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Review Article

Iron Deficiency Anemia: A Comprehensive Review of Epidemiology, Pathophysiology, Diagnosis, and Clinical Implications

Elham F. Hamzah¹*

¹Department of Clinical Biochemistry, Hammurabi College of Medicine, University of Babylon, 51002 Hillah, Babylon, Iraq

*Corresponding Author: Elham F. Hamzah

Department of Clinical Biochemistry, Hammurabi College of Medicine, University of Babylon, 51002 Hillah, Babylon, Iraq

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Abstract: Iron deficiency is the leading cause of anemia among populations in industrialized and developing countries throughout the world. Here we will also highlight the heterogeneous etiology of IDA and we will discuss about the mechanisms involved in the clinical presentation, that is to say about diagnostic clues different taking into considerations some specific populations like women, children and elderly. The review also covers new insights into the genetics of IDA, such as iron refractory iron deficiency anemia (IRIDA) and also highlights prevalence of IDA in chronic disease and surgery. The impact of IDA on behaviour and cognition, physical function, quality of life, and pregnancy outcome are highlighted. An awareness of these patterns is important for pre-emption, early diagnosis and appropriate treatment.

Keywords: Iron Deficiency Anemia, Iron Metabolism, Epidemiology, TMPRSS6, IRIDA, Pregnancy, Nutritional Anemia, Iron Absorption, Chronic Disease.

Introduction

1. Introduction to Iron Deficiency Anemia

IDA is the result of depletion of body iron stores until erythropoiesis (red cell production) is limited (Bermejo *et al.*, 2009). It is the most prevalent type of chronic maternal anemia worldwide, and is estimated to affect 2-5% of adult men and postmenopausal women in Western countries (Bermejo *et al.*, 2009) (Goddard *et al.*, 2000). The magnitude of this health problem is staggering, with approximately 3 billion individuals affected by iron deficiency globally (Marushko *et al.*, 2023). Iron is indispensable for many physiological functions such as oxygen transport, DNA synthesis and electron transport (Burz *et al.*, 2018). The WHO defines anemia as hemoglobin level <130 g/L in men over 15 years, <110 g/L in pregnant women and <120 g/L in nonpregnant women older than 15 years (Kumar *et al.*, 2020). IDA specifically denotes anemia due to insufficient iron for the production of normal red blood cells, which present as microcytic and hypochromic with incomplete hemoglobin synthesis (Kumar *et al.*, 2020).

Iron deficiency anemia is usually caused by one of three major mechanisms: insufficient dietary iron intake, poor absorption of iron, or loss of blood (Rayas *et al.*, 2019). Of these, blood loss—specifically from gastrointestinal sources—is a most prevalent cause in men and postmenopausal women (Lukina *et al.*, 2020). Added risk factors for women are menstruation, pregnancy and breast-feeding (Lukina *et al.*, 2020). Whereas the diagnosis of IDA was traditionally straightforward and could be diagnosed by routine laboratory analyses used in most healthcare centers, interpretation of such results requires to be critically interpreted due to confounders (Grotto, 2010). A diagnosis of IDA is an indicator that work-up should be pursued to diagnose the underlying cause; IDA can be a sign of a life-threatening illness that should be treated (Burz *et al.*,2018).

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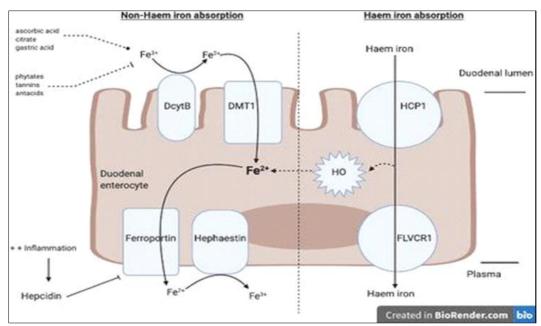


Figure 1: The two different iron absorption pathways

2. Global Epidemiology and Affected Populations

IDA is a worldwide public health problem, with an estimated prevalence of 1.5–1.6 billion people, 1 and iron deficiency makes up approximately 50% of cases of anemia. (Api *et al.*, 2015) (Nehar *et al.*, 2024) Based on World Health Organization (WHO) report on anemia, it has been found to have a 24.8% prevalence rate among the global population while among specific sub-groups, it has the high." est prevalence among preschool-aged children (47.4%), pregnant women 41.8% and in women of reproductive age who do not suffer pregnancy (30.2%) (Shayo *et al.*, 20128). (Kumar *et al.*, 2022) (McLean *et al.*, 2009)

Epidemiology and classification Iron deficiency anemia (IDA) is not evenly distributed geographically, and developing countries carry the largest burden in part because of insufficient dietary iron availability, chronic loss of blood due to parasitic infections, such as hookworm infestation and malaria, and limited access to healthcare services. (Scrimshaw, 1984) (Shaw *et al.*, 2011) The prevalence of IDA varies between 10-20% in industrial countries, whereas it is much higher in Africa, South-East Asia, and Eastern Mediterranean countries. (Scrimshaw, 1984) (Ciampo *et al.*, 2020).

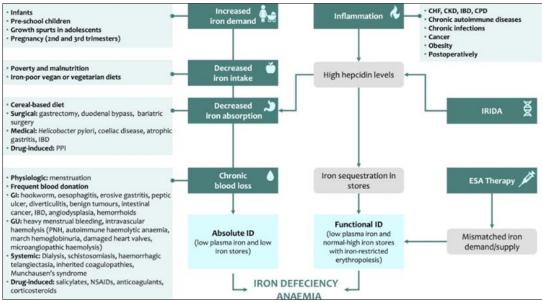


Figure 2: Various etiologies of iron deficiency anemia. CHF, chronic heart failure; CKD, chronic kidney disease; CPD, chronic pulmonary disease; ESA, erythropoiesis-stimulating agents; IBD, inflammatory bowel disease; ID, iron deficiency; IRIDA, iron-refractory iron deficiency anemia; NSAIDs, Nonsteroidal anti-inflammatory drugs; PNH, paroxysmal nocturnal hemoglobinuria; PPI, proton-pump inhibitors

Females in reproductive age are especially vulnerable and approximately 32.5-33% of them suffer from ID due to IDA worldwide. (Faria *et al.*, 2015) (Nehar *et al.*, 2024) Additionally, prevalence grows to 40-50% during pregnancy, the surge being attributed to augmented physiological conditions. (Farias *et al.*, 2020) (Obianeli *et al.*, 2024) The high rates of incidence in females are due to physiologic requirements linked to menstruation, pregnancy, and breastfeeding that result in increased iron needs. (Mawani *et al.*, 2016)

Children are a second large population where there is significant impact of iron deficiency, which affects about 42% of children under age 5 throughout the world. (Kumar *et al.*, 2022) The rates of prevalence are particularly high in children 6-59 months, ranging from 10 to 33% in the US and African countries respectively. (Ciampo *et al.*, 2020) The 1st-3rd year is the phase of life with the greatest susceptibility, which coincides with great growth and development. (Apu *et al.*, 2023).

IDA is deeply conditioned by socioeconomic status, and the poorest are at highest risk. (Armstrong *et al.*, 2015) This discrepancy has been attributed to poor dietary intake, inadequate health care access, and an increased prevalence of parasitary infections. (Mawani *et al.*, 2016) Moreover, in India it was found that 80 % of children of 6–35 months and 58 % children of 36–59 months of age are anemic and iron deficiency is the chief cause. (Kumar *et al.*, 2022); (Nair *et al.*, 2015). Although international initiatives are taking place to deal with this worldwide public health problem, the prevalence of iron deficiency increases over the past 10 years. This draws attention for a better therapeutic strategy, especially among those living in a less developed country. (Armstrong *et al.*, 2015) The Copenhagen Consensus Centre has labelled iron deficiency as the world's number one health challenge, with the economic and disease burden occurring primarily in women of reproductive age. (Armstrong *et al.*, 2015)

3. Etiology and Risk Factors

Iron-deficiency anemia (IDA) is a disorder of disturbed iron balance in which there is insufficient iron for erythropoiesis. This discrepancy is usually found to be due to, essentially, 3 main mechanisms (Bermejo *et al.*, 2009): insufficient iron intake, restricted iron absorption and loss of iron, mainly by blood. Of these mechanisms, blood loss is the most common cause among adult males and postmenopausal women, frequently from a gastrointestinal source (Bermejo *et al.*, 2009).

In women of childbearing age, iron requirements are substantially elevated due to oenophysiological reasons. Menstrual cycle, pregnancy and lactation are associated with very high iron requirements and, as such, women are at a high risk of IDA (Abu-Ouf *et al.*, 2015) (Mawani *et al.*, 2016). In pregnancy itself, low weight gain is a strong predictor of iron deficiency (Abu-Ouf *et al.*, 2015). Elevated iron requirement during pregnancy in case of its insufficient supplementation can lead to the idea of maternal anemia and affects the child's iron status (Obuchowska *et al.*, 2022).

Children are also another high risk group, during the period bet ween 1-3 years during the period of rapid growth and development, was found to be most at risk (Apu *et al.*, 2023). In children and adolescents, growth periods can cause a high demand for iron and the lack of an appropriate diet can result in the development of IDA (Yoon, 2011). Diet is an important contributing factor for the development of IDA. Inadequate consumption of iron is the cause of as many as 50% of IDA cases in industrialized nations (Abu-Ouf *et al.*, 2015). The low pH in the stomach promotes iron uptake, which takes place mostly in the duodenal and jejunal segments. As a result, acidic compounds such as ascorbic acid will increase the absorption of iron when administered with it (Abu-Ouf *et al.*, 2015). There are many ways by which gastrointestinal disorders cause IDA. Chronic NSAID use, celiac disease, and Helicobacter pylori infection are all etiologies leading to mucosal injury that can inhibit iron absorption (Frater, 2021) (Chey *et al.*, 2007) (Hill *et al.*, 2005) (Dube *et al.*, 2005). Furthermore, H. pylori infection has been recognized as a cause of iron deficiency anemia refractory to oral iron treatment (Yoon, 2011). Bariatric surgeries also frequently cause iron deficiency due to gut anatomy modification and decremented absorption (Frater, 2021) (Gloy, 2013).

Chronic inflammatory diseases are a major risk group for IDA. Among these are congestive heart failure, chronic kidney disease, inflammatory bowel disease and rheumatoid arthritis (Frater, 2021) (Stein *et al.*, 2016). In such settings, functional iron deficiency frequently arises: They are unable to meet the increased demand of the erythron for iron even though their iron deposits are apparently adequate (Sheikh *et al.*, 2021) (Levi *et al.*, 2016) (Thomas *et al.*, 2013). This pathobiology describes the iron deficiency also observed in the cancer (Hashemi *et al.*, 2017).

Parasitiasis in less developed countries is a major problem for IDA. Hookworm is known to cause up to 73% of the cases of severe IDA in Africa (Frater, 2021) (Hotez *et al.*, 2006). These parasites are responsible for chronic blood loss and consequently contribute to the anemia of inflammation, thereby lowering the availability of iron in the host (Shaw *et al.*, 2011). The risk of IDA is strongly associated with socioeconomic factors, and poverty is a primary determinant (Armstrong *et al.*, 2015). People of lower SES are frequently subject to a combination of deprivations that contribute to poor dietary iron availability, chronic blood loss due to infections and lack of access to health-care services (Shaw *et al.*,

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2011). In addition to anemia, iron deficiency has broad effects on the immune system, such as impaired B and T-cell activity, diminished phagocytosis and reduced macrophage killing capacity (Frater, 2021) (Scrimshaw *et al.*, 1997). It is also linked to higher risk of malaria and mortality from infection (Frater, 2021) (Oppenheimer, 2001).

4. Pathophysiology of Iron Deficiency Anemia

IDA is the end-result of a continuum of negative iron balance. It has three stages: 1) depletion of iron stores, followed three) by iron-deficient erythropoiesis and, eventually, the appearance of 4) iron deficiency anemia (Araujo *et al.*, 2023). The first phase is when the body's need for iron exceeds the amount taken in or absorbed and there is a depletion of ferritin and hemosiderin stores, but hemoglobin levels are still normal. Once these stores are depleted, the second phase is initiated, in which iron availability for erythropoiesis is reduced despite the appearance of adequate iron stores (Sheikh *et al.*, 2021).

Iron has many vital functions in the body besides oxygen transport it is involved in enzyme systems, DNA synthesis, collagen formation, metabolism of vitamin D and maintenance of fundamental cellular processes (Yang *et al.*, 2023). Thus, iron deficiency may affect various organ systems to a great extent, prior to the occurrence of anemia. At stage 3 of the deficiency, there is inadequate iron for normal hemoglobin formation, so microcytic and hypochromic RBCs of IDA develop (Kumar *et al.*, 2020).

There are two major types of iron deficiency which lead to the development of anemia, absolute and functional iron deficiency. Absolute iron deficiency is responsible for the total body iron store depletion or exhaustion, and it is mainly caused by increased iron loss, insufficient iron diet uptake or malabsorption (Bermejo *et al.*, 2009). In contrast, functional iron deficiency is a condition in which there is seemingly available iron storage (as indicated by normal or high serum ferritin and stainable bone marrow iron), but not enough iron is being taken up by erythroid precursors(Sheikh *et al.*, 2021) (Thomas *et al.*, 2013). The latter form is prevalent in chronic inflammation, cancers, and some genetic defects, such as thalassemia and sickle cell anemia (Yang *et al.*, 2023) (Pinto *et al.*, 2020).

The progression of IDA affects many body functions other than oxygen delivery. Iron deficiency may impair cognitive development, immune function and physical work capacity (Yang *et al.*, 2023) (McCann *et al.*, 2020) (Houston *et al.*, 2018). Moreover, other recent work underlines hepcidin as an important modulator of iron homeostasis and a major actor in the pathophysiology of IDA (Nehar *et al.*, 2024). It regulates the absorption of iron from the intestine and its release from macrophages, and is involved in the aetiology of both iron-deficiency anemia and iron overload.

Laboratory evaluation of IDA includes various parameters. Generally, blood haemoglobin level less than 13 g/dl in males and less than 12 g/dl in females is considered subnormal (Abu-Ouf *et al.*, 2015). Its features include a low mean corpuscular volume of $\leq 80 \mu \text{m}^3$, low mean hemoglobin and serum ferritin level ≤ 30 ng/ml (Sheikh *et al.*, 2021). Further testing in cases of indeterminate ferritin levels includes TIBC (increased in IDA), serum iron (decreased), transferrin saturation levels (decreased) Sheik *et al.*, 2021.

Acid condition in the stomach enhances the absorption of iron, mainly in the duodenum and part 2 of the jejunum. This explains the reason why co-ingestion of acidic compounds, including ascorbic acid, enhances iron absorption (Abu-Ouf *et al.*, 2015). This knowledge of these physiological processes is necessary to develop treatments that target the pathophysiology of iron deficiency anemia.

5. Clinical Manifestations

Iron deficiency anemia (IDA) has diverse clinical symptoms that are developed while the condition becomes more aggravated. The following are the most common symptoms of a tracheomalacia.

- Tiredness and weakness: They are symptoms arising from a reduced oxygen carrying capacity which toward discomfort or ability to meet trials of everyday living (Fatigue and). (Nyambura, 2024) (Nehar *et al.*, 2024).
- Paleness: Particularly visible on skin, mucous membranes, and nail beds (Nyambura, 2024) (Mandziy et al., 2021).
- Neurological manifestations: Vertigo and headache in severe cases syncope (Mandziy et al., 2021).
- Shortness of breath, particularly on exertion (Mandziy *et al.*, 2021) Escortbayan.
- Cognitive Disturbance: Difficulties in concentration, attention and cognitive performance (Nehar *et al.*, 2024) (Nazar *et al.*, 2016) (Halterman *et al.*, 2001).
- Developmental considerations: In childhood, IDA can lead to motor and cognitive developmental retardation (Nazar *et al.*, 2016).
- Abnormal sensory system: Other studies have also reported that IDA during infancy can result in various forms of auditory and visual system dysfunction with delayed auditory and visual latency and increased in auditory and visual latency that persists after treatment infancy (Nazar *et al.*, 2016) (Algarin *et al.*, 2003).

- Abnormal cravings (pica): In particular pagophagia (craving for ice), a possible diagnostic pointer (Sheikh *et al.*, 2021). Decreased work capacity: In adults, iron deficiency can lead to a profound reduction in productivity and quality of life (Nazar *et al.*, 2016).
- Immunosuppression: Higher risk of infection due to weaker immune response (Sheikh et al., 2021).

The extent of symptoms usually relates to the degree of anemia, although non-anemic iron deficiency may also lead to fatigue in women (Nazar *et al.*, 2016) (Verdon *et al.*, 2003). It should be remembered that the symptoms of IDA may occur suddenly, sometimes over time the patient adjusts to anemia and may be asymptomatic until the hemoglobin falls appreciably. Presentations may depend on the demographic profile, and women of reproductive age, pregnant ladies, and children are more likely to develop symptomatic IDA (Abu-Ouf *et al.*, 2015) (Arce, 2023). The absence of these symptoms should be evaluated with appropriate laboratory tests before definitive diagnosis, as many symptoms are non-specific and may be due to other diseases (Shine, 2020).

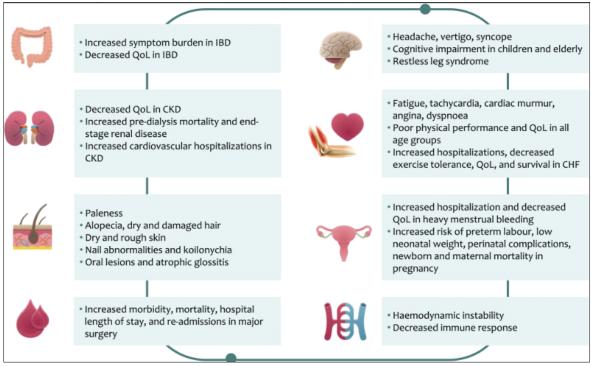


Figure 3: Clinical implications of iron deficiency anemia. CHF, chronic heart failure; CKD, chronic kidney disease; IBD, inflammatory bowel disease; QoL, quality of life

6. Diagnostic Approaches and Laboratory Findings

Iron Deficiency Anaemia (IDA) is usually diagnosed using very cheap general laboratory tests that can be done in any clinical environment. While diagnosis of the disease is generally simple, interpretation of the result must be very cautious as confounding factors are common (Grotto, 2010). Characterization for anemia often begins with clinical presentation followed by laboratory detection for iron indices and hematological profile (Sheikh et al., 2021). Complete blood count (CBC) is the first line test, and IDA is defined as low hemoglobin (below 13g/dL in men, and below12 g/dL females) low mean corpuscular volume (MCV \leq 80µm³ and low mean corpuscular haemoglobin (MCH) (Sheikh et al., 2021) (Shine, 2020). These results demonstrate the microcytic, hypochromic status of erythrocytes generated in iron-deficient erythropoiesis (Kaya, 2013). Other red cell indices especially the RDW may be useful for diagnosis, as a high RDW is frequently observed in IDA (Zhu et al., 2010).

Serum ferritin concentration is generally accepted as the most sensitive single laboratory test for the diagnosis of iron deficiency (Shine, 2020) (Zhu, 2010). Optimal levels \leq 30 ng/ml are typically diagnostic of IDA (Sheikh *et al.*, 2021). The elevated levels of ferritin in our patients may suggest ferritin-related due to similar reasons as above pointing to macrophage activation, however, the role of ferritin in HLH predisposed patients needs further elucidation (Marsh *et al.*, 2010). Since ferritin is an acute-phase reactant, it is possible that the level may be raised in inflammation, infections, as well as in malignancies; therefore, interpretation should be see in the light of clinical scenario (Kaya, 2013). In populations with high prevalence of inflammation diseases, it has been suggested by some the lower normal level for ferritin should be raised to $100 \mu g/l$ in order to increase the sensitivity of diagnosis (Zhu *et al.*, 2010).

For cases with a ferritin level that is indeterminate, further iron studies are suggested as follows:

- Serum iron (decreased in IDA)
- TIBC (increased in IDA)
- Saturation of transferrin (low in IDA, usually <16%)
- Unsaturated iron binding capacity (UIBC) (which is increased in IDA) (Sheikh *et al.*, 2021)(Yoon *et al.*, 2015) (Obuchowska *et al.*, 2022).

Note that some of these iron indices can be influenced by numerous physiological and pathologic conditions, such as inflammation or infection, dietary intake and even circadian rhythm, which may hamper their diagnostic roles (Albaroudi *et al.*, 2018). New markers like serum transferrin receptor (sTfR) have recently been identified as a possible diagnostic tool mainly for differentiating between absolute and functional iron deficiency (Kaya, 2013). Unlike ferritin, sTfR is not markedly influenced by inflammation and, accordingly, could be more accurate in individuals with inflammation related to underlying chronic diseases (Almashjary, 2024).

The process of diagnosis should also differentiate the absolute iron deficiency (lack of iron reserves) and functional iron deficiency (adequate reserves but ineffective in incorporation in erythroid precursors) (Sheikh *et al.*, 2021) (Thomas *et al.*, 2013). This difference is also of great significance in treatment for patients with chronic inflammatory disease, cancer and some genetic diseases (Hashemi *et al.*, 2017).

Importantly, when IDA is confirmed, it should be further assessed for the etiology of IDA given that it can indicate a more serious disorder that requires specific treatment (Shine, 2020). In adults, especially in men and in postmenopausal women, evaluation of the gastrointestinal (GI) tract using esophagogastroduodenoscopy and colonoscopy may be appropriate to exclude malignancy or other bleeding sources in association with IDA (Zhu *et al.*, 2010). Early diagnosis of IDA is crucial, particularly in children, as uncontrolled IDA may result in serious complications as development delay, malaise and learning disorders (Albaroudi *et al.*, 2018) (Walter *et al.*, 1989).

Laboratory diagnosis of IDA represents the end of a continuum of negative iron balance that begins with the exhaustion of iron stores, is characterized by iron-deficient erythropoiesis, and culminates with anemia (Araujo *et al.*, 2023). This highlights the need for global methods of diagnosis that allow for the identification of iron deficiency status before the appearance of the anemic condition, especially in vulnerable groups of the population (Yoon *et al.*, 2015).

CONCLUSION

Iron deficiency anemia is a major health problem in the world with a variety of causes and clinical manifestations. From dietary deficiencies and long-term blood loss to genetic variants and malabsorption caucuses, a diagnostician's and treater's game plan for IDA must be multifaceted. The prevalence is higher in women, children and patients with chronic diseases and is associated with cognitive impairment, physical performance impairment and impairment in quality of life. New discoveries in the molecular pathogenesis of diseases such as IRIDA may offer added dimensions to individualized therapy. Therefore, to overcome IDA, there is a need for better clinical awareness of the condition and public health measures that emphasise iron supplementation, dietary counselling, and screening in high risk groups.

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