

[1-6] *Department of Pathobiology and Biomedical Sciences, Faculty of MLT, University of Agriculture, Multan, Pakistan*

Keywords
Iron deficiency anemia; Iron metabolism; Ferritin; Hepcidin; Iron supplementation.

Article History

Received:16-02-2026

Revision:22-03-2026

Accepted:11-05-2026

Published:10-07-2026

Corresponding Author

Muhammad Ahsan

Department of Pathobiology and Biomedical Sciences, Faculty of Medical Laboratory Technology, University of Agriculture, Multan, Pakistan.

Email: m.ahsannisar1485@gmail.com

ORCID ID: 0000-0001-7989-5406

DOI:10.69837/pjammr.v4i2.106

How to Cite This Article: Ahsan M, Nasir H, Ahmad A, Babur H, Amjad Z, Khan U. Iron deficiency anemia: A comprehensive narrative review. Pak J Adv Med Med Res. 2026;4(2):25–36.

ABSTRACT

Background: Iron deficiency anemia (IDA) is the most prevalent nutritional disorder and the most common cause of anemia worldwide, affecting almost two billion people. It remains a significant public health challenge, especially in low- and middle-income countries, among infants, adolescents, pregnant women, and women of reproductive age. Although prevention and treatment are effective, morbidity and poor quality of life persist because of delayed diagnosis and treatment.

Objectives: The goal of the study is to summarize the current evidence on the epidemiology, pathophysiology, clinical presentation, diagnosis, treatment, and prevention of iron deficiency anemia, and to review recent advances and future perspectives for this disease.

Methods: PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library were searched to conduct a narrative review. Systematic reviews, meta-analyses, randomized controlled trials, observational studies, and clinical guidelines from international groups relevant to the clinical question were prioritized for inclusion and considered if published between 2020 and 2025. Where appropriate, landmark studies were featured to provide historical context. Retrieved information was critically analyzed and synthesized to provide an updated perspective on current concepts of iron-deficiency anemia.

Results: Iron deficiency anemia has been shown to adversely affect cognitive performance, immune function, physical performance, pregnancy outcomes, and quality of life. The discovery of the hepcidin pathway and the physiological role of hepcidin–ferroportin have improved diagnosis and personalized treatment approaches. Serum ferritin is the most useful diagnostic biomarker, and soluble transferrin receptor and hepcidin assays are useful in complex clinical settings

Conclusion: Iron deficiency anemia needs to be targeted at its source through early diagnosis, evidence-based treatment, and effective public health interventions to help reduce the global burden of IDA. Further study of new biomarkers and treatments could improve patients' lives and contribute to global efforts to reduce anemia.

INTRODUCTION

Iron deficiency anemia (IDA) is the most common micronutrient deficiency and the leading cause of anemia worldwide, affecting individuals across all age groups and socioeconomic settings. There are estimated to be almost 2 billion people worldwide affected, making IDA a significant public health problem, especially in low- and middle-income countries (LMICs). Infants and children, women of reproductive age, and pregnant women have greater physiological iron requirements, lower iron intake, frequent infections, and less access to health care, resulting in a greater burden. Despite being largely preventable and treatable, IDA remains a major contributor to morbidity, poor cognitive and physical development, decreased productivity at work, adverse pregnancy outcomes, and higher health care costs globally. [1,2]. Iron is involved in many physiological functions, such as oxygen transport, respiration, DNA synthesis, immune function, and enzyme reactions. The majority (two-thirds) of the body's iron is found as hemoglobin in erythrocytes; the remaining iron is stored as ferritin and hemosiderin, or used by enzymes and myoglobin. Intestinal absorption, storage, and recycling by macrophages, as well as physiological losses of iron, must be tightly controlled to maintain homeostasis. A peptide hormone, hepcidin, is the main regulator of systemic iron metabolism by regulating the release and absorption of iron via ferroportin. Loss of this regulatory pathway contributes to absolute and functional iron deficiency. [3,4]. Iron deficiency occurs when iron losses, physiological requirements, and absorption rates exceed dietary intake. These conditions include chronic gastrointestinal bleeding, menstrual blood loss, pregnancy, malnutrition, malabsorption syndromes, inflammatory bowel disease, chronic kidney disease, parasites, and repeated blood donation. The situation can be different, though, in chronic inflammatory diseases, as the body maintains sufficient iron stores. Still, iron is not mobilized from macrophages, and elevated hepcidin levels suppress intestinal iron absorption. As a result, the distinction between absolute and functional iron deficiency is more important in clinical practice. [5,6]. The signs and symptoms of IDA include: decreased exercise tolerance, fatigue and weakness, pallor, impaired cognitive function, decreased immunity, restless legs syndrome, glossitis, koilonychia, and pica. Iron deficiency in children has been linked to decreased neurocognitive functioning and academic performance. In contrast, in pregnancy it has been linked to decreased risks of preterm delivery, low birth weight, maternal morbidity, and perinatal mortality. Such negative results highlight the need for early identification and intervention. [7,8]. The diagnosis of IDA is based on clinical examination and laboratory examinations. In uncomplicated cases, serum ferritin is the most sensitive and specific marker of depleted iron stores; however, in inflammatory conditions, its use may be limited because it is an acute-phase reactant. Other biomarkers have also enhanced diagnostic accuracy, including transferrin saturation, soluble transferrin receptor, reticulocyte hemoglobin content, and serum hepcidin, particularly in patients with chronic inflammatory diseases, chronic kidney disease, and malignancy. With improvements in these diagnostic tools, treatment options can be tailored more precisely to each patient and detected earlier. [9,10]. Treatment of IDA involves identifying and addressing the underlying cause and replenishing iron stores. Oral iron supplementation should be considered first-line treatment for most patients, as it is effective, readily available, and inexpensive. Intravenous iron formulations have, however, been gradually accepted because of their enhanced efficacy in patients with malabsorption, chronic inflammatory conditions, chronic kidney disease, inflammatory bowel disease, or contraindications to oral iron therapy. Besides therapeutic interventions, the following preventive measures remain very important for reducing IDA worldwide: dietary diversification, food fortification, iron supplementation programs, and public health education and awareness. [11,12]. This review provides a comprehensive overview of the epidemiology, pathophysiology, risk factors, clinical manifestations, diagnostic approaches, recent therapeutic advances, and preventive strategies for iron deficiency anemia. It also highlights emerging evidence regarding iron metabolism and contemporary management recommendations to support evidence-based clinical practice and improve patient outcomes.

Materials and Methods

Literature Search Strategy

This narrative review was conducted through a comprehensive search of the published medical literature to summarize current evidence regarding the epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment, and prevention of iron deficiency anemia (IDA). Electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and the Cochrane Library, were systematically searched to identify relevant studies. The search primarily included articles published between January 2020 and June 2025, while landmark studies and internationally recognized guidelines published before 2020 were included when considered essential for historical context and foundational understanding. The search strategy incorporated combinations of Medical Subject Headings (MeSH) terms and free-text keywords, including "iron deficiency anemia," "iron metabolism," "hepcidin," "ferritin," "oral iron therapy," "intravenous iron," "diagnosis," "treatment," "pregnancy," "children," "chronic kidney disease," and "public health." Boolean operators (AND, OR) were applied to optimize retrieval of relevant publications. Eligible articles included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective observational studies, clinical practice guidelines, consensus statements, and high-quality review articles published in English. Studies lacking sufficient scientific rigor, conference abstracts, editorials, letters to the editor, duplicate publications, non-English articles without reliable translations, and studies with limited relevance to the objectives of this review were excluded. The retrieved literature was independently screened for relevance based on titles, abstracts, and full-text articles. Data regarding epidemiology, pathophysiology, clinical presentation, laboratory diagnosis, therapeutic interventions, preventive strategies, and recent advances were extracted and critically synthesized. Preference was given to publications from internationally recognized organizations, including the World Health Organization (WHO), the American Society of Hematology (ASH), the British Society for Hematology (BSH), and peer-reviewed journals indexed in PubMed, Scopus, and Web of Science, to ensure the accuracy, reliability, and contemporary relevance of the evidence presented in this review. Although this was a narrative review, the literature search was performed using a structured methodology based on PRISMA principles to enhance transparency.

Epidemiology of Iron Deficiency Anemia

IDA is the most common nutritional deficiency, and the most common cause of anemia globally, in people of all ages and from all socio-economic groups. The World Health Organization (WHO) estimates that 1.9 billion people on earth are anemic, and nearly half of them are anemic due to iron deficiency. IDA remains a public

health problem despite major advances in health-care systems and nutritional interventions, and the prevalence is high, especially in low- and middle-income countries (LMICs) where poverty, food insecurity, infectious disease, and inadequate access to health-care contribute to this. [13,14]. IDA burden varies across the world by age, sex, geographic region, and socio-economic status. During menstrual bleeding, while as a result of pregnancy and lactation women have higher iron demand, this makes them one of the most vulnerable groups. According to WHO, about 30–40% of all female individuals in the 15–49 age group are anemic, and in the case of women, iron deficiency is the leading cause of anemia. Pregnant women are at even higher risk due to the additional iron needs for fetal growth, development of the placenta, and increased blood volume in the mother. There is evidence that untreated maternal ID affects fetal neurodevelopment, low birth weight, maternal morbidity and mortality, and preterm birth. [13,15]. IDA is also a disproportionately high burden among children and adolescents because of their growth spurts, dietary iron deficiencies, frequent infections, and parasitic infestations. So far, iron deficiency in infancy and childhood has been linked with suboptimal cognitive function, lower psychomotor performance, lower educational attainment, and lifelong behavioral problems. While adequate iron supplementation and food fortification programs have helped to lower the prevalence of the disease in several high-income countries, childhood IDA is still a big problem in many developing countries. [14,16]. Older people are also a high-risk group. Iron deficiency is common in this age group, with chronic gastrointestinal blood loss caused by peptic ulcer disease, colorectal malignancy, inflammatory bowel disease, prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs), and age-related malabsorption. Moreover, several chronic inflammatory conditions, chronic kidney disease, heart failure, and malignancies can cause iron deficiency, with or without normal or elevated iron stores, by impeding iron mobilization via hepcidin. Therefore, it is increasingly important to differentiate between absolute and functional iron deficiency in geriatric medicine. [17]. There continues to be a significant geographical variation in IDA prevalence. Nutritional deficiencies, recurrent parasitic infections, malaria, lack of sanitation and access to health care services are responsible for persistently high prevalence in South Asia and sub-Saharan Africa. In other developed countries, however, much has been accomplished in the fight against iron deficiency, largely because of advances in nutrition, routine prenatal care, food fortification, and early screening programs. However, IDA remains a significant public health problem in vulnerable groups of people in high-income countries, such as older adults, patients with chronic diseases, migrants, and refugees. [13,18]. Iron Deficiency Anemia is a significant public health problem in Pakistan among women, children, and adolescents. Anemia is prevalent among pregnant women and children less than five years old in all the national nutrition surveys that have been conducted. These factors include low dietary diversity, low income, multiple pregnancies with short inter-pregnancy intervals, intestinal parasitic infection, poor maternal nutrition, and low awareness of iron supplements. The disease burden is even higher among rural populations due to limited access to healthcare services and preventive nutrition programs. National iron supplementation and maternal health programs have enhanced awareness, but implementation gaps affect program effectiveness. The establishment, strengthening, and routine implementation of community nutrition programs, fortification policies, and screening will continue to play a crucial role in reducing the burden of IDA in Pakistan. [19]. While age-standardized mortality due to IDA has decreased over the last 30 years, recent analyses of the Global Burden of Disease (GBD) suggest that the overall prevalence remains high due to population growth and aging, and because nutritional inequities have not been resolved. There is also growing evidence that IDA is a significant cause of disability adjusted life years (DALYs), loss of productivity in the workforce, a loss of education, and health-care costs globally. Thus, iron deficiency anemia is a hematological, as well as a major socioeconomic and public health problem that could be prevented, diagnosed, and treated. [20].

Pathophysiology of Iron Deficiency Anemia

Iron is a micronutrient and a key factor in many biological processes, such as oxygen transport, cellular respiration, DNA synthesis, mitochondrial energy production, and immune regulation. About 65-70% of body iron is bound to hemoglobin in circulating erythrocytes, a smaller percentage is in myoglobin, and some of the remaining iron is in iron-containing enzymes and storage proteins (ferritin and hemosiderin). There is no active physiological iron excretory mechanism in the human body, and systemic iron homeostasis is largely regulated by controlling the intestinal absorption of Fe, Fe recycling by macrophages, and Fe storage in the liver and reticuloendothelial system. These well-balanced mechanisms, if disrupted, will eventually result in iron deficiency and the development of iron deficiency anemia (IDA). [21,22].When the iron supply is normal, most of it is absorbed in the upper part of the small intestine, mostly in the duodenum. Heme iron is most readily absorbed and comes from foods that are mainly of animal origin.Heme iron is absorbed more readily and is obtained primarily from animal-based foods. Non-heme iron is bound as Fe^{3+} and needs to be reduced to ferrous (Fe^{2+}) iron by duodenal cytochrome b before it can be transported into enterocytes by divalent metal transporter-1 (DMT1). In enterocytes, iron can be stored in ferritin or released into the circulation by the only known iron exporter, ferroportin. After entering the bloodstream, iron is released in combination with transferrin for use by the bone marrow in erythropoiesis or for storage in the liver, spleen, and macrophages. [22,23].Hepcidin is a peptide hormone produced by the hepatocytes that is the major regulator of systemic iron metabolism. Hepcidin is a molecule that regulates iron homeostasis by binding to ferroportin on enterocytes, macrophages, and hepatocytes, which results in internalization and degradation of ferroportin. Hepcidin increases during inflammation, resulting in decreased iron absorption from the intestine and inhibiting the release of iron from body stores. In contrast, a decrease in hepcidin expression will lead to increased iron availability for erythropoiesis. The level of hepcidin may be modulated by body iron stores, inflammatory cytokines, erythropoietic activity, hypoxia, and circulating iron levels. This regulatory pathway is now considered the main one to be important for understanding both absolute and functional iron deficiency. [23,24].Iron deficiency occurs when the amount of iron consumed and/or absorbed is less than what is needed for the body, or when iron is lost from the body at a higher rate than it is replenished. There are three successive stages of the development of iron deficiency. The first stage is depletion of iron stores, which is indicated by decreased serum ferritin levels and normal hemoglobin concentration. In the second phase, iron-deficiency erythropoiesis occurs when the amount of transferrin saturation decreases, and the amount of iron available to the bone marrow is insufficient, causing impaired hemoglobin synthesis. The last stage is symptomatic iron-deficiency anemia, with decreased hemoglobin levels, microcytes, hypochromic cells, and reduced oxygen-carrying capacity of red blood

cells. [21,25].Absolute iron deficiency is usually caused by an excessive loss of blood, by the lack of dietary iron, by greater physiological needs, or by decreased gastrointestinal absorption. Chronic gastrointestinal bleeding as a result of peptic ulcer disease, colorectal malignancy, inflammatory bowel disease, and long-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) is one of the most common causes in adults. Menstruation and pregnancy greatly increase iron requirements, especially in women of reproductive age, where they can be easily deficient. Impaired iron absorption occurs in the presence of malabsorption disorders, including celiac disease, autoimmune gastritis, Helicobacter pylori infection, and previous bariatric surgery. [24,26].Functional iron is different from absolute iron, as the total body iron can be normal or even high. Still, the demand for iron in erythropoiesis is not met by the mobilization of stored iron from macrophages and hepatocytes. This condition is associated with chronic inflammatory diseases, chronic kidney disease, malignancy, rheumatoid arthritis, inflammatory bowel disease, and chronic infections. Excessive hepcidin production is due to inflammatory cytokines, especially IL-6, which leads to reduced ferroportin activity and sequestration of iron in the reticuloendothelial system. For this reason, circulating iron concentration is reduced in the presence of normal tissue iron levels, resulting in anemia of inflammation and/or mixed iron-deficiency states. [23,27].Iron deficiency affects various organ systems beyond hematopoiesis. Deficient hemoglobin formation decreases oxygen-carrying capacity to peripheral tissues, causing fatigue, weakness, decreased exercise tolerance, and decreased work capacity. Iron also contributes to neuronal development, neurotransmitter synthesis, and mitochondrial activity; thus, deficiency can affect cognitive function, memory, concentration, and psychomotor development, especially in infants and children. Moreover, iron deficiency has been linked to an impaired immune response, susceptibility to infections, disturbed thermoregulation, restless legs syndrome, and decreased quality of life. These systemic effects underscore the need for early diagnosis and prompt correction of iron deficiency to prevent irreversible effects. [25,28].Recent developments in molecular biology have provided new insights into iron metabolism and led to the discovery of new biomarkers, such as soluble transferrin receptor, reticulocyte hemoglobin content, and serum hepcidin, that are useful for earlier diagnosis and personalized therapy. Further studies of the iron regulatory pathways may provide more sensitive diagnostic tests and specific therapeutic approaches for patients with absolute iron deficiency and those with functional iron deficiency. [22,29].

Etiology and Risk Factors of Iron Deficiency Anemia

Iron deficiency anemia (IDA) develops when iron losses, impaired absorption, or increased physiological requirements exceed dietary iron intake, resulting in depletion of body iron stores and impaired erythropoiesis. The etiology of IDA is multifactorial and varies according to age, sex, physiological status, geographical region, and underlying medical conditions. Identification of the primary cause is essential because successful management depends not only on iron replacement but also on correction of the underlying disorder. [30,31]. Inadequate dietary iron intake remains one of the most common causes of IDA, particularly in developing countries. Diets predominantly composed of cereals, legumes, and plant-based foods contain mainly non-heme iron, which has significantly lower bioavailability than heme iron obtained from meat, poultry, and fish. Furthermore, dietary inhibitors such as phytates, polyphenols, calcium, and tannins reduce intestinal iron absorption, whereas vitamin C and organic acids enhance non-heme iron absorption. Malnutrition, food insecurity, and poor dietary diversity therefore remain major contributors to iron deficiency worldwide, particularly among children and economically disadvantaged populations. [30,32]. Chronic blood loss is the leading cause of iron deficiency anemia in adults. In premenopausal women, excessive menstrual bleeding (menorrhagia) represents the most frequent cause of iron depletion. Pregnancy further increases iron requirements because of expanding maternal blood volume, placental development, and fetal growth, making pregnant women particularly susceptible to iron deficiency. Repeated pregnancies with short interpregnancy intervals further increase the risk of developing anemia. In men and postmenopausal women, chronic gastrointestinal blood loss should always be investigated, as it may indicate peptic ulcer disease, colorectal carcinoma, gastric malignancy, inflammatory bowel disease, angiodysplasia, hemorrhoids, or prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs). [31,33]. Impaired intestinal iron absorption represents another important cause of IDA. Iron absorption primarily occurs in the duodenum and proximal jejunum; therefore, disorders affecting these regions significantly reduce iron uptake. Celiac disease, autoimmune atrophic gastritis, inflammatory bowel disease, Helicobacter pylori infection, bariatric surgery, and extensive small bowel resection are well-recognized causes of malabsorption-related iron deficiency. In addition, prolonged use of proton pump inhibitors may reduce gastric acid secretion, impairing the conversion of ferric iron to the more absorbable ferrous form and consequently decreasing iron absorption. [34,35]. Several chronic medical conditions contribute to functional iron deficiency through inflammation-mediated disruption of iron homeostasis. Chronic kidney disease, chronic heart failure, rheumatoid arthritis, inflammatory bowel disease, chronic liver disease, malignancies, and persistent infections increase circulating inflammatory cytokines, particularly interleukin-6 (IL-6), which stimulates hepatic hepcidin production. Elevated hepcidin inhibits ferroportin-mediated iron export from enterocytes and macrophages, thereby reducing circulating iron availability despite adequate or increased iron stores. Consequently, patients may develop functional iron deficiency or anemia of chronic disease, often requiring specialized diagnostic evaluation and individualized treatment strategies. [36].Infants, young children, and adolescents represent high-risk groups because of rapid growth and increased iron requirements. Exclusive breastfeeding beyond six months without appropriate iron-rich complementary feeding, low birth weight, prematurity, frequent infections, and parasitic infestations substantially increase the risk of iron deficiency during childhood. During adolescence, accelerated growth and, in females, the onset of menstruation further increase physiological iron demands. Iron deficiency during these developmental stages may adversely affect neurocognitive function, learning ability, behavior, and physical growth, emphasizing the importance of early nutritional intervention and routine screening. [32,37]. Older adults also experience an increased risk of iron deficiency anemia because of multiple coexisting factors, including chronic gastrointestinal blood loss, reduced dietary intake, age-related malabsorption, polypharmacy, chronic inflammatory disorders, and malignancies. Because gastrointestinal malignancy may present solely as iron deficiency anemia in elderly patients, comprehensive gastrointestinal evaluation is recommended, particularly in men and postmenopausal women without an obvious source of blood loss. Early identification of the underlying etiology is essential for improving patient outcomes and

excluding serious pathology. [31,38]. Socioeconomic and environmental determinants play an equally important role in the development of IDA. Poverty, inadequate healthcare access, poor sanitation, recurrent parasitic infections, malaria, and limited nutritional awareness remain major contributors in many low- and middle-income countries. Women with limited education, large family size, poor antenatal care, and low household income are particularly vulnerable. Public health strategies, including dietary diversification, food fortification, iron supplementation programs, deworming initiatives, maternal health services, and health education, have demonstrated significant reductions in the prevalence of iron deficiency when implemented effectively. [39].Understanding the diverse causes and risk factors of iron deficiency anemia enables clinicians to adopt a comprehensive diagnostic approach that identifies both nutritional deficiencies and underlying pathological conditions. Management should therefore focus not only on correcting anemia but also on addressing the precipitating cause to prevent recurrence and improve long-term clinical outcomes. [40].

Diagnostic Evaluation of Iron Deficiency Anemia

The accurate diagnosis of iron deficiency anemia (IDA) should be based on a systematic approach that includes both clinical evaluation and laboratory investigations to confirm iron deficiency and determine its severity and cause. The importance of early diagnosis is that iron deficiency can persist for several months before the development of anemia, allowing appropriate interventions to be implemented and preventing further progression of the disease and its consequences. Current diagnostic tools incorporate classical hematological variables with new, emerging biomarkers which enhance the diagnostic accuracy, especially in patients with chronic inflammatory diseases and complex clinical conditions. [41,42]

Clinical Assessment

The first step in evaluation is a thorough medical history and physical exam. Dietary habits, menstrual history, pregnancy, gastrointestinal symptoms, previous gastrointestinal surgery, chronic diseases, family history of hematological disorders, medication history, especially nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs), and blood donation history should be assessed. Fatigue, weakness, dizziness, exertional dyspnea, palpitation, headache, decreased exercise tolerance, pica and RLS are common symptoms. Patients with moderate or severe anemia may have pallor of the conjunctiva, skin, tachycardia, koilonychia, glossitis, and a systolic flow murmur. Determining the possible source of chronic blood loss is an important part of the diagnostic workup. [41,43]

Complete Blood Count (CBC)

A full blood count (FBC) is the first lab test used if IDA is suspected. The hemoglobin concentration decreases in proportion to the severity of the anemia; the mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) are generally decreased, indicating microcytic, hypochromic erythrocytes. Red cell distribution width (RDW) is often elevated due to increased variation in RBC size, especially in the early stages of the disease. These findings are highly indicative of iron deficiency, but the same abnormalities can be seen in thalassemia and anemia of chronic disease, so further iron tests are needed. [42,44]

Peripheral Blood Smear

Peripheral blood smears are useful for obtaining morphological information. Classical abnormalities are microcytosis, hypochromia, anisocytosis, poikilocytosis, elliptocytes, and rare pencil-shaped erythrocytes. In late stages of the disease, blood red cell size and form may vary. The peripheral smear also helps rule out other causes of microcytic anemia such as thalassemia, sideroblastic anemia, and lead poisoning. [44,45]

Iron Studies

Serum ferritin is considered the most sensitive and specific laboratory test for diagnosing absolute iron deficiency, as it reflects total body iron stores. In the absence of diseases associated with iron deficiency, serum ferritin levels of less than 15-30 ng/mL are strongly indicative of low iron stores. It is also an acute-phase reactant, so it is not very useful in chronic inflammatory, infective, liver, or malignant diseases, where it may be normal or raised. [45,46]. Other iron tests involve the serum iron level, total iron-binding capacity (TIBC), and transferrin saturation (TSAT). Patients with IDA tend to have low serum iron, high TIBC, and low transferrin saturation (<20%), indicating a reduced availability of iron for red blood cell production. These parameters are complementary to ferritin level measurements and help enhance diagnosis, especially in cases of an ambiguous ferritin level. [46]

Emerging Biomarkers

Recent developments have led to the emergence of several biomarkers to enhance diagnosis in complex clinical situations. The concentration of soluble transferrin receptor (sTfR) is elevated in iron deficiency. Still, it is relatively spared of the influence of inflammation and can be used to distinguish iron deficiency from anemia of chronic disease. Likewise, the soluble transferrin receptor-to-log ferritin index has proved to be a good discriminator in inflammatory diseases. [47].Hepcidin has become an interesting biomarker due to its role in regulating systemic iron metabolism. Low hepcidin levels are seen in absolute iron deficiency, and high levels are seen in inflammatory conditions that lead to functional iron deficiency. Hepcidin assays are not available in most clinical laboratories, but are being assessed for personalized diagnostics and therapy. [48] Reticulocyte hemoglobin content (Ret-He or CHr) is an early indicator of availability of iron for erythropoiesis because it reflects the hemoglobin content of newly formed reticulocytes. The decrease in reticulocyte hemoglobin can be used to detect iron deficiency earlier than changes in conventional hematological indices, and it can be especially useful for assessing the effectiveness of iron treatment and diagnosing early iron deficiency. [49]

The study of bone marrow iron to measure body iron stores.

The gold standard for assessing iron stores remains bone marrow aspiration with Prussian blue staining, which directly demonstrates the presence or absence of stainable iron in macrophages. Due to its invasiveness, discomfort, and limited clinical utility, routine bone marrow examination is not performed. It is reserved for cases where lab diagnosis remains inconclusive or bone marrow disease is suspected. [50]

Diagnostic Algorithm

The patient with suspected IDA should be evaluated by a systematic approach starting with the clinical assessment and CBC, followed by peripheral blood smear and serum ferritin level measurement. If the ferritin result is inconclusive or inflammatory conditions are present, additional tests may be performed, such as hepcidin, soluble transferrin receptor, reticulocyte hemoglobin analysis, and transferrin saturation. If iron deficiency has been confirmed, further evaluation of the underlying disease should be performed using the appropriate gastrointestinal, gynecological, nutritional, or chronic inflammatory disease evaluation to guide definitive treatment and prevent recurrence. [42,50].

Table 1. Major Causes and Risk Factors of Iron Deficiency Anemia

Category	Common Causes	Clinical Examples
Inadequate dietary intake	Low iron consumption, poor dietary diversity, vegetarian or vegan diets without adequate supplementation	Malnutrition, food insecurity, diets rich in phytates and low in heme iron
Increased physiological requirements	Increased iron demand exceeding dietary intake	Pregnancy, lactation, infancy, adolescence, rapid growth, multiple pregnancies
Chronic blood loss	Persistent iron loss through bleeding	Menorrhagia, gastrointestinal bleeding, colorectal cancer, peptic ulcer disease, hemorrhoids, inflammatory bowel disease, hookworm infection
Impaired iron absorption	Reduced intestinal absorption of iron	Celiac disease, Helicobacter pylori infection, bariatric surgery, inflammatory bowel disease, autoimmune gastritis, prolonged proton pump inhibitor use
Functional iron deficiency	Adequate iron stores with impaired iron utilization due to inflammation	Chronic kidney disease, heart failure, rheumatoid arthritis, chronic infections, malignancy
Parasitic and infectious diseases	Increased iron loss or inflammation	Hookworm infestation, schistosomiasis, malaria
Repeated blood loss or donation	Continuous depletion of iron stores	Frequent blood donation, repeated surgical procedures, trauma
Genetic and rare disorders	Less common causes affecting iron metabolism	Iron-refractory iron deficiency anemia (IRIDA), hereditary disorders affecting iron regulation
Socioeconomic factors	Poor nutrition and limited healthcare access	Poverty, poor sanitation, inadequate antenatal care, limited nutritional education

Table 1 summarizes the major etiological factors and risk conditions associated with iron deficiency anemia. Nutritional deficiency, chronic blood loss, impaired intestinal absorption, and increased physiological iron requirements remain the principal causes worldwide. In contrast, chronic inflammatory diseases contribute to functional iron deficiency through hepcidin-mediated dysregulation of iron metabolism.

Table 2. Laboratory Diagnosis of Iron Deficiency Anemia

Investigation	Typical Finding in Iron Deficiency Anemia	Diagnostic Significance
Hemoglobin (Hb)	Decreased	Confirms severity of anemia
Mean corpuscular volume (MCV)	Decreased	Indicates microcytic anemia
Mean corpuscular hemoglobin (MCH)	Decreased	Indicates hypochromic erythrocytes
Red cell distribution width (RDW)	Increased	Early marker of anisocytosis
Peripheral blood smear	Microcytosis, hypochromia, anisopoikilocytosis, pencil cells	Supports diagnosis and excludes alternative causes
Serum ferritin	Low (<15–30 ng/mL)	Best indicator of depleted iron stores in uncomplicated IDA
Serum iron	Decreased	Reflects reduced circulating iron
Total iron-binding capacity (TIBC)	Increased	Indicates increased transferrin production
Transferrin saturation (TSAT)	<20%	Demonstrates reduced iron availability for erythropoiesis
Soluble transferrin receptor (sTfR)	Increased	Helpful in differentiating IDA from anemia of chronic disease
Reticulocyte hemoglobin content (Ret-He/CHr)	Decreased	Early marker of iron-restricted erythropoiesis
Serum hepcidin	Low in absolute IDA; elevated in functional iron deficiency	Assesses iron regulation and inflammatory status
Bone marrow iron staining	Absent stainable iron	Gold standard for assessing iron stores; rarely required clinically

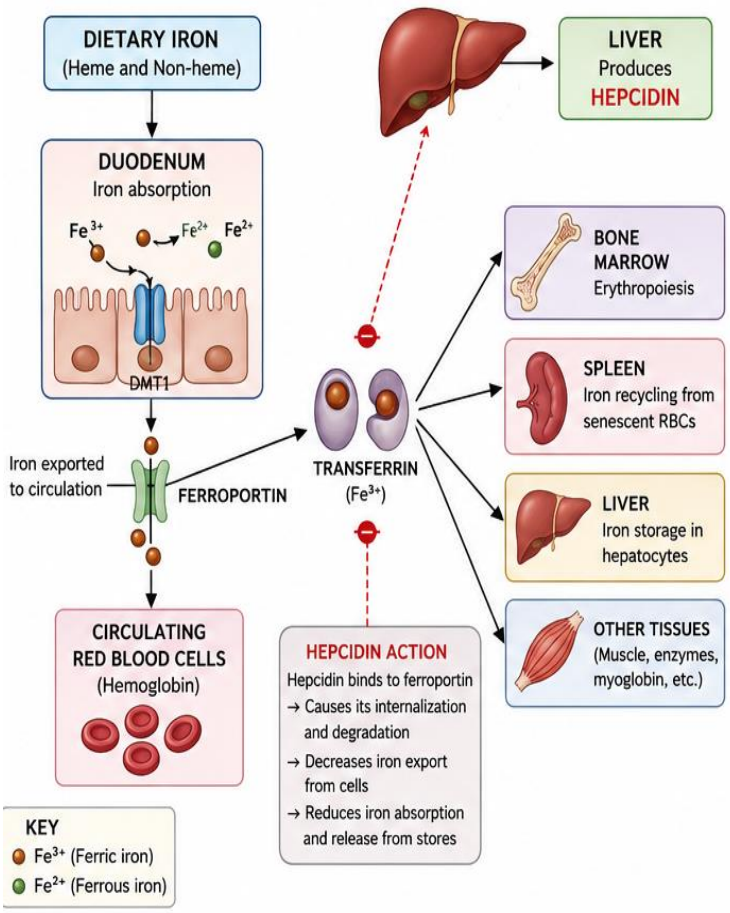
Table 2 outlines the principal laboratory investigations used for diagnosing iron deficiency anemia. Serum ferritin remains the preferred biomarker for assessing iron stores, while transferrin saturation, soluble transferrin receptor, reticulocyte hemoglobin content, and hepcidin improve diagnostic accuracy in patients with chronic inflammatory disorders or equivocal laboratory findings.

Table 3. Comparison of Oral and Intravenous Iron Therapy

Characteristic	Oral Iron Therapy	Intravenous Iron Therapy
Route of administration	Oral tablets or capsules	Intravenous infusion
Common preparations	Ferrous sulfate, ferrous fumarate, ferrous gluconate	Ferric carboxymaltose, iron sucrose, ferric derisomaltose, ferumoxytol
Indications	Mild-to-moderate iron deficiency anemia	Severe anemia, malabsorption, inflammatory bowel disease, chronic kidney disease, intolerance to oral iron, need for rapid iron replacement.
Bioavailability	Variable; influenced by diet and gastrointestinal absorption	Nearly 100% bioavailability
Time to hematologic response	2–4 weeks	Often within 1–2 weeks
Total duration of therapy	Usually 3–6 months after normalization of hemoglobin	Often completed in one or a few infusion sessions
Advantages	Inexpensive, widely available, convenient	Rapid correction of iron deficiency, bypasses gastrointestinal absorption, better adherence in selected patients.
Limitations	Poor gastrointestinal tolerance, reduced adherence, slower response	Higher cost, infusion facility required, monitoring during administration
Common adverse effects	Nausea, constipation, diarrhea, abdominal discomfort, metallic taste	Infusion reactions, transient hypotension, headache, arthralgia; severe hypersensitivity reactions are rare with newer formulations
Preferred patient groups	Uncomplicated iron deficiency anemia	Chronic kidney disease, inflammatory bowel disease, pregnancy (second and third trimester when indicated), ongoing blood loss, functional iron deficiency

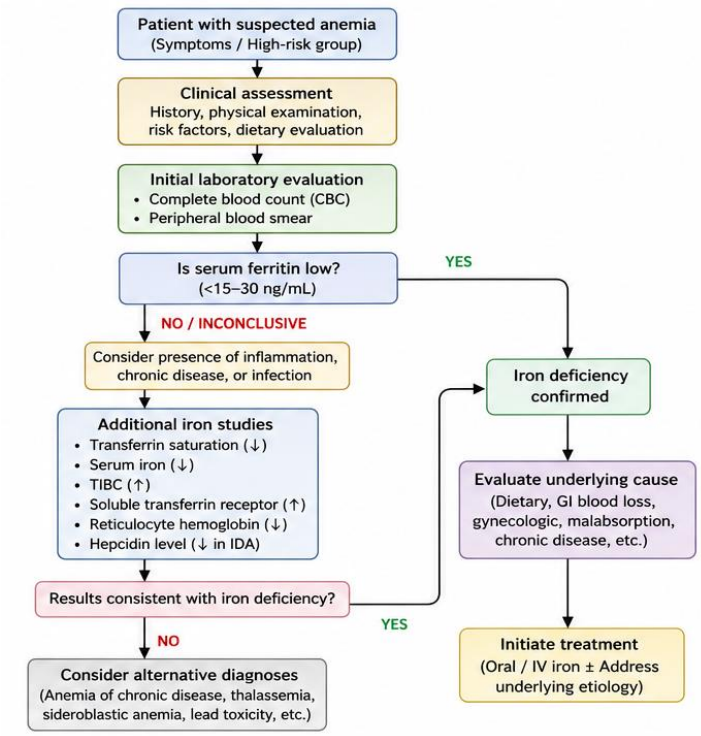
Table 3 compares the characteristics of oral and intravenous iron therapy for the treatment of iron deficiency anemia. Oral iron remains the first-line treatment for most uncomplicated patients because of its low cost and accessibility. In contrast, intravenous iron provides faster and more effective iron replacement in patients with malabsorption, chronic inflammatory disorders, chronic kidney disease, intolerance to oral preparations, or when rapid correction of iron deficiency is clinically indicated.

Figure 1. Overview of Iron Metabolism and Hepcidin-Regulated Iron Homeostasis.



Iron is absorbed predominantly in the duodenum through divalent metal transporter-1 (DMT1) after dietary ferric iron (Fe^{3+}) is reduced to ferrous iron (Fe^{2+}). Following absorption, iron is exported from enterocytes into the circulation by ferroportin, where it binds to transferrin for transport to the bone marrow for erythropoiesis and to the liver, spleen, and other tissues for storage and utilization. Hepcidin, a peptide hormone synthesized by the liver, is the principal regulator of systemic iron homeostasis by promoting ferroportin internalization and degradation, thereby reducing intestinal iron absorption and the release of iron from macrophages and hepatic stores. Decreased hepcidin expression enhances iron availability for erythropoiesis, whereas increased hepcidin levels contribute to iron sequestration and functional iron deficiency.

Figure 2. Diagnostic Algorithm for the Evaluation and Management of Iron Deficiency Anemia.



The diagnostic evaluation of suspected iron-deficiency anemia begins with a clinical assessment, including a detailed medical history, physical examination, and a complete blood count with a peripheral blood smear. Serum ferritin is the preferred initial laboratory marker for assessing iron stores. In patients with normal or equivocal ferritin levels, particularly in the presence of chronic inflammation, additional investigations including serum iron, total iron-binding capacity (TIBC), transferrin saturation (TSAT), soluble transferrin receptor (sTfR), reticulocyte hemoglobin content (Ret-He), and serum hepcidin may improve diagnostic accuracy. Once iron deficiency is confirmed, evaluation of the underlying etiology—including dietary insufficiency, gastrointestinal blood loss, gynecological causes, malabsorption syndromes, or chronic inflammatory disorders—should be performed to guide appropriate treatment and prevent recurrence.

Management and Treatment of Iron Deficiency Anemia

The main aims of iron deficiency anemia (IDA) management include replenishing iron stores, restoring normal hemoglobin levels, relieving symptoms, enhancing quality of life, and identifying and addressing the cause of iron deficiency to prevent recurrence. Treatment will be based on the severity of anemia, etiology, comorbidities, the need for correction of anemia, and the patient's tolerance to iron supplementation. There is no "one-size-fits-all" treatment recommended for all patients, as current international guidelines call for treatment to be tailored to each patient's clinical presentation and laboratory parameters. In most cases, oral iron should be used first, and intravenous iron is indicated in clinical situations requiring rapid, more effective iron replacement. [51,52].

Dietary Modification

Nutritional counseling is an essential part of the management of IDA, especially in those with a poor diet. Iron-rich foods: red meat, poultry, fish, liver, eggs, legumes, beans, lentils, spinach, fortified cereals, dried fruits, should be encouraged. Heme iron is highly bioavailable compared to non-heme iron from plants. In addition to the above, vitamin C-rich foods like oranges, tomatoes, and guavas also increase the absorption of non-heme iron by converting it to its more absorbable form, ferrous iron, in the intestinal tract. On the other hand, tea, calcium-rich foods, or phytate-containing cereals can interfere with iron absorption and should not be taken at the same time as an iron supplement or an iron-rich food. The nutritional approach, in most cases, is not sufficient to treat existing anemia but can be a valuable supportive component of pharmacologic treatment and preventive measures. [53].

Oral Iron Therapy

Oral iron supplementation is the first-line treatment for most patients with mild to moderate IDA and is the most affordable, effective, and accessible option. Typical iron salts that are used are ferrous sulfate, ferrous fumarate, and ferrous gluconate. The available evidence indicates that elemental iron doses of 40–100 mg daily or every other day are the most effective dosage to optimize iron absorption and to minimize the gastrointestinal side effects, ranging from inhibition of iron absorption by hepcidin to diarrhea. If the treatment is effective and adherence to it is good, hemoglobin levels rise by around 1- 2 g/dL in 2- 4 weeks. Therapy should be continued for at least 3 months after hemoglobin normalization to replenish iron stores fully. [51,54]. The main drawback of oral iron therapy is gastrointestinal adverse effects. Often, the occurrence of nausea, constipation, abdominal discomfort, diarrhea, epigastric pain, and metallic taste diminishes treatment adherence. Iron may be better tolerated when taken with food, but it can be less well absorbed. Before starting IV therapy, other options to try include alternate-day dosing, elemental iron doses of less than 20 mg/day, or switching to a different oral iron formulation if intolerance develops. [54,55].

Intravenous Iron Therapy

Increased recognition and use of IV iron have developed in the treatment of IDA, especially in individuals who cannot tolerate oral iron, have compromised gastrointestinal absorption, are at risk of rapid iron replacement, and those who are experiencing persistent blood loss. The indications for clinical use are inflammatory bowel disease, chronic kidney disease (CKD), severe anemia that needs to be corrected quickly, functional iron deficiency, and poor compliance with oral treatment. Modern iron formulations (ferric carboxymaltose, iron sucrose, ferric derisomaltose, ferumoxytol) allow large doses of iron to be administered over a short period and have better efficacy and safety profiles than earlier formulations. Within 2-4 weeks after infusion, most patients show substantial improvement in hemoglobin concentration. [52,56]. Intravenous iron is well tolerated, but may cause transient adverse effects such as headache, nausea, flushing, arthralgia, hypotension, and infusion site reactions. Although rare, extreme hypersensitivity reactions are still possible with newer formulations, and adequate monitoring during administration is still recommended. [56].

Blood Transfusion

Transfusion of red blood cells is not recommended as routine therapy for iron-deficiency anemia because it does not replace iron stores and only temporarily corrects anemia. Transfusion should be used to restore oxygen-carrying capacity in patients with severe anemia and cardiac instability, acute blood loss, acute cardiovascular decompensation, or when Hb is very low and immediate restoration of oxygen-carrying capacity is essential. Always provide iron replacement with transfusion; this is to correct the underlying iron deficiency and prevent recurrence. [57].

Monitoring Treatment Response

It is important to monitor the treatment response clinically and biochemically. Improvement from fatigue and exercise tolerance usually occurs within a few weeks of the start of treatment. Reticulocytosis occurs within 7–10 days, and the hemoglobin concentration rises by about 1–2 g/dL every 2–3 weeks thereafter. The iron and CBC levels should be retested every 4 to 8 weeks for therapeutic response and to confirm iron stores replenishment. If the patient does not respond to treatment, treatment adherence, continued blood loss, malabsorption, incorrect diagnosis, or treatment of other inflammatory diseases should be evaluated. [52,58]

Management of Iron Deficiency Anaemia in Chronic Kidney Disease.

Chronic kidney disease patients are highly susceptible to iron deficiency due to low dietary intake, altered gastrointestinal iron absorption, chronic inflammation, frequent blood draws, and erythropoiesis-stimulating agent therapy. Periodic monitoring of SF and TS is recommended in CKD patients per international nephrology guidelines. Since IV iron is more effective for iron replacement and in enhancing ESA responsiveness, it is generally preferred in individuals on hemodialysis. It is especially important to have specific treatment plans when iron deficiency is functional because of high hepcidin levels, which is common in CKD. [59]

Management During Pregnancy

Fetal growth and development, placental development, and the increased blood volume of the mother all contribute to the significantly increased iron demands of pregnancy. The simple blood test for anemia is advised throughout pregnancy. Oral iron is the initial treatment for mild anemia, and intravenous iron may be beneficial in the second or third trimester in women who are severely anemic, unable to tolerate oral iron, or do not respond to it. Early correction of ID in mother helps prevent low birth weight, postpartum hemorrhage, maternal morbidity, and preterm birth. [60]

Functional Iron Deficiency

Functional iron deficiency is not absolute iron deficiency, since the total level of body iron stores can be normal or even elevated. Still, iron is not available for erythropoiesis due to the increased hepcidin in the presence of inflammation. It is a common disease in chronic kidney disease, heart failure, inflammatory bowel disease, rheumatoid arthritis, and cancer. Treatment is directed towards treating the

underlying inflammatory disorder, and IV iron is administered as indicated. New drugs in development target hepcidin and are likely to be a new treatment option for patients with functional iron deficiency. [61].Treatment of iron deficiency anemia is a multifaceted process involving correction of iron deficiency and identification and treatment of its cause. Optimal clinical outcomes with minimal recurrence and long-term complications are achieved through individualized therapy based on disease severity, patient characteristics, and associated comorbidities.

Every component must include a Prevention and Public Health Strategies section.

This is because iron deficiency anemia (IDA) is a common health problem and a significant public health problem that is widespread and can have a significant impact on women's health, fetal development, work productivity, and health care costs. Interventions at the individual, community, and national levels on nutrition, infectious diseases, socioeconomic determinants, and healthcare access need to be coordinated and effective for prevention. The World Health Organization (WHO) suggests that IDA can be prevented through a comprehensive approach that includes dietary diversification, food fortification, iron supplementation, regular screening of high-risk groups, and prevention of infections. [62,63]

Food Fortification and Dietary Diversification

Food fortification is one of the most cost-effective public health interventions for preventing ID. In many countries, fortification of staple foods such as wheat flour, rice, maize flour, and infant cereals with iron has substantially helped curb iron deficiency. Dietary diversification also bolsters iron intake by making it easier to eat iron-rich foods, such as red meat, poultry, fish, legumes, green leafy vegetables, and fortified cereals, more regularly. Vitamin C-rich foods should also be encouraged in public health campaigns to facilitate non-heme iron absorption, and communities should be reminded not to drink tea/coffee or consume calcium-rich foods right before or after iron-rich foods, as this would hinder iron absorption. [63,64]

Iron Supplementation Programs

The prevention of iron deficiency through routine iron supplementation remains a key practice recommended for populations at elevated risk of iron deficiency. For pregnant women, WHO recommends iron and folic acid supplementation at a daily dose of 200 micrograms to reduce maternal anemia, low birth weight, and preterm birth. There is also a recommendation for preventive supplementation for infants, young children, adolescent girls and women of reproductive age in areas of high anemia prevalence. Community-based supplementation (CBS) is effective at substantially reducing anemia levels and associated outcomes compared with primary health care delivery systems. [62,65]

Infection Control and Deworming

In many low- and middle-income countries, parasitic infections (such as hookworm and schistosomiasis) are significant causes of chronic blood loss and iron deficiency. Control of anemia is part of the overall deworming program, sanitation, availability of good drinking water, and malaria prevention strategies. Supplementation with iron, along with infection prevention programs, is more effective at reducing anemia than iron supplementation alone. [66]

Maternal and Child Health Programs

Maternal and child healthcare services offer valuable opportunities for early detection and prevention of iron deficiency. Basic prevention measures are routine antenatal screening, nutritional counseling, iron and folic acid supplementation, birth spacing, breastfeeding support, and timely introduction of iron-rich complementary foods. School-based nutrition education and anemia screening programs also support early detection and intervention for children and adolescents, helping to prevent potential long-term effects of iron deficiency on growth, cognition, and school performance. [65,67]

Pakistan Perspective

Iron-deficiency anemia is still a major public health problem in Pakistan and especially among young children and women of reproductive age who are pregnant. Some of the contributing factors are inadequate dietary intake, multiple pregnancies, poverty, poor access to health care, parasites, and low nutrition awareness. The national burden of IDA can be reduced by strengthening national food fortification programs, expanding antenatal supplementation programs, enhancing community nutrition education, conducting school-based screening, and integrating the prevention of IDA into primary healthcare services. Ongoing monitoring and population-based research are needed to evaluate the effectiveness of the program and to inform public health evidence-based policy decisions. [68]

Future Perspectives

Advances in the field of iron metabolism, in recent years, have changed the way iron deficiency anemia is understood and treated, providing opportunities for more sophisticated diagnostics and treatments. The potential therapies are the most exciting: those that target the hepcidin–ferroportin pathway, the key control point in systemic iron homeostasis. Patients with functional iron deficiency due to chronic inflammatory diseases, chronic kidney disease, and heart failure may benefit from experimental agents that inhibit overactive hepcidin or promote ferroportin function, thereby increasing iron availability. There are several hepcidin inhibitors and ferroportin modulators currently in clinical trials. [69]The use of nanotechnology is also a new method for iron replacement therapy. Nanoparticle-based iron formulations aim to enhance iron bioavailability, minimize gastrointestinal adverse effects, and enable targeted delivery of iron to tissues while minimizing oxidative stress. These preparations are still being studied, but preliminary research indicates that they could be alternative, safer, and more effective iron therapy formulations for certain patient populations. [70]Technology, such as artificial intelligence (AI) and machine learning, is also becoming an increasingly important part of healthcare systems to aid in the early detection of iron deficiency anemia (IDA). An automated method for identifying high-risk patients prior to clinically significant anemia could be developed by combining predictive algorithms with electronic health record data, complete blood count parameters, biochemical markers, and demographics. These technologies have the potential to enhance diagnostic accuracy, inform optimal treatment options, and facilitate population-based screening programs. [71]IDA management in the future is anticipated to be directed towards personalized

medicine, where treatment strategies will be customized based on the individual's genetic susceptibility, inflammatory status, iron metabolism markers, and therapeutic response. These promising methods need to be confirmed by ongoing research in translation and carefully designed clinical trials to enhance long-term patient outcomes. [69–71]

Limitations

This narrative review aims to compile and summarize existing evidence related to the epidemiology, pathogenesis, diagnosis, prevention, and treatment of iron deficiency anemia. Several caveats must be noted, however. The review is mainly based on published literature and international clinical guidelines, which could result in publication bias and variations in outcomes reported. Differences in study design, diagnostic criteria, and patient populations may limit comparisons between studies. Further, new disease markers and drugs are being developed, and new evidence may change how this is recommended. Hence, the outcomes must be taken in the context of the updated clinical guidelines and the individual patient.

Conclusion

IDA is the most common nutritional deficiency disorder. It is the most common indicator of anemia among people of all ages, particularly in women, children, and low- and middle-income countries. Despite its high preventability and treatability, IDA remains a significant cause of morbidity, mental retardation, physical inactivity, poor birth outcomes, and poor quality of life. Appropriate clinical assessment and laboratory evaluation are critical for early recognition, prompt diagnosis, and effective treatment. There is current evidence to suggest a holistic approach in which iron deficiency is corrected, and the underlying cause is identified and treated. Oral iron is the first-line therapy in uncomplicated cases, whereas those with malabsorption, chronic inflammatory disorders, or severe anemia will benefit from intravenous iron, which is rapid and effective. Prevention strategies such as nutritional education, iron supplementation, maternal health assistance, infection control, routine screening of vulnerable groups, and food fortification play a crucial role in mitigating the global disease burden. New therapeutic approaches targeting hepcidin, new iron formulations, artificial intelligence–assisted diagnostics, and personalized treatment strategies hold promise to enhance the future treatment of iron deficiency anemia. Further research, more effective public health campaigns, and greater access to evidence-based treatment are critical to ensuring that the overall burden and impact of this widely distributed disorder are reduced globally in the long term.

Acknowledgments

The authors acknowledge the valuable contributions of researchers, healthcare professionals, and international organizations whose work has advanced the understanding of iron deficiency anemia. The authors also appreciate the efforts of clinicians and public health workers involved in the prevention, diagnosis, and management of iron deficiency anemia worldwide.

Conflict of Interest: The authors declare no conflicts of interest related to this review article.

Funding: The authors received no financial support from any funding agency in the public, commercial, or not-for-profit sectors for the preparation of this manuscript.

Data Availability Statement

No new datasets were generated or analyzed during the preparation of this review. All information presented is derived from previously published studies, international guidelines, and publicly available literature cited in the reference list.

Ethical Approval

Ethical approval was not required because this study is a narrative review based exclusively on previously published literature and did not involve human participants, animals, or identifiable patient data.

Authors' Contributions (ICMJE)

Muhammad Ahsan: Contributed to literature review, manuscript drafting, critical revision of the intellectual content, and approved the final manuscript.
Hammad Nasir: Participated in literature search, data interpretation, manuscript writing, language editing, critical revision, and approved the final manuscript.
Ali Ahmad: Contributed to data acquisition, literature review, manuscript revision, and approved the final manuscript.
Hammad Babur: Assisted in literature search, critical appraisal of the evidence, manuscript editing, and approved the final manuscript.
Zuriya Amjad: Conceived and designed the review, coordinated the literature search, drafted the manuscript, supervised the project, critically revised the manuscript, and approved the final version.
Uswah Khan: Participated in literature review, data synthesis, manuscript editing, critical revision for important intellectual content, and approved the final manuscript.
ICMJE Statement

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