Editorial

Global Burden and Trends of Iron Deficiency with and without Anemia

Prof. Dr. Azhar Masud Bhatti
Editor-in-Chief

Introduction

Iron deficiency (ID) and iron deficiency anemia (IDA) are global health issues frequently encountered in daily clinical practice. Iron deficiency without anaemia is poorly recognised by clinicians despite its high prevalence, probably because of suboptimal screening recommendations. Diagnosing IDWA relies on a combination of tests, including haemoglobin and ferritin levels, as well as transferrin saturation.

Iron deficiency anaemia (IDA) currently affects 1.2 billion people and iron deficiency without anaemia (IDWA) is at least twice as common. ID is the most common nutritional deficiency worldwide, affecting up to 25% of the global population, or nearly 2 billion people[1]. Recent 2024-25 research highlights that iron deficiency remains a critical global health crises with studies projecting the burden persist through 2050.

Children and women of reproductive age are particularly affected by ID due to increased iron requirements. ID arises when the body's iron stores, particularly those in macrophages and hepatocytes, are depleted. Because most iron—approximately 25 mg daily—is used for hemoglobin (Hb) synthesis to support the production of around 200 billion red blood cells each day, IDA is the most evident consequence of ID. This often leads to the mistaken belief that ID and IDA are the same. However, ID is a broader condition that can precede the onset of IDA or impact other tissues beyond those involved in red blood cell production.

ID can be classified into three stages. In the first stage, which is characterized as mild ID, iron stores are depleted but the production of iron-dependent proteins is maintained. It was previously believed that the absence of iron stores had no adverse health effects. However, accumulating evidence suggests that even mild ID can lead to symptoms such as fatigue, cognitive impairment, reduced aerobic performance, compromised immune function, and poor sleep quality. The prevailing body of research strongly supports the need to prevent and manage even mild ID, not only in growing individuals and menstruating and pregnant women, but also in endurance athletes and the elderly to promote optimal health and development. In the second stage, also known as iron-deficient erythropoiesis, the requirements for iron in erythropoiesis are no longer fully met, but Hb synthesis and erythropoiesis are maintained. Also, the production of iron-dependent proteins may be disrupted. The third stage is IDA, characterized by impaired Hb production. In IDA, erythrocytes are typically microcytic (smaller than normal red blood cells, with a mean corpuscular volume (MCV) below 80 fL) and hypochromic (paler due to reduced Hb content). However, in early stages, red blood cells may appear normocytic (normal size, MCV 80–100 fL) and normochromic before becoming microcytic as the deficiency worsens[1].

Prevalence of Iron Deficiency

The prevalence of ID is higher in developing countries compared to developed ones, although it is not limited to economically disadvantaged regions. In developing countries, ID typically arises from inadequate dietary intake of iron and is often associated with parasitic infections that cause bleeding. Additionally, malaria, HIV/AIDS, and tuberculosis contribute to high prevalence rates in some regions[2].

In Pakistan, Iron Deficiency Anemia (IDA) is a severe public health crisis, especially among women and young children. National data indicates that more than half of children under five and over 40% of women of reproductive age suffers from some form of anemia.

Children under Five, approximately 53.7% are anemic, with 28.9% specifically diagnosed with IDA. Women of Reproductive Age (WRA), about 42.7% are anemic, with 18.4% experiencing IDA. Pregnant Women, prevalence is exceptionally high, with some reports estimating that 51% to over 70% are anemic. Iron Deficiency Anemia in Pakistan is a major contributor to high maternal mortality, preterm births, and impaired cognitive and physical development in children.

According to the World Health Organization (WHO), anemia affects 30% of non-pregnant women, 37% of pregnant women, and 40% of children under five worldwide. Despite other causes like malaria, thalassemia, and sickle cell trait, ID remains the leading cause of anemia, making IDA the most common form of the condition. It is estimated that more than 1.2 billion people suffer from IDA worldwide, with prevalence varying significantly between low- and high-income countries[3,4].

In the least developed countries, particularly in sub-Saharan Africa, the prevalence of anemia among children aged 6–59 months often exceeds 60%, with some countries reporting rates as high as 86%. Data show that IDA affects up to 72.8% of children in certain regions (e.g., Ethiopian Somali region), and ID alone may affect over 90% in highly vulnerable subpopulations[4,5]. While national averages for IDA typically range from 12% to 46%, local studies in high-risk groups (e.g., breastfed infants or those exposed to

infections and food insecurity) report extremely high rates, sometimes exceeding 60–70%[5].

In developing countries, anemia affects 20–39.9% of women of reproductive age in many regions, with some countries—such as Papua New Guinea and parts of Indonesia—reporting severe anemia prevalence exceeding 70%. Specific regional data point to anemia prevalence rates as high as 72.9% among women of reproductive age in Indonesia and up to 89.7% in Papua New Guinea, with a significant proportion attributable to ID and compounded by infections such as malaria and helminthiasis[6].

The WHO Global Health Observatory data shows that anemia rates in pregnancy have remained largely unchanged over time, with rates decreasing from 41% in 2000 to only 37% in 2019.

In children, a review of 44 studies conducted across 19 European countries revealed that 2–25% of infants aged 6–12 months were iron deficient, with higher rates among those from lower socioeconomic backgrounds and those who drank cow's milk during their first year. For children aged 12–36 months, ID prevalence ranged from 3% to 48%, while the rate of IDA was as high as 50% in Eastern Europe, but less than 5% in Western Europe[7].

The WHO classifies the public health significance of anemia into four categories based on prevalence estimates in specific populations: "normal" (<5%), "mild" (5–19.9%), "moderate" (20.0–39.9%), and "severe" (≥40%)[8]. Given the magnitude of the issue, the WHO has set a target to reduce the prevalence of anemia among women of reproductive age, including adolescent girls, by 50% by the year 2030.

Pathophysiology

Iron is an essential element and is controlled primarily by dietary intake, intestinal absorption and iron recycling.[9] Dietary iron can be found in two forms: haem and non-haem iron. Haem iron is easily absorbable and arises from haemoglobin (Hb) and myoglobin in the form of animal meat, poultry and fish. Non-haem iron is mostly found in plant food but is not as easily absorbable. Compounds such as phytate, oxalate, polyphenols and tannin, which are found in plants, diminish the uptake of non-haem iron, as do some drugs, such as proton pump inhibitors. Ascorbic acid, citrate and gastric acid, conversely, facilitate iron absorption.[10] In a healthy diet, approximately 5–15 mg of elemental iron and 1–5 mg of haem iron are ingested daily although only 1–2 mg is ultimately absorbed into the intestine, predominantly in the duodenum and proximal jejunum.

The two different iron absorption pathways. Non-haem absorption pathway (left): insoluble ferric iron (Fe^{3+}) is reduced to absorbable ferrous iron (Fe^{2+}), which is carried out by the enzyme duodenal cytochrome B (DcytB). The divalent metal transporter 1 (DMT1) imports Fe^{2+} across the apical surface and into the cell, which can then be either stored as ferritin or exported into circulation through ferroportin. Prior to exiting the enterocyte, Fe^{2+} must be oxidised back to Fe^{3+} by hephaestin or ceruloplasmin. Haem absorption pathway (right): the haem carrier protein (HCP1) transports haem iron directly into the enterocyte. Once inside the enterocyte, haem iron can either be released into plasma via the haem exporter FLVCR1 or be converted back into Fe^{2+} via the haem oxidase (HO) enzyme. The ferroportin receptor then releases Fe^{2+} into the plasma. Hepcidin, a hepatic peptide hormone, controls ferroportin, the sole iron exporter, by promoting its endocytosis. Hepcidin production and circulation are regulated by plasma iron concentration and iron stores. Hepcidin is increased in the presence of inflammation.

Causes of Iron Deficiency

Iron has both a storage pool and a functional pool. The storage pool is the reticuloendothelial system which consists of the liver, spleen and lymph nodes. The functional pool consists of red blood cells, bone marrow and cardiac and skeletal muscle. Iron is absorbed in the duodenum via specific transporters and is carried by transferrin molecules to the storage and functional pools. Iron deficiency can be absolute or functional.

Causes of iron deficiency can be grouped into the following categories: inadequate dietary intake, increased body needs, reduced absorption, chronic inflammation and chronic blood loss.

Inadequate intake can result from iron-deficient diets. Athletes and those performing in demanding sports have increased iron needs and are at a higher risk of developing iron deficiency.

Iron absorption occurs mainly in the proximal small intestine.

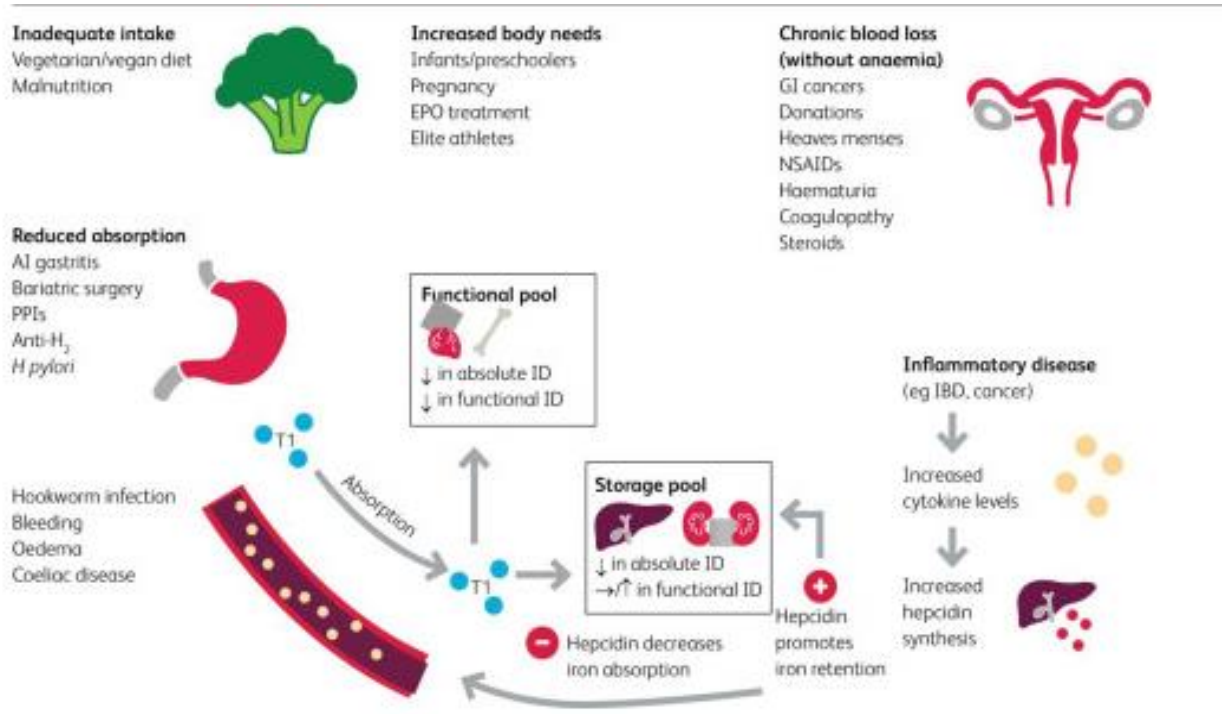
Bariatric surgery patients are highly susceptible to ID due to a decreased absorptive surface area and/or reduced gastric acid secretion.

Less commonly, Helicobacter pylori infection may cause ID due to reduced iron absorption and blood loss.[11]

The consumption of coffee, tea or calcium (in supplements or dairy products) has been reported to reduce iron absorption.

Chronic inflammation, such as in coeliac disease, inflammatory bowel disease (IBD) and HF, increases hepcidin production, blocking iron transporters and reducing absorption, and causes iron entrapment within storage pools.

The main causes of ID and IDA include low dietary iron intake and insufficient iron absorption during periods of life when iron requirements are particularly high, such as during periods of growth in children and adolescents, as well as during the reproductive years in women, especially during pregnancy and postpartum. Chronic GI bleeding, heavy menstrual bleeding, and malabsorption conditions like celiac disease and inflammatory bowel disease (IBD), where the integrity of the cells lining the GI tract is compromised, can also lead to IDA[11]. IDA occurs in 60–80% of patients with IBD.



AI gastritis = autoimmune gastritis; anti H2 = anti histamine-2 receptor (H2 receptor antagonist); EPO = erythropoietin; GI cancers = gastrointestinal cancers; H pylori = Helicobacter pylori; IBD = inflammatory bowel disease; NSAIDs = non-steroidal anti-inflammatory drugs; PPIs = proton pump inhibitors; Tf = transferrin.

Figure No.1: Causes of iron deficiency.[11]

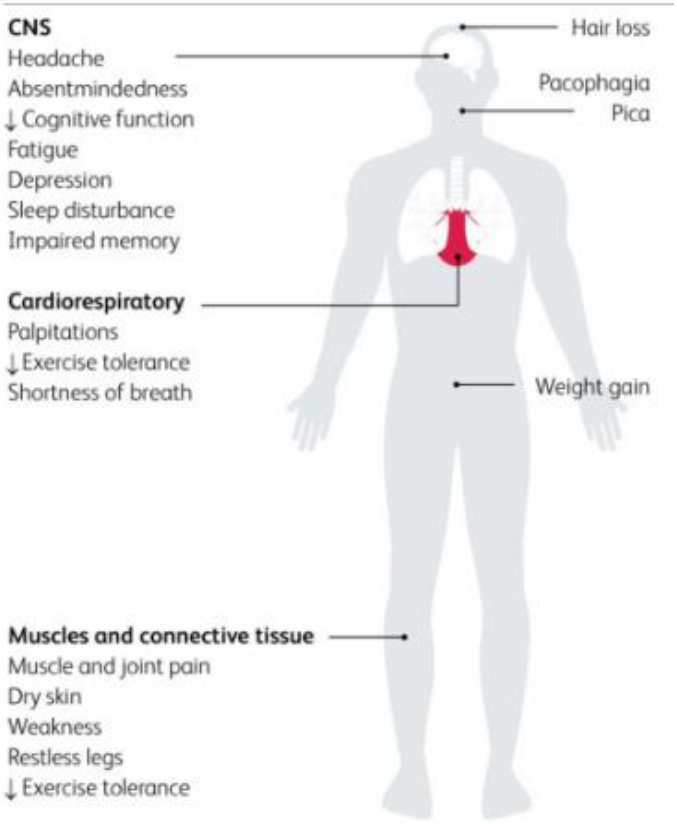


Figure No. 2: Effects of iron deficiency on the human body.[12]

Assessment and diagnosis

The WHO defines anaemia as blood Hb level below 130 g/L in men and 120 g/L in women. In isolated iron deficiency, serum ferritin (the storage molecule for iron) should be less than 30 ug/L. However, ferritin is an acute phase protein and can be increased in the presence of inflammation. Thus, if there is evidence of concomitant inflammation, such as elevated C reactive protein, ferritin less than 100 ug/L is indicative of IDA.[13] Transferrin, the iron transporter, is generally elevated; however, it is a negative acute phase protein and therefore, can be normal or reduced in chronic inflammatory states.[14]

Serum iron and transferrin saturations (TSAT) will be reduced with TSAT less than 20% required for the diagnosis of IDA. See Table 1 for the breakdown of diagnostic criteria for IDA.

Signs and Symptoms of Iron deficiency

There are so many signs and symptoms of iron deficiency, few are describe below:

Pica (Odd Cravings): An intense, strange desire to consume non-food substances such as ice (pagophagia), dirt, paper, or clay.

Spoon-Shaped Nails (Koilonychia): Nails that are thin, brittle, and break easily, or that curve upward in the center, forming a shape like a spoon.

Sore or Swollen Tongue (Glossitis): A tongue that appears unnaturally smooth, inflamed, or swollen, sometimes causing difficulty with swallowing.

Restless Legs Syndrome (RLS): An uncontrollable, uncomfortable urge to move your legs, often accompanied by tingling or itching, which frequently occurs at night.

Angular Cheilitis (Mouth Cracks): Painful, cracked, or ulcerated sores that develop in the corners of the mouth.

Management and Treatment

Iron deficiency anemia (IDA) management involves identifying the root cause (e.g., blood loss, poor absorption) and replenishing iron through oral supplements (ferrous sulfate/fumarate) or IV iron for severe cases. Iron replenishment can occur via three routes: oral iron, parenteral oral and transfusion of packed red cells. Each route has its benefits and limitations mentioned in Table 2.

Table No.1: Diagnostic criteria for iron deficiency anaemia

Serum markers	Diagnosis for IDA
Haemoglobin	<130 g/L males <120 g/L females <110 g/L in pregnancy
Ferritin*	<30 ug/L if no inflammation <100 ug/L if inflammation
Transferrin†	Raised
Total iron binding capacity	Raised
Iron	Reduced
Transferrin saturations	<20%
Mean corpuscular volume	Low

Table No.2: A list of common conditions and patient groups who have an increased risk of developing iron deficiency anaemia

Background	Cause of iron deficiency anaemia	Cause of blood loss	Recommended route of iron replacement
Congestive cardiac ailure	Poor nutrition Decreased GI absorption	Antiplatelet and/or anticoagulant use	Intravenous
Chronic kidney disease		Dialysis and frequent blood sampling	Intravenous
Inflammatory bowel disease		Chronically inflamed and ulcerated bowel	Intravenous
Elderly		Medications (antiplatelet, anticoagulant, anti-inflammatories, anti-depressants)	Oral
Malignancy	Poor nutrition Loss of healthy blood cells Damage to the bone marrow	Bleeding tumour	Intravenous
Surgery	Dependent on cause for surgery requirement	Excessive bleeding either pre and/or post-operatively	Intravenous or oral
Pregnancy	Poor nutrition Increased iron demands to mother and fetus	–	Intravenous or oral

Oral Iron Supplementation: The first-line treatment, often involving daily or alternate-day intake of tablets like ferrous sulfate, fumarate, or gluconate. Taking iron with vitamin C (e.g., orange juice) can enhance absorption, while taking it on an empty stomach is generally recommended, though taking it with food can reduce side effects.

Intravenous (IV) Iron: Used if oral iron is not tolerated, ineffective due to malabsorption, or in cases of severe anemia or chronic blood loss.

Addressing the Underlying Cause: Essential for long-term management, which may include treating heavy menstrual bleeding, gastrointestinal bleeding, or correcting nutritional deficiencies.

Dietary Adjustments: Increasing intake of iron-rich foods such as legumes, lean meat, and fortified cereals.

Monitoring and Duration: Treatment typically continues for 3-6 months to fully replenish iron stores, with monitoring of hemoglobin levels.

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